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U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review[1]	
STNs	PM0000973.PD1, PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10 and PM0000973.PD11
Common Attributes	
Submission date	September 04, 2020
Receipt date	September 04, 2020
Applicant	R.J. Reynolds Vapor Company
Product manufacturer	R.J. Reynolds Vapor Company
Application type	Standard
Product category	Electronic Nicotine Delivery Systems (ENDS) (VAPES)
Product subcategory	Closed E-liquid,[2] ENDS Component[3]
Cross-Referenced Submissions	
All STNs	None
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	• Update to Premarket Tobacco Product Application (PMTA) Review Process: Reviewing Late Amendments (October 30, 2023) • Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications (June 3, 2024) • Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications (June 3, 2024)
Recommendation	
Issue marketing granted orders for the new tobacco products subject to this review.	

[1] Product details, amendments, and dates provided in the Appendix. STN means submission tracking number including product static identification number (PD) if applicable. PMTA means premarket tobacco application.
[2] For PM0000973.PD1.
[3] For PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10 and PM0000973.PD11.

Technical Project Lead (TPL):	/S/ Apostolos Alexandridis, Ph.D., M.P.H. Epidemiologist Division of Population Health Science Office of Science
Signatory Decision:	Concur with TPL recommendation and basis of recommendation /S/ Matthew Farrelly, Ph.D. Director Office of Science

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1. EXECUTIVE SUMMARY

Based on the information provided in the applications and other scientific data, as described in this Technical Project Lead (TPL) review, I find that permitting the marketing of the new products listed above ("new products" or "subject ENDS") 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 postmarket requirements.

1.1. APPH STANDARD

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

The statute further specifies that, in assessing 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, young adults, and other vulnerable populations. As the statutory text makes clear, it is the applicant's burden to make a "showing"—with sufficient supporting information—that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole. In determining whether permitting the marketing of 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 lower risk products).

In making the APPH assessment specifically for a noncombusted tobacco product such as an electronic nicotine delivery system (ENDS), FDA weighs, among other things, the negative public health impact stemming from youth initiation and use of the product against the potential positive public health impact stemming from adults who use CC transitioning away, i.e., completely switching, from CC to the ENDS product or significantly reducing smoking of CC. In order to show that the marketing of an ENDS is APPH, an applicant must show that the benefits, including those to adults who use CC, outweigh the risks, including those to youth, resulting in a net benefit to the public health. As the known risks of the product increase or decrease, the burden of demonstrating a substantial enough benefit likewise increases or decreases.

Current scientific literature demonstrates that ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than CC, and biomarker studies demonstrate significantly lower exposure to HPHCs among people who exclusively used ENDS compared to people who currently smoke CC. However, whether this is true for any particular new ENDS 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 use CCs may experience a reduction in health risks if they switch completely to ENDS, or if they use both products but substantially reduce their CC smoking.

For flavored ENDS [4] (i.e., ENDS with e-liquid flavors other than tobacco, such as fruit), there is a known and substantial risk of youth initiation and use; accordingly, an applicant has a higher burden to establish that the likely benefits to adults who use CC outweigh that risk. For tobacco-flavored ENDS the risk to youth is lower compared to flavored ENDS; accordingly, a lesser showing of benefit may suffice.

Before determining that permitting the marketing of a new tobacco product would be APPH, FDA also considers the impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and tobacco use. Such mitigation efforts include advertising and promotion restrictions (e.g., measures such as limiting advertising to platforms that are predominantly used by adults and using advertising content and methods that are not known to resonate with youth); sales access restrictions (e.g., measures such as selling products only in face to face interactions, in adult-only facilities, or via websites that require robust age verification); and device access restrictions (e.g., technologies that require adult user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product). FDA evaluates these measures in the context of the overall public health evaluation of the product, weighing the known risks to youth against the benefit to adults. In the case of flavored ENDS, the risk of youth initiation and use is well documented and substantial. Experience shows that advertising and promotion restrictions and sales access restrictions cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH.[5] Rather, for flavored ENDS, only the most stringent mitigation measures – specifically device access restrictions – have such mitigation potential.[6] In contrast, the risk of youth initiation and use with tobacco-flavored ENDS is lower. Restrictions on advertising and promotion and sales access for tobacco-flavored ENDS could mitigate that more limited risk and impact the overall net benefit assessment. In addition, 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.

[4] The term "flavored ENDS" in this review refers to an ENDS product with any characterizing flavor other than tobacco, including menthol flavor. For the purposes of this review, it is synonymous with "non-tobacco-flavored ENDS."
[5] *See* FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry* 44 (Apr. 2020) ("The reality is that youth have continued access to ENDS products in the face of legal prohibitions and even after voluntary actions by some manufacturers."); *see also id*. at 45 (noting "data that many youth obtain their ENDS products from friends or sources in their social networks").
[6] Device access restrictions are novel and their use in the current marketplace is limited. To the extent flavored ENDS applicants claim to have device access restrictions (which, as components or parts of the product, would be discussed in the product formulation and engineering sections of a PMTA, rather than solely in the marketing plan), FDA's approach is to engage in further scientific review of those applications.

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 fully assess the risks and benefits of the product, the applicant has failed to carry its statutory burden of demonstrating that the product's benefits outweigh the risks.

1.2. SUBJECT APPLICATIONS

FDA reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate that marketing of the products would be APPH. The applications demonstrate that the new products have the potential to benefit adults who smoke CC and completely switch to the new products, or significantly reduce their smoking of CC, and that such benefit outweighs the risk to youth. We conclude that the marketing of the new products, subject to certain marketing restrictions and postmarket requirements, is APPH.

FDA's evaluation of these PMTAs determined that they contain sufficient information to characterize the new products' composition and design, and that there are adequate process controls and quality assurance procedures to help ensure the new products are manufactured consistently. The applicant provided the target specifications, range limits, and test data necessary to characterize the new products' design; adequately characterized the components and sub-components of the new products; and provided a description of operation and validation of function for various protection mechanisms for the new products. The new products were compared to CC and ENDS because the applicant identified that the new products are intended for adults who currently smoke CC and adults who currently use ENDS.

FDA's conclusions regarding the adult benefits of the new products are based on our evaluation of their abuse liability; cancer and noncancer risks; adult perceptions about the new products, including those who do not use tobacco; and adult and youth use behaviors. Importantly, based on the information provided in the PMTAs, the new products' abuse liability (i.e., ability to promote continued use, dependence, or addiction) in ENDS-naïve adults is lower than that of CC and higher than that of 4 mg nicotine gum. With ENDS experience, adults who use CC might reach nicotine levels that are higher than those observed in the applicant's submitted study, and more comparable to CC. Therefore, the new products' abuse liability is likely similar to that of CC in ENDS-experienced adults. The new products have a nicotine salt formulation, which is known to be associated with higher nicotine exposures that are comparable to CC. A recently published study has also demonstrated that the nicotine flux (i.e., the nicotine emission rate) of the tested Vuse Alto product (Rich Tobacco, 5% nicotine) is similar to CC (Talih et al., 2023). Their similar nicotine delivery to CC suggests that these new products may be a more substitutable replacement for CC and facilitate complete switching/CC cessation more than ENDS with lower nicotine delivery or nicotine gum. Because the new products have an abuse liability similar to CC, it is likely that adults who completely switch to the new products will also maintain ENDS use without reinitiating CC use. The nicotine levels may pose an addiction risk for non-tobacco users. However, this risk is no higher than that of other currently available tobacco products (such as CC) because the abuse liability of the new products is not likely to exceed that of CC even among those who gain experience using the new products.

The toxicological evaluation of the new products indicates that the noncancer hazard risk to users of the new products is likely to be lower relative to CC. In addition, the new products' cumulative estimated lifetime cancer risk ($ELCR_c$) predicts that people who exclusively use the new products will have lower cancer risks than people who smoke CC. When compared to the median for CTP-authorized ENDS as of February 2024, the new products' $ELCR_c$ are a mixture of higher (i.e., PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11) and lower risk (i.e., PM0000973.PD3). However, based on the small number of CTP-authorized ENDS, Tiers 1-4 $ELCR_c$ comparison to CC is considered an appropriate toxicological assessment for the new products. Based on the chemical evaluation of the new products' aerosols, the new products have lower levels of many carcinogenic HPHCs (e.g., carbonyls, volatile organic compounds (VOCs), metals) compared to CC. These findings, taken together with abuse liability findings, suggest that these new products will benefit adults who smoke CC and completely switch to the new products, or significantly reduce CC, as compared to those who continue to use CC exclusively.

Regarding tobacco use behavior, the applicant submitted data from two repeated cross-sectional surveys and a 12-month longitudinal study. In one of the applicant's cross-sectional studies (conducted in 2018-2019), about 92% of participants who reported current established use of Vuse Alto also reported a prior history of CC use and about 27% reported former established use of CC. Since the applicant's submission, data from PATH Study Wave 7 (2022-2023) were released. Epidemiology found that the findings of the applicant's cross-sectional studies were consistent with analysis of PATH Study Wave 7.

Longitudinal transitions in tobacco use behavior in adults who use CC (i.e., the transition to dual use or complete switching) were evaluated using the Colorado Longitudinal Study and the PATH Study Waves 1-3. The results of these analyses indicated that complete switching does occur among adults using CC or among adults with dual use of ENDS and CC, although estimates of the magnitude of switching over a given period differed. The applicant also found that among adults with dual use of ENDS and CC, daily use of ENDS is a strong predictor of both complete switching and significant reduction in CC use. However, these analyses were not brand, product, or flavor-specific, and conclusions regarding complete switching were bridged from all ENDS users. Furthermore, the magnitude of estimates concerning complete switching are lower than those typically seen in the current literature. Therefore, no data were provided on complete switching by adults who use the new products.

In the likelihood of use studies, which assessed perceptions, appeal, and intent to use, people who currently use tobacco (i.e., current established CC use, current established non-CC tobacco use, current tobacco experimentation) reported the greatest intent to purchase the new products. In support, analyses reviewed by epidemiology demonstrated that the new products are widely used by adults who use ENDS. Additionally, among current tobacco users who indicated any interest in purchasing Vuse Alto, "to stop smoking" was a main reason for interest in using Vuse Alto.

Taken together, use behavior findings demonstrated that the new products are widely used by adults who use tobacco products such as CC, or formerly used tobacco products such as CC. Most adults who initiate use of the new products are expected to currently use CC. Additionally, many adults who use the new products are expected to be former CC users, which may be indicative of complete switching. However, for these new products, the behavioral findings

alone are not sufficient to demonstrate the potential adult benefit of the new products. Rather, it is the balance of findings concerning abuse liability, toxicant exposure, use behavior, and likelihood of use that demonstrate the potential adult benefit of the new products.

In terms of the risks to non-users, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. However, the risk of the new products to youth are likely to be low compared to other ENDS. Surveillance via the National Youth Tobacco Survey has consistently indicated that use of tobacco-flavored ENDS accounts for a small fraction (6.4% in 2023) of middle and high school student ENDS use compared to other flavors (e.g., fruit, candy, mint). This surveillance has also demonstrated that, among youth who used ENDS in 2023, 8.7% reported using "Vuse" products as their usual brand. The applicant's likelihood of use study findings indicated that those who did not use tobacco generally perceived similarly high risk and addictiveness for Vuse Alto, other ENDS, and CC, though Vuse Alto and other ENDS were generally rated slightly lower risk and addictiveness compared to CC. Appeal of Vuse Alto products was low among those who did not use tobacco and almost identical to appeal of other ENDS. Those who did not use tobacco were also less likely to select "Rich Tobacco" or "Golden Tobacco" as flavors of most interest compared to menthol and fruit flavors. Compared to groups currently using tobacco, groups who did not use tobacco had significantly lower intentions to purchase Vuse Alto. While purchase intent was low across groups that used tobacco, the young adult subsample of those with current established CC use and former tobacco use did have significantly higher purchase intent than their full sample counterparts. Given this, and the strong evidence regarding the impact of youth exposure to marketing on youth appeal and initiation of tobacco use, a marketing authorization for the new products should include marketing restrictions and postmarket requirements to help ensure that youth exposure to tobacco marketing is limited. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit adults who use CC who switch completely or significantly reduce their CC use would outweigh the risk to youth, provided the applicant follows marketing restrictions and postmarket requirements aimed at reducing youth exposure and access to the products.

The applicant proposed a(b) (4) shelf life for the new products. The applicant did not provide sufficient data for chemical and microbial stability that would allow FDA to evaluate whether all new products are stable over the proposed shelf life of(b) (4) . However, the lack of microbial and chemical stability data for(b) (4) does not preclude a finding that the marketing of the new products is APPH. Overall, the applicant provided adequate chemical stability, leachables, and microbial stability data and bridging rationale to support a shelf life of (b) (4) for PM0000973.PD2 and PM0000973.PD3, and a shelf life of(b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11. Therefore, based on the data provided by the applicant, any marketing authorization for the new products should limit the shelf life of the new products accordingly, while also allowing for shelf life to be extended with postmarket submissions of additional stability data.

Although engineering noted two limitations regarding potential unintentional activation and dry puffing these limitations do not preclude a finding that marketing of the new products is APPH. First, the new products are airflow activated, and therefore pose some risk of overheating, fires, and explosions from unintentional activation and dry puff conditions. Sustained or repeated pressure differential can cause continued activation and overheating of the heating element,

particularly under low e-liquid levels that can lead to dry puff conditions. Although the applications did not adequately address the potential unintentional activation of the new products, this limitation is acceptable from engineering's perspective because the product-specific design and protection mechanisms (e.g., battery short circuit protection (UL 1642) and 5-second maximum puff duration) may mitigate these risks. Users can also remove the cartridge from the power unit to prevent unintentional activation, which further mitigates the risk. Currently, there is limited information available in published literature on the risks of unintentional activation of ENDS, so there are not sufficient data to be able to determine the acceptable level of mitigation from an engineering perspective. Notably, as of the date of the TPL, there have been no AEs reported to the FDA Safety Reporting Portal (SRP) associated with the unintentional activation of the new products. Therefore, given the above, this limitation of evidence can be addressed through the manufacturer's postmarket reporting obligations that will allow FDA to monitor and assess reported adverse events of overheating, fires, and explosions associated with unintentional activation and dry puff conditions.

Second, the new products may increase exposure to HPHCs under dry puff conditions because operation of the new products under low e-liquid levels could cause thermal decomposition of the e-liquid or heating element. The lack of HPHC aerosol data or thermal profile of the heating element under dry puff conditions is a limitation. However, this limitation does not preclude a finding that marketing of the new products is APPH. The design features and control mechanisms of the new products (e.g., ceramic wick, battery short circuit protection, and 5-second maximum puff duration) may mitigate the risks associated with dry puffing. Additionally, the potential impact of increased HPHC exposure from dry puff conditions can be weighed against other evidence submitted by the applicant. The applicant provided HPHC aerosol yields of the new products under non-intense and intense puffing conditions, showing lower levels of HPHCs compared to CC. This information offsets the risk of increased exposure to HPHC aerosols from dry puffing, which is expected to be limited to infrequent and brief exposures near the end-of-life of the new products. Furthermore, a review of adverse experiences (AEs) submitted to the FDA SRP do not show any cases of AEs in the new products specifically attributed to the risks related to unintentional activation and dry puffing.

Therefore, based on the information provided in the PMTAs and the available evidence, I find that permitting the marketing of the new products, subject to certain marketing restrictions and postmarket requirements, is APPH. The PMTAs contain sufficient evidence to show that the new products have the potential to benefit adults who smoke CC and switch completely to the new products, or significantly reduce their CC use, that outweighs the product-specific risk to youth. I also recommend limiting shelf life to (b) (4) for PM0000973.PD2 and PM0000973.PD3, and a shelf life of (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11. The MGOs for the new products should note that these shelf lives may be extended to (b) (4) with additional stability data submitted in postmarket reports.

FDA has examined the potential environmental effects of issuing MGOs for the new products 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 Vuse Alto. A complete Vuse Alto ENDS is composed of a rechargeable power unit (device) (PM0000973.PD1), a prefilled replacement cartridge containing the e-liquids, and an accessory USB charger for the power unit. The cartridges contain e-liquids identified by the applicant as containing the following characterizing flavors: Golden Tobacco (PM0000973.PD2, PM0000973.PD6, PM0000973.PD10), and Rich Tobacco (PM0000973.PD3, PM0000973.PD7, PM0000973.PD11), each available in 5%, 2.4%, or 1.8% nicotine content, respectively. The power unit and cartridge settings are not adjustable by the user.

2.2. REGULATORY ACTIVITY

On September 4, 2020, FDA received seven PMTAs from R.J. Reynolds Vapor Company ("the applicant"). FDA issued an Acceptance letter to the applicant on September 16, 2020. FDA issued a Filing letter to the applicant on October 15, 2020. FDA issued a Deficiency letter to the applicant on May 19, 2023, followed by a Correction letter on June 14, 2023. The applicant submitted responses to the Deficiency letter on August 16, 2023 and September 22, 2023.

Refer to Appendix B for a complete list of amendments received by FDA.[7]

2.3. SCOPE OF REVIEW

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

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer	Review Date	Reviewer	Review Date
Regulatory	Kekeli Messan	4/17/2023	N/A	N/A
Engineering	Simeon Kang	5/18/2023	Simeon Kang	7/15/2024
Engineering (Addendum)	Simeon Kang	6/13/2023	N/A	N/A
Chemistry	Stephanie Daniels	5/18/2023	Stephanie Daniels	7/15/2024
Chemistry (Addendum)	Stephanie Daniels	6/13/2023	N/A	N/A
Microbiology	Prashanthi Mulinti	5/18/2023	Nikhil Kumar	7/8/2024
Toxicology	Atinuke Ajiboye	5/18/2023	Mamata De	7/16/2024
Toxicology (Addendum)	Berran Yucesoy	5/19/2023	N/A	N/A
Toxicology (Addendum)	Abhijit Ghosh	6/12/2023	N/A	N/A

[7] (b) (4)

Discipline	Cycle 1		Cycle 2	
	Reviewer	Review Date	Reviewer	Review Date
Behavioral and Clinical Pharmacology (BCP)	Colin Cunningham	5/18/2023	Victoria Downs	7/15/2024
Medical	Julie Clement	5/18/2023	Julie Clement	7/15/2024
Medical (Addendum)	Julie Clement	6/14/2023	N/A	N/A
Epidemiology	Kimberly Nguyen	5/18/2023	Eunice Park-Lee	7/15/2024
Social Science	Lexie Perreras	5/18/2023	Marjorie Margolis	7/15/2024
Environmental Science	Ronald Edwards	5/18/2023	Susana AddoNtim	7/9/2024
OCE – BIMO	Akif Niaz	6/23/2022	Akif Niaz	7/9/2024
OCE – Manufacturing/Lab	Jiali He	6/17/2022, 9/1/2022, 9/22/2022, 9/23/2022, 9/26/2022, 12/29/2022, 1/2/2023, 1/18/2023	N/A	7/8/2024

Table 2. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer	Review Date	Reviewer	Review Date
Statistics	N/A	N/A	N/A	N/A
OCE – DPAL[8]	Miranda Nelson	N/A	Gina Sutedja	N/A
OHCE	Emily Talbert	2/8/2023	Emily Talbert	5/7/2024
TPST	Vy Nguyen	5/20/2022, 5/15/2023	Vy Nguyen	3/15/2024

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

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

Per the engineering review:

- The applicant does not provide any comparison to currently marketed ENDS for the new products.

Per the chemistry review:

[8] During the preliminary assessment meetings for the first and second cycle reviews, DPAL stated they did not have any concerns to convey.

- Fourteen CC and six currently marketed ENDS were used as comparison products. The applicant stated the 14 CCs were selected as comparison products based on consumer market survey data. The comparison ENDS were chosen to ensure coverage of a range of aerosol deliveries as well as a range of flavors and to cover the market leadership among closed ENDS marketed in the U.S. in 2017 and 2019. The comparison ENDS are in the same product category and subcategory as the new products. The applicant's rationale for selection of the comparison products is acceptable from a chemistry perspective.

Per the microbiology review:

- The applicant measured pH, VG, PG, NNN, and NNK in 36 commercially available comparison ENDS using aerosol data. These products are in the same product category and subcategory as the new products and are pre-filled with nicotine-containing e-liquids. However, aerosol stability data is not reflective of conditions that can exist in e-liquids during shelf life. Additionally, no microbiology-relevant parameters were measured in the e-liquids for these comparison products; therefore, a comparison of how product characteristics affects shelf life between the products under review and comparison ENDS could not be made. However, the applicant provided microbial stability test data, measured in e-liquids, for the products subject to this review (see Section 3.1.5). Therefore, the lack of microbial stability test data measured in the e-liquids of the comparison products is acceptable from a microbiology perspective because the microbial stability test data for the new products are sufficient to evaluate shelf life from a microbiology perspective.

Per the toxicology review:

- The applicant provided data from fourteen CC and indicated that these cigarettes reflect the current state of the US CC market. This data was used for the HPHC comparative analysis studies. A different CC comparison product, Marlboro Gold, was used for in vitro toxicity studies because at the time testing was initiated, it was among the market leading brands of CC according to the applicant. Also, the applicant submitted recently published peer-reviewed studies in which many of the same HPHCs were measured, including cigarettes that are currently on the market, using common puffing protocols (e.g., ISO and HCI) across the studies. Therefore, from a toxicological perspective the applicant's rationale for using the selected CC as comparison products is appropriate, and the use of average CC data from the published toxicology literature is an appropriate representation of the CC category.
- Twenty-two closed ENDS were chosen as the market comparison ENDS to "ensure coverage of a range of aerosol deliveries as well as a range of flavors (tobacco, menthol, and fruit)" and because of their market leadership amongst closed ENDS at the time studies were initiated. The data from these market comparison ENDS were used in comparative HPHC analysis studies. For in vitro toxicity studies, select new products (i.e., PM0000973.PD2-PD6) were compared against a comparison ENDS (i.e., JUUL Mint). The rationale for this comparison was that JUUL Mint was the market-leading brand in the closed ENDS subcategory at the time of the studies. From a toxicological perspective, the applicant's rationale for selecting these comparison ENDS for HPHC analysis and in vitro studies is adequate.

Per the medical review:

- Studies CSD170501 and CSD170303 used several ENDS other than those that are the subjects of the PMTAs, which limits the ability to draw conclusions on the health effects of the new products from the studies.
- Studies CSD170501 and CSD190202 included additional comparison products (CC and 4 mg nicotine gum). However, limitations in study designs including small sample sizes and short durations of exposure limit the ability to draw conclusions on health risks of the new products compared to the comparison products.
- However, the health effects of the new products were assessed based on the totality of the evidence reviewed (including adverse events reported in the clinical studies that contained PMTA products, AEs submitted to SRP, and review of published literature). The totality of the evidence provided comparisons to CC and to other ENDS. The applicant identified adults who smoke CC or use ENDS as the intended user population. Therefore, the comparisons provided were appropriate to draw conclusions regarding health effects per medical perspective.

Per the BCP review:

- The applicant compared the new products to usual brand (UB) CC and 4 mg nicotine gum in all key studies that provided data on abuse liability or use behaviors. From a BCP perspective, the data and rationale to support the applicant's chosen comparison product (UB CC) were appropriate for comparison to the new products. Current CC smokers interested in switching to ENDS are the applicant's stated intended users of the new products, and subjective effects data from the abuse liability assessment suggests that the new products have some appeal to CC smokers. The comparison to nicotine gum was also appropriate since this product may be used by CC smokers who are motivated to stop smoking and may use the Vuse Alto as an alternative to nicotine replacement therapies (NRT) such as nicotine gum.

Per the epidemiology review:

- The applicant's observational studies include CC smokers and evaluated if the use of CC changes by different use patterns of the new products. Based on the observational studies submitted by the applicant, it is likely that adults who smoke CC are the intended user population for the new products. Another important comparison based on evidence in the applications is the use of the new products among adults who currently smoke CC versus adults who do not currently smoke CC. From an epidemiology perspective, the use of CC as a comparison product is appropriate for these studies because adults who currently smoke CC are a likely user population.

3.1.2. Synthesis

The applicant provided comparisons between the new products and CC, as well as other ENDS, in their submitted studies and literature reviews.

The applicant compared the new products to a range of CC and ENDS for the purposes of comparative HPHC analyses. The in vitro toxicity studies included Marlboro Gold, a leading brand of CC (at the time of study), and JUUL Mint, a leading ENDS product (at the time of the study) which contains nicotine salts and is in the same category and subcategory as the new products. In clinical studies, the applicant used participants' UB CC, new products, and 4 mg nicotine gum to collect data on abuse liability. Because the applicant states that the

new products are intended for both current cigarette users and current ENDS users, the rationale for their selection of CC and ENDS comparison products is appropriate. The rationale for selecting nicotine gum as a comparison product is also appropriate as the applicant states that the new products may be used by cigarette smokers who are motivated to stop smoking and may use the new products as an alternative to NRT such as nicotine gum. As TPL, I agree with the chemistry, toxicology, medical, and BCP disciplines that the applicant provided adequate rationale for the selection of appropriate comparison products for their analytical, clinical, and nonclinical studies. As TPL, I agree with the applicant's use of CC, other ENDS, or both as comparison products in observational studies given that the applicant's stated target population of the new products includes both product categories.

Microbiology and medical reviews noted limitations with the comparison products provided in the applications (i.e., lack of microbiology data for ENDS other than the new products used in the clinical studies). However, the lack of comparison product information was acceptable from microbiology and medical perspectives based on the totality of other evidence reviewed.

Overall, as TPL, I agree with the chemistry, microbiology, toxicology, BCP, medical, and epidemiology conclusions that CC and other ENDS are appropriate comparison products because the applicant's stated intention is to market the new products to adults who currently use tobacco products, specifically those who smoke CC or use other ENDS. For the purposes of the APPH assessment, I consider CC to be the primary comparison products since the applicant's studies demonstrate that their products are primarily used by adults who smoke CC, use other ENDS, or use both CC and ENDS, and because the largest public health benefit associated with the new products is among individuals who smoke CC and completely switch to ENDS or use the new products to quit all tobacco products.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

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

3.2.1.1. Product design and composition

Per the engineering review:

- The Vuse Alto ENDS system is a power unit (PM0000973.PD1) that works in combination with closed e-liquid cartridges (PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, PM0000973.PD11). The applicant provided a complete list of components and sub-components, uniquely identifiable materials, locations with product schematics and functions, as well as information on the tamper-evident system for the new products. The applicant provided manufacturing controls and procedures, which specify that the cartridges are designed to be pre-filled and not meant for disassembly, minimizing the potential for leaks.
- The applicant provided target specifications, test data, and manufacturing specifications, or a scientific rationale as to why a design parameter does not have

target specifications for the necessary design parameters. The applicant also provided procedures and quality control measures for packaging.

- The applicant provided a minimum airflow rate required to activate the new products and provided scientific explanation for why the new products cannot be unintentionally activated, though this explanation is limited. The applicant stated (b) (4) s, this is a limitation of the evidence and does not affect engineering's overall conclusion. This limitation does not affect engineering's overall conclusion because there is insufficient information available in published literature on the risks of unintentional activation of ENDS. The product-specific design and protection mechanisms may mitigate the risks of unintentional activation of the new products, which include a 5-second maximum puff duration and battery short-circuit protection. Users can also remove the cartridge from the power unit to prevent unintentional activation. The adverse event reports to date for the new products do not indicate an increased level of concern. A review of the adverse experiences (AE) submitted by the applicant as well as a search of AE reports submitted to FDA SRP do not show any cases of the device overheating due to unintentional activations. There is insufficient data to determine the acceptable level of mitigation from an engineering perspective.
- The applicant provided scientific rationale for why the new products mitigate the risks of dry puffing, including physical properties of the ceramic wick, published literature that ENDS users are generally able to avoid dry puffs, and the lower wattage operating range of the new products. However, the study cited by the applicant demonstrates that dry puffing may result from thermal decomposition of e-liquid components rather than only from the wick itself, and that users may not be able to accurately identify dry puffs (Visser et al., 2021). Moreover, a recent study reported that the use of Vuse Alto products under low or depleted e-liquid conditions, during the final puff sessions, can cause the heating element temperatures to increase, resulting in degradation of the heating element and potential release of metals into the aerosols (Saleh et al., 2021). Therefore, operation of the new products under low e-liquid levels could cause thermal decomposition of the e-liquid or heating element, resulting in increased HPHCs during dry puff conditions. The applicant did not provide thermal profile information of the heating element or HPHC aerosol yields under dry puff conditions. Although this is a limitation of the evidence regarding the risk of dry puffing, this limitation does not affect engineering's overall conclusion because the risk associated with dry puffing is partially mitigated by the design and control mechanisms of the new products (e.g., the ceramic wick which is more resistant to heat during dry puff conditions, battery short circuit protection, and a 5-second maximum puff duration).
- No engineering-related AE for the product design or composition were reported to FDA.

Per the chemistry review:

- The power unit in PM0000973.PD1 is cylindrical and comprises 16 components with a nominal weight of 16 g. The battery in the power unit is a 3.7 V (nominal) rechargeable lithium-ion battery.
- The weight of the e-liquid is approximately 2.1 g; however, differences in flavor and nicotine concentrations may result in a slight variation of the e-liquid weight.
- The nicotine source is tobacco-derived and meets USP as well as European Pharmacopoeia (Ph.Eur) standards.
- CAS ((b) (4) information indicates that the nicotine is (b) (4) . (b) (4) and the greatest unknown impurity (molecules that were detected but structures could not be identified) are present at (b) (4) %.
- Long-term stability data demonstration that the nicotine has a shelf-life of (b) (4) (b) (4).
- The e-liquids in PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11 contain (b) (4) (b) (4) that may raise public health concerns. Assessment of the toxicological and sensory effects of the nicotine salts is discussed in toxicology, medical, BCP, and social science reviews.

Per the microbiology review:

- The applicant provided adequate information on the type and concentration of humectants and preservatives in the new products.
- The new products contain humectants (b) (4)), which may also function as preservatives, and may impact microbial activity during product shelf life.
- The applicant provided adequate stability data to assess the impact of the humectants on the microbial stability of the finished new products for (b) (4) of shelf life for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11, and for (b) (4) of shelf life for PM0000973.PD2 and PM0000973.PD3 (see 3.1.5 below).

3.2.1.2. Manufacturing

Per the engineering review:

- The applicant provided a description of the manufacturing process including steps and controls. The evidence provided by the applicant regarding manufacturing controls for the new products included procedures for incoming materials, quality controls to ensure products meet specifications, procedures to handle non-conforming products, procedures to handle complaints, quality control procedures from (b) (4) for raw ingredients used in the manufacturing of bulk e-liquids, procedures, and quality checks to ensure lot-to-lot consistency of the finished product, and descriptions and procedures for storage conditions of both central and regional distribution centers. The information provided in the PMTAs regarding manufacturing controls for the new products is acceptable from an engineering perspective.

Per the chemistry review:

- The PMTAs provided adequate, detailed information regarding the manufacturing steps and controls demonstrating that the new products can be manufactured in a consistent manner from a chemistry perspective. This information included:

- (b) (4)

The applicant practices the "first in-first out" protocol of the raw material, semi-finished and finished products.

Per the microbiology review:

- The new products include a power unit (device) and e-liquids which contain tobacco-derived nicotine but do not include (b) (4) . Therefore, microbiology does not need information related
- (b) (4)
- The applicant provided a description of the manufacturing process for their finished new products, including: (b) (4) The information provided by the applicant is acceptable from a microbiology perspective.

3.2.1.3. Product life cycle

Per the engineering review:

- The applicant states the power unit is cycled 500 times and provides test procedures and test data for charge (b) (4) Due to the cartridge simplicity and materials, the product life cycle of the cartridge is unlikely to be of concern. No additional information regarding product life cycle is necessary from an engineering perspective.

3.2.1.4. Product stability

Per the chemistry review:

- The intended shelf-life of the new products is (b) (4) .
  - Overall, the applicant provided adequate chemical stability data for PM0000973.PD2, PM0000973.PD3, and PM0000973.PD10 under non-intense and intense puffing regimens for the duration of the intended shelf life.

- The applicant did not provide any chemical stability data for PM0000973.PD7 and PM0000973.PD11. For PM0000973.PD6, the applicant provided chemical stability data that supported only a shelf life of (b) (4) under a non-intense puffing regimen, which does not adequately characterize chemical stability.
- For PM0000973.PD2 (Golden Tobacco 5%), PM0000973.PD3 (Rich Tobacco 5%), and PM0000973.PD10 (Golden 1.8%), long-term chemical stability studies were conducted up to (b) (4) under non-intense puffing regimen, and up to (b) (4) (b) (4) for PM0000973.PD6 (Golden Tobacco 2.4%). Increases in HPHCs per puff were detected when comparing the first and last timepoints for some constituents, such as acetaldehyde, acrolein, acetyl propionyl, formaldehyde, diacetyl, (b) (4), total nicotine, free nicotine, nicotine salt, and propylene glycol. The increases in the constituents detected in the chemical stability studies are relatively minor and are not likely to cause additional health concerns and are therefore acceptable from a chemistry perspective.
- Summary details of the analytical methods used for chemical stability testing of the new products and the full validation reports (number of replicates, LOD, LOQ, accuracy/recovery, precision, and linearity) of the methods were sufficient from a chemistry perspective.
- Overall, the applicant provided adequate leachables data for PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, and PM0000973.PD10 under non-intense and intense puffing regimens that supported a shelf life of (b) (4), but not for the duration of the proposed shelf life of (b) (4). For the proposed shelf life of (b) (4), the applicant provided only non-intense leachables data for PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, and PM0000973.PD10, which does not adequately characterize chemical stability for the intended shelf life of (b) (4).
- The applicant did not provide any leachables data for PM0000973.PD7 and PM0000973.PD11.

- Although the applicant did not provide adequate chemical stability data for PM0000973.PD6, PM0000973.PD7 and PM0000973.PD11, and did not provide adequate leachables data for PM0000973.PD7 and PM0000973.PD11, the missing chemical stability and leachables data can be bridged due to:
  - Identical or nearly identical quantities of all the ingredients; (b) (4) in the Rich Tobacco products (PM0000973.PD3, PM0000973.PD7, and PM0000973.PD11) compared to the Golden Tobacco flavored products (PM0000973.PD2, PM0000973.PD6, and PM0000973.PD10).
  - Chemical stability and leachable data for Golden Tobacco (PM0000973.PD2 and PM0000973.PD10) which represent the full range of the nicotine concentration (1.8% to 5.0%)
  - Chemical stability and leachable data for Golden Tobacco (PM0000973.PD2 and PM0000973.PD10) covering the various PG/VG ratios
  - Therefore, for the Golden Tobacco products, the chemical stability data from PM0000973.PD2 and PM0000973.PD10 can be bridged to PM0000973.PD6 based on data for the highest and lowest nicotine

concentrations provided. Additionally, the chemical stability and leachable data from the Golden Tobacco product PM0000973.PD10 can be bridged to the Rich Tobacco product PM0000973.PD11 based on similarity of ingredient characteristics. Lastly, the bridged chemical stability data and the provided leachables data from PM0000973.PD6 can be bridged to PM0000973.PD7 based on similarity of ingredient characteristics.

- Simulated leachable studies were performed (b) (4)
- (b) (4)
  0 was analytically equivalent and thus acceptable from a chemistry perspective.
- (b) (4) were detected in the leachable studies at (b) (4) (long-term conditions) and (b) (4) (ambient conditions) using non-intense and intense regimens for PM0000973.PD2 and under intense only for PM0000973.PD6 and PM0000973.PD10. Two one-sided t-test (TOST) analysis determined that the % difference at (b) 8 and (b) (4) were analytical equivalent and thus acceptable from a chemistry perspective.
- Summary details of the analytical methods used for leachable and extractable testing of the new products and the full validation reports (number of replicates, LOD, LOQ, accuracy/recovery, precision, and linearity) of the methods are sufficient from a chemistry perspective.
- For PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, and PM0000973.PD10 the applicant provided leachable data over the proposed shelf life of the new products (b) (4)) for long-term and (b) (4) (b) (4) for accelerated storage conditions only under a non-intense puffing regimen. For intense puffing regimen, the applicant only provided leachable data up to (b) (4) .
- The data provided only support a (b) (4) shelf life for all the new products.

Per the microbiology review:

- The applicant did not state the proposed container closure system (CCS), shelf life, or storage conditions for the bulk e-liquids. Further, no stability data are provided in support of the bulk e-liquids. However, finished new product stability data can provide assurance of new product stability over the proposed shelf life from a microbiology perspective.

- The proposed shelf life of the finished e-liquid cartridges is (b) (4) . In the original PMTA submission, stability studies were performed on aerosols and not on e-liquids contained in cartridges.
    - Overall, the applicant provided adequate microbial stability data only for PM0000973.PD2 for the duration of the proposed shelf life of (b) (4) . For PM0000973.PD3, PM0000973.PD6, and PM0000973.PD10, the applicant provided adequate microbial stability data that support a shelf life of (b) (4) (b) (4) but not (b) (4) .
    - The applicant did not provide microbial stability data for PM0000973.PD7 and PM0000973.PD11.
- Microbial stability data from PM0000973.PD2 can be bridged to PM0000973.PD3, data from PM0000973.PD6 can be bridged to PM0000973.PD7, and data from PM0000973.PD10 can be bridged to PM0000973.PD11 due to:
    - Identical or nearly identical quantities of all the ingredients; specifically, the f (b) (4) in Rich tobacco products compared to the Golden tobacco flavored products.
    - Microbial stability data for Golden Tobacco (PM0000973.PD2, PM0000973.PD6, PM0000973.PD10) which represent the full range of the nicotine concentration.
    - Microbial stability data for Golden Tobacco (PM0000973.PD2, PM0000973.PD6, PM0000973.PD10) covering the various PG/VG ratios.
    - All products subject to this review use the same container closure system (CCS).
    - Therefore, the microbial stability data and bridging rationale provided by the applicant support a shelf life of (b) (4) for PM0000973.PD2 and PM0000973.PD3, but a shelf life of only (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11.
- The applicant provided (b) (4) of stability test data (i.e., a_w, TAMC, TYMC[9]) for Golden Tobacco (5.0%, 2.4%, and 1.8%) and Rich Tobacco (5.0%) products in PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, and PM0000973.PD10. Additionally, the applicant provided (b) (4) of stability test data (i.e., a_w, TAMC, TYMC) from a packaging study of PM0000973.PD2. Based on the e-liquid composition (i.e., flavors PG, VG, and nicotine concentrations) and CCS, data from PM0000973.PD2 can be bridged to PM0000973.PD3, and data from PM0000973.PD6 and PM0000973.PD10 can be bridged to PM0000973.PD7 and PM0000973.PD11, respectively.
- The a_w increased between 0 and (b) (4) of storage in all new products [PM0000973.PD2 (↑ (b) (4)); PM0000973.PD3 (↑ (b) (4) %); PM0000973.PD6 (↑ (b) (4) %); PM0000973.PD10 (↑ (b) (4) %)]. Additionally, a_w increased (↑ (b) (4) %) between (b) (4) and (b) (4) months of storage in PM0000973.PD2. However, a_w at all time points measured is < (b) (4) 2; it is generally recognized that a_w at which there is no microbial proliferation is < 0.6. Therefore, the increase in a_w is acceptable from a microbiology perspective. Further, TAMC and TYMC measured at all time points were below the limit of

[9] a_w: water activity; TAMC: total aerobic microbial count; TYMC: total yeast and mold count

quantification (BLOQ) and are therefore acceptable from a microbiology perspective.

- The applicant provided TSNA data (NNN and NNK) measured in e-liquids for Golden Tobacco (5.0% and 1.8%) and Rich Tobacco (5.0%) representing PMTAs PM0000973.PD2, PM0000973.PD10, and PM0000973.PD3, respectively; TSNA levels were below the limit of quantification (BLOQ) at every time point tested. However, the products tested at each time point over shelf life were manufactured at different times. Therefore, FDA is unable to evaluate trends in the provided TSNA data because different manufacturing batches could result in batch-to-batch differences. However, the products tested at the (b) (4) point were manufactured on the same date as the products tested in the long-term stability study of a_w, TYMC, and TAMC, so the TSNA data at (b) (4) time point provides additional support for a shelf life of (b) (4) for these products. The lack of TSNA data in PM0000973.PD6 is acceptable from a microbiology perspective because TSNAs were BLOQ in the products with the highest and lowest nicotine concentration (highest: PM0000973.PD2, PM0000973.PD3; lowest: PM0000973.PD10).
- The applicant indicated that their microbial stability test methods (i.e., a_w, TAMC, TYMC) follow compendial procedures (e.g., USP <922>, USP <61>, FDA BAM) with no notable deviations from the published standards. Further, the methods use control samples and acceptance criteria to ensure they are fit for their intended purpose. The applicant outlined the minimum requirements for validation of their analytical methods and indicated that their validation procedures follow the recommendations described in ISO 17025:2017. Therefore, because the methods follow published standards and use verification controls, the microbial stability data provided by the applicant are acceptable from a microbiology perspective.
- Overall, the stability data provided by the applicant supports a shelf life of (b) (4) (b) (4) for PM0000973.PD2 and PM0000973.PD3, but a shelf life of only (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11. As CCS and product composition (i.e., humectants) could potentially affect a_w and tobacco product stability during complete shelf life of the products, additional stability testing data beyond (b) (4) is needed to support the applicant's proposed shelf life of (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11. Therefore, at this point in time, a shelf life of (b) (4) and not the proposed (b) (4) is acceptable for these new products from a microbiology perspective.

3.2.1.5. Product test data

Per the engineering review:

- The applicant provided test data for draw resistance, puff count, airflow rate, and heating element diameter. The information provided by the applicant is adequate from an engineering perspective.

Per the chemistry review:

- In comparison to mainstream smoke of CC, the new products have 40%-100% lower acetaldehyde, acrolein, and formaldehyde aerosol yields under non-intense and intense puffing regimens. Aerosol yields for acrylonitrile, 4-aminobiphenyl, 1-aminonaphthalene, 2-aminonaphthalene, ammonia, anabasine, benzene, B[a]P, 1,3-

butadiene, cadmium, chromium, crotonaldehyde, (b) (4) , isoprene, lead, nickel, NNK, NNN, and toluene were below limit of detection in the new products, while all were detectable in the mainstream smoke of comparison CC. In comparison to mainstream smoke of CC, the new products have 2%-9% (0.93-0.98 mg/puff) higher nicotine yields.

- The following increases were observed in the aerosols of the new products compared to comparison ENDS (blu PLUS 2.4%, Logic Pro 2.4%, Mistic 2.0, JUUL 5.0%, myblu 2.4% and Vuse Solo G2 4.8%), under non-intense and intense puffing regimens:
    - total nicotine, 5%-9% (0.01-0.08 mg/puff)
    - acetaldehyde, 2%-1,984% (22-1,340 ng/puff)
    - acetyl propionyl, 2%-756% (1-62 ng/puff)
    - diacetyl, 11%-1,907% (16-191 ng/puff)
    - formaldehyde, 3%-9,217% (12-2,394 ng/puff)
- Although the above listed constituents are higher than the ENDS comparison products, the yields are lower compared to CC and thus acceptable from a chemistry perspective.
- Summary details of the analytical methods used for HPHC testing of the new products and ENDS and CC comparison products were provided and are acceptable from a chemistry perspective.

3.2.2. Synthesis

As TPL, I agree with the engineering conclusions that these PMTAs contain sufficient information describing target specifications, manufacturing specifications, and manufacturing processes including quality control procedures for the new products. The applicant's test data adequately demonstrate that the new products meet the manufacturer's specifications and are produced consistently.

The engineering review noted two limitations regarding potential unintentional activation and dry puffing; however, these limitations do not preclude an APPH finding for the new products and can be addressed through postmarket reporting. The engineering review indicated that as the new products are airflow activated, there is a risk of overheating, fires, and explosions from unintentional activation and dry puff conditions. Sustained pressure differentials such as inside an airplane cabin during flight may cause continued activation and overheating of the heating element, particularly under low e-liquid levels that can lead to dry puff conditions. The applicant did not provide an adequate scientific explanation for why the new products cannot be unintentionally activated, which is a limitation of the evidence. However, this limitation does not preclude an APPH finding for the new products because the product-specific design and protection mechanisms (including a 5-second maximum puff duration and battery short-circuit protection) may mitigate these risks. Users can also remove the cartridge from the power unit to prevent unintentional activation. Finally, given there is limited information available in published literature on the risks of unintentional activation of ENDS, the true risk is unknown. This limitation can be addressed through the manufacturer's postmarket reporting obligations that allows FDA to monitor and assess all reported adverse events including those related to overheating, fires, and explosions or associated with unintentional activation and dry puff conditions.

The engineering review also indicated that the new products may increase exposure to HPHCs in dry puff conditions because operation of the new products under low e-liquid levels could cause thermal decomposition of the e-liquid or heating element. The lack of HPHC aerosol data or thermal profile of the heating element under dry puff conditions is a limitation, but this limitation does not preclude an APPH finding for the new products. The design features and control mechanisms of the new products (e.g., ceramic wick, battery short circuit protection, and 5-second maximum puff duration) partially mitigate the risks associated with dry puffing, and the potential impact of increased HPHC exposure from dry puff conditions can be weighed against other evidence submitted by the applicant. The applicant provided HPHC aerosol yields of the new products under non-intense and intense puffing conditions, showing lower HPHC levels compared to CC, and this information offsets the risk of increased exposure to HPHC aerosols from dry puffing, which is expected to be limited to infrequent and brief exposures near the end-of-life of the new products. Furthermore, a review of AE information submitted by the applicant as well as a search of AE reports submitted to FDA SRP do not show any cases of the device overheating due to unintentional activations or dry puffing of the new products.

As TPL, I agree with the chemistry conclusions that these PMTAs contain sufficient ingredient information to characterize the new products' composition. In addition, the applicant implemented manufacturing procedures and quality control measures for all e-liquids to ensure the new products are manufactured in a consistent manner. HPHC data shows that the new products' aerosols have fewer HPHCs than CC smoke and many of the HPHCs present in the aerosols have comparatively lower potencies (i.e., lower magnitude or severity of toxicological effect at a given dose or exposure level) than those present in CC smoke (see Section 3.5).

As TPL, I also agree with the microbiology conclusions that these PMTAs contain sufficient ingredient information to characterize the new products' composition. The applicant provided adequate manufacturing related information regarding quality control parameters, procedures, and validations used to control and monitor potential microbial contamination of the new products, which are acceptable from a microbiology perspective.

The applicant proposed a (b) (4) shelf life for the new products. The applicant provided adequate chemical stability and leachables data for PM0000973.PD2, PM0000973.PD3, and PM0000973.PD10 to support a shelf life of (b) (4) but did not provide any chemical stability or leachables data for PM0000973.PD7 and PM0000973.PD11 and did not provide adequate chemical stability data for PM0000973.PD6. The applicant provided adequate microbiology stability data for PM0000973.PD2 to support the intended shelf life of (b) (4) (b) (4), and for PM0000973.PD3, PM0000973.PD6, and PM0000973.PD10 to support a shelf life of (b) (4) The applicant did not provide microbial stability data for PM0000973.PD7 and PM0000973.PD11. For PM0000973.PD6, PM0000973.PD7 and PM0000973.PD11, the missing chemical stability, leachables, and microbial stability data were adequately bridged from PM0000973.PD2, PM0000973.PD3, and PM0000973.PD10 based on similarity of ingredient characteristics or providing the data for the highest or lowest nicotine concentrations. Overall, the applicant did not provide sufficient data for chemical and microbial stability that would allow FDA to evaluate whether the products are stable over the proposed shelf life of (b) (4) . However, the applicant provided adequate chemical stability, leachables, and microbial stability data and bridging rationale to support

a shelf life of (b) (4) for PM0000973.PD2 and PM0000973.PD3 (shelf life bridged from PM0000973.PD2), and a shelf life of (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11.

As aerosol constituent levels can change over the product's shelf life, and CCS and product composition (i.e., humectants) could potentially affect a_w and microbial stability during complete shelf life of the products, additional stability testing data is needed to determine the stability of these products for the proposed (b) (4) shelf-life. However, because the chemical and microbial stability data is acceptable and indicates that the new products are low risk for microbial growth over the period tested and because there are no other stability concerns, the lack of chemical and microbial stability data through (b) (4) does not preclude an APPH finding for the new products. Therefore, based on the chemical and microbial stability information provided by the applicant, a marketing authorization for the new products should note that submitted stability data support that the new products remain stable for (b) (4) for PM0000973.PD2 and PM0000973.PD3 and (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11.

3.3. ABUSE LIABILITY

The applicant included one clinical study (CSD190202) evaluating the abuse liability (i.e., nicotine pharmacokinetics (PK) and subjective effects) of the new products. This study compared the new products in PM0000973.PD2 and PM0000973.PD6 (Golden Tobacco 5% and Golden Tobacco 2.4%, respectively) against UB CC and 4 mg nicotine gum. In addition, the applicant included machine-generated aerosol nicotine yields for all the new products to support bridging abuse liability parameters across flavors and nicotine concentrations. The applicant also included an ambulatory puff topography study (CSD190203) to support bridging of study CSD190202 to all new products. This study evaluated the new products in PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, and PM0000973.PD7 (Golden Tobacco 5%, Rich Tobacco 5%, Golden Tobacco 2.4%, Rich Tobacco 2.4%, respectively), (b) (4)

3.3.1. Discipline key findings

The following discussion is based on key findings provided in the BCP review.

3.3.1.1. Abuse liability

Per the BCP review:

- "Abuse liability" refers to the ability of the product to promote continued use and the development of addiction and dependence. This can be relevant to determining the likelihood that addicted users of one nicotine product would switch to another. For example, if a new tobacco product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted. Abuse liability evaluations include pharmacokinetic (PK) evaluations and consider the addictiveness and abuse potential of the tobacco products and the exposure to nicotine during product use.
- The applicant conducted a clinical study (CSD190202) to assess the abuse liability of the new products in 5% and 2.4% nicotine concentrations and in the Golden

Tobacco flavor (PM0000973.PD2 and PM0000973.PD6, respectively). This was a single-center, randomized, open-label, crossover study to evaluate nicotine PK and product liking of the new products in PM0000973.PD2 and PM0000973.PD6, 4 mg nicotine gum, and UB CC. Subjects were CC smokers (≥ 10 CC per day for ≥ 6 months prior to screening), 21 to 60 years of age. The study was a 9-day confinement study with 4 acclimation periods and 4 test sessions (one for each test product). Acclimation periods lasted 1.5 days to provide familiarity with the tested new products and nicotine gum prior to the corresponding clinical test session. Subjects were told to use these products ad libitum for a minimum of 6 times during the acclimation period. Acclimation periods were followed by a 4-hour test session where subjects used the assigned product for that session: their UB CC, the new products (either PM0000973.PD2 or PM0000973.PD6) ad libitum for 10 minutes, or one piece of nicotine gum ad libitum for 30 minutes (in accordance with package labeling). Baseline measurements were collected at the 5 minute and 0.5-minute time points. Outcomes were assessed at pre-defined intervals up to 240 minutes relative to the start of study product use. Behavioral outcomes were assessed on a 0-10 scaled for outcomes including product liking, overall intent to use again, product effects, urge to smoke, and overall product liking.

- In ENDS-naïve exclusive CC smokers, both the nicotine C_{max} (baseline-adjusted maximum plasma nicotine concentration) and AUC (baseline-adjusted area under the nicotine concentration-versus-time curve) over the 240-minute testing session were lower for PM0000973.PD2 and PM0000973.PD6 compared to UB CC and slightly greater than 4 mg nicotine gum. The nicotine T_{max} (time to baseline-adjusted maximum plasma nicotine concentration) for the new products were statistically significantly shorter than that of UB CC, and statistically significantly longer than that of 4 mg nicotine gum.
- Participants rated PM0000973.PD2 and PM0000973.PD6 statistically significantly lower than UB CC for product effects, product liking, overall intent to use again, and overall product liking, but higher than 4mg nicotine gum. Urge to smoke ratings were statistically significantly higher for 4 mg nicotine gum compared to tested new products. Although the abuse liability profile of PM0000973.PD10 is likely not identical to that of PM0000973.PD2 and PM0000973.PD6 , the similarity of the latter two products' nicotine PK profiles and subjective effects ratings, combined with the fact that the new product with 1.8% nicotine is the lowest nicotine concentration among the new products, allows BCP to conclude that the abuse liability profile of the new products with 1.8% nicotine concentration and Golden Tobacco flavor is likely lower than that of CC, but higher than that of nicotine gum.
- In order to bridge to the remainder of the new products (i.e., Rich Tobacco), the applicant provided machine-generated aerosol nicotine data for all the new products. The machine-generated aerosol nicotine values showed that total aerosol nicotine (mg/puff) was similar among all flavors of Vuse Alto products that contained the same specified nicotine content (single nicotine concentration). These data allowed BCP to conclude that the abuse liability of Vuse Alto Rich Tobacco flavor in the 5%, 2.4%, and 1.8% nicotine concentrations are likely similar to the abuse liability profiles of Vuse Alto Golden Tobacco 5%, 2.4%, and 1.8%.
- The applicant also included one puff topography study (CSD190203) to evaluate puffing behaviors with Vuse Alto 5% and 2.4% in Golden and Rich Tobacco flavors. However, this study had limitations. The device recorded ENDS data constantly,

even when the device was not in use (e.g., sleeping overnight). Thus, interpuff intervals were grossly overestimated. Furthermore, the applicant's data analysis pooled data for all flavors within a single nicotine concentration, meaning that the effects of flavors on puffing topography could not be evaluated. Despite these limitations, the data from this study showed that users' puff duration fell between the machine generated intense and non-intense puffing regimen's puff durations, lending clinical context to the machine generated aerosol nicotine values.

- The applicant submitted a randomized controlled switching study of inexperienced ENDS users with Vuse Solo Original G2 4.8%, (CSD170501). Due to design differences that exist between Vuse Alto and Vuse Solo products, the data from this study could not be directly bridged to the new products. The study did, however, demonstrate that nicotine exposure increased with users experience of Vuse Solo products, such that nicotine exposure was similar to that from CC by the fifth day. Additionally, a study from peer-reviewed literature comparing the design characteristics and nicotine flux of Vuse Original 4.8% and Vuse Alto Rich Tobacco 5% concluded that Vuse Alto Rich Tobacco 5% (PM0000973.PD3) is the higher-powered device and can produce a nicotine flux that is similar to Marlboro Red (Talih et al., 2023). Evidence from the pharmacokinetic and machine generated aerosol study, (CSD190202), showed that the abuse liability profiles are similar among the new products. This suggests that all the new products have potential to achieve a nicotine flux similar to CC.
- Existing research suggests that experienced ENDS users can attain higher plasma nicotine concentrations than inexperienced ENDS users (Farsalinos et al., 2015; Hiler et al., 2017), and plasma nicotine C_{max} among experienced ENDS users can reach similar levels to those of CC smokers (D'Ruiz et al., 2015; Spindle et al., 2017). ENDS associated with CC-like nicotine exposures are more likely to promote switching (Guerrero-Cignarella et al., 2018). Overall, these data suggest that experienced users of the new products can attain nicotine exposures that are similar to CC, which may facilitate switching from CC in adult individuals who smoke.
- The applicant did not directly investigate the initiation likelihood of this product among non-tobacco users, or progression to regular use among tobacco non-users or youth. However, the applicant-sponsored clinical data indicate lower abuse liability of the new products among adult cigarette-smoking ENDS-naïve users compared to UB CC. Nonusers, including youth, who initiate use of the new products may progress to regular ENDS use. However, the abuse liability of new products does not exceed that of CC among experienced ENDS users.

3.3.2. Synthesis

Per the BCP review, the applicant-submitted one clinical study (CSD190202) that evaluated the abuse liability of the new products in ENDS-naïve people who smoke CC. This study included adults who smoke CC and investigated nicotine PK and product liking of the new products in PM0000973.PD2 and PM0000973.PD6 (Golden Tobacco 5% and Golden Tobacco 2.4%, respectively), 4 mg nicotine gum, and UB CC.

The results of this clinical study showed that nicotine C_{max}, $AUC_{0\text{-}15}$ and $AUC_{0\text{-}240}$ for PM0000973.PD2 and PM0000973.PD6 were statistically significantly lower than that of UB CC, while statistically significantly higher than that of 4 mg nicotine gum. Similarly, subjective effects including overall product liking and overall intent to use again were lower

than UB CC, but higher than 4mg nicotine gum. Although the submitted abuse liability study did not assess Golden Tobacco 1.8% nicotine product (PM0000973.PD10), I agree with the BCP review that the conclusions from the tested products in PM0000973.PD2 and PM0000973.PD6 can be bridged to the 1.8% product due to similar nicotine PK profiles and subjective effect ratings between products with 5% and 2.4% nicotine content. In addition, the puff topography study (CSD190203) reviewed by BCP provided sufficient clinical context for the machine-generated aerosol nicotine data submitted for all products, confirming that the data from PM0000973.PD2 and PM0000973.PD6 can also be bridged to Rich Tobacco 1.8%, 2.4%, and 5% nicotine products in PM0000973.PD3, PM0000973.PD7, PM0000973.PD11. As TPL, I agree with the BCP review conclusion that among people who are inexperienced with ENDS use, the new products are associated with a lower abuse liability than CC.

The BCP review notes different lines of evidence from the applicant's clinical studies and the published literature suggesting that as people gain experience with ENDS products, they can attain higher nicotine C_{max}. Although the findings cannot be bridged to the new products, the applicant's biomarkers of exposure (BOEs) study (CSD170501) demonstrated that nicotine C_{max} increased to levels comparable to CC over five days of ENDS use. This finding is also well-supported in the literature. The BCP review cites additional published studies that have demonstrated that people with experience using ENDS can achieve C_{max} comparable to CC. Other studies have demonstrated that ENDS capable of producing C_{max} comparable to CC are more likely to promote switching. As noted in the BCP review, a published study has demonstrated that the nicotine flux of Vuse Alto products is similar to CC (Talih et al., 2023). As noted above (Section 3.2.1.5), the nicotine yield per puff was 2%-9% higher in the new products compared to mainstream smoke from comparison CC. However, the findings of the applicant's clinical study (CSD190202), taken in consideration with the nicotine flux findings reported by Talih et al., do not suggest that abuse liability is higher than CC.

Additionally, the new products have a nicotine salt formulation. The literature has also established that nicotine salt formulations make ENDS more palatable, facilitate ease of use, and are often associated with high nicotine exposures, comparable to CC, and above that of free-base nicotine formulations (Boykan et al., 2019; Goniewicz et al., 2019; Hajek et al., 2020; O'Connell et al., 2019; Yingst et al., 2019). These findings regarding experience with ENDS, nicotine flux, and the use of nicotine salt formulations, taken together, provide evidence to suggest that the abuse liability of the new products is similar to CC among adults with experience using ENDS, including those who use CC.

As TPL, I agree with the BCP conclusion that the abuse liability of the new products is above that of 4 mg nicotine gum and below that of CC for adults who smoke CC but do not have experience using ENDS. I also agree that the abuse liability of the new products increases with use experience and is likely comparable to that of CC for adults who smoke CC and have experience using ENDS. These levels of abuse liability are likely to be sufficient to sustain nicotine dependence among adults who use CC, even those that are ENDS-naïve. As adults who use the new products gain experience with them, higher nicotine exposures are likely. This is potentially beneficial for adults trying to switch from CC to ENDS, as they are more likely to have satisfactory results and not resume CC smoking, thus being exposed to lower levels of toxicants. Their similar nicotine delivery to CC suggests that these new products may be more substitutable for CC and facilitate complete switching/CC cessation

more than ENDS with lower nicotine delivery or nicotine gum. Because the new products have an abuse liability similar to CC, it is likely that adults who completely switch to the new products will maintain ENDS use and not resume CC smoking, which is likely associated with lower health risks than continued CC smoking.

Some users of other ENDS may use the new products or switch to exclusive use of the new products. The applicant did not provide results from clinical studies of adults who exclusively use other ENDS. However, from a public health perspective complete switching from CC to ENDS is the most important tobacco use transition (see also Section 3.4.1.1 below). Therefore, conclusions regarding the substitutability of the new products for CC are the most relevant conclusions from the BCP review to determine adult benefits of the new products, and to support overall APPH decision-making.

Collectively, the data suggest that the abuse liability of the new products is lower than that of CC among adults without experience using ENDS. The nicotine levels that adults who use the new products might reach, and corresponding abuse liability, indicate that the addiction risk of the new products is no higher for adults than other currently available tobacco products. While the nicotine levels may pose an addiction risk for those who do not use tobacco, as discussed in 3.4.2.3 below, appeal of the new products is low among those who do not use tobacco and therefore the risk of addiction for those who do not use tobacco does not outweigh the potential benefits to adults currently using CC. As discussed further in Section 3.4.2., abuse liability that approaches that of CC among those with ENDS use experience. Additionally, the nicotine salt formulation may make the new products a suitable substitute to CC among people who smoke CC and want to quit smoking; thus, the new products may facilitate complete or partial switching from CC.

3.4. USER POPULATIONS

The applicant submitted results from several observational studies. Three studies were applicant-sponsored: the National Tobacco Behavior Monitor (NTBM), Total Tobacco Migration Tracker (TTM), and the Colorado Longitudinal Study. The NTBM and TTM were cross-sectional surveys of adults of legal age to purchase tobacco products and were conducted in 2018-2019. Adults reported use of any ENDS products, including the new products, as well as other tobacco use patterns. The Colorado Longitudinal Study was a longitudinal survey of adults in Colorado who used ENDS and was conducted in 2014-2016. The applicant also submitted secondary analyses of the Population Assessment of Tobacco and Health (PATH) Study Waves 1-3 (2013-2016). Of these studies, the Colorado Longitudinal Study and the PATH Study provided a longitudinal assessment of ENDS use over time among populations of adults who are current established users of CC, while the NTBM provided data specific to the new products. Data from the TTM was used to bridge to other ENDS.

The applicant submitted results from three online likelihood of use (LOU) studies. These studies were conducted among adults (18-75 years old) and weighted to represent the United States population by CC smoking status, with different selected new products evaluated in each study, (b) (4)

3.4.1. Discipline key findings

The following discussion is based on key findings provided in discipline reviews.

3.4.1.1. Intended user populations (target population)

Per the BCP review:

- The applicant stated that the intended user population(s) for the new products are current adult tobacco users, including current CC smokers and current ENDS users. The applicant submitted one clinical study evaluating the new products in exclusive cigarette smokers, and one clinical study evaluating the new products in ENDS and CC dual users. These data provide adequate evidence to inform use behavior in those populations.
- As complete switching from CC to ENDS confers the greatest public health benefit, CC is the primary comparison product of interest when evaluating use of ENDS. No studies evaluating switching between other ENDS and the new products were provided or required.

Per the epidemiology review:

- The likely user population for Vuse Alto ENDS are current and former adult CC smokers. Data from the applicant's NTBM study characterizing users of these new products found that 91.6% of adult current established Vuse Alto users reported a history of CC smoking, with 64.5% of all users reporting they were current established smokers, and 27.1% reporting they were former established smokers. No users of the new products reported being current or former experimenters with CC. Additionally, 8.4% of users of the new products were never CC users.
- The applicant bridged data about other ENDS, including Vuse Solo, to the new products. Using data from the submitted NTBM study, the applicant demonstrated that Vuse Alto users were similar in demographic characteristics and tobacco use histories to other Vuse users, namely Vuse Solo. Data from the TTM and NTBM studies also noted that Vuse Solo users closely resemble ENDS users overall. The applicant also bridged results from the NTBM and TTM that were general to all ENDS, or current ENDS users, to the new products. Based on these findings, the new products were adequately bridged to Vuse Solo or other ENDS.
- The submitted observational studies, bridging that was conducted between other Vuse products including Vuse Solo (not subject to this review) to Vuse Alto, and additional analyses included in the epidemiology review provided sufficient information to evaluate the patterns of use of the new products in adult smokers.

3.4.1.2. Current tobacco users

Per the social science review:

- The applicant conducted three online likelihood of use (LOU) surveys. In these studies, participants were first presented with an image that included labeling for the new products. Second, participants responded to questions assessing purchase intentions; label comprehension; risk and addictiveness perceptions; product appeal; flavors, nicotine concentrations, and power unit designs of most interest; and main reasons for use and anticipated use behaviors.
- Although the applicant did not provide information about the source, validity, or reliability of survey items used to measure key variables, the scales did not appear to have serious measurement validity issues. The applicant used a large, demographically diverse panel and data were weighted using raking to represent the U.S. population by gender, age, race/ethnicity, region, and education level among three CC user groups (i.e., current established CC smokers, former

established CC smokers, never established CC smokers). Selected analyses were conducted with the full sample and the young adult (aged 18-30 years) subsample.

- Among current tobacco user groups, mean perceived risk (full sample, M = 4.9-5.5; young adult sample, M = 4.7-5.6) and perceived addictiveness (full sample, M = 5.2-5.8; young adult sample, M = 5.1-5.9) for Vuse Alto with 1.8%, 2.4%, and 5% nicotine were above the midpoint of the 7-point scales. Current users rated perceived risk and addictiveness as similar for Vuse Alto and other ENDS. Generally, current users perceived risk and addictiveness as lower for Vuse Alto compared to CC.
- Mean perceived appeal ratings for Vuse Alto with 1.8%, 2.4%, and 5% nicotine were at or below the midpoint of the 7-point scale (full sample, M = 3.3-4.3; young adult sample, M = 3.4-4.4). Current users rated perceived appeal as similar for Vuse Alto and other ENDS. Current established CC smokers rated Vuse Alto as significantly less appealing than CC.
- Mean intentions to purchase Vuse Alto with 1.8%, 2.4% or 5% nicotine were generally below the midpoint of the 10-point scale (full sample, M = 3.5-5.1; young adult sample, M = 3.9-5.5). Current user groups had significantly higher purchase intentions compared to non-user groups.
- Among the new products with 1.8% nicotine content (PM0000973.PD10, PM0000973.PD11), current established cigarette smokers selected Rich Tobacco (PM0000973.PD11) as a flavor of most interest. However, other current tobacco user groups selected Rich Tobacco (PM0000973.PD11) and Golden Tobacco (PM0000973.PD10) as flavors of most interest less often than other flavors with 1.8% nicotine (i.e., menthol and non-menthol, non-tobacco flavored products not subject to this PMTA review).
- Among the new products with 2.4% and 5% nicotine content (PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7), all current user groups tended to select Rich Tobacco with 2.4% (PM0000973.PD7) and 5% nicotine content (PM0000973.PD3) and Golden Tobacco with 2.4% (PM0000973.PD6) and 5% nicotine content (PM0000973.PD2) as flavors of most interest less often than other flavors with 2.4% or 5% nicotine (i.e., menthol and non-menthol non-tobacco flavored products not subject to this PMTA review).
- Current tobacco users, including established cigarette smokers, generally indicated "to stop smoking" was a main reason for interest in using Vuse Alto. Further, current established CC smokers who indicated that they would continue to use Vuse Alto if they tried and liked it were significantly more likely to report they would “cut down on the number of traditional cigarettes I smoke and use Vuse Alto instead of some cigarettes” than other use behaviors.

Per the BCP review:

- Switching, dual or poly use, and tobacco cessation
    - The abuse liability information provided (see Section 3.3) suggests that abuse liability and nicotine exposures of the new products are lower than CC among inexperienced ENDS users.
    - The applicant submitted a randomized controlled switching trial of inexperienced ENDS users with Vuse Solo Original G2 4.8% (CSD170501). Due to design differences that exists between Vuse Alto and Vuse Solo products, the data from this study cannot be directly bridged to the new products. The study did, however, demonstrate that nicotine exposure

increases as users gained experience with Vuse Solo products, such that nicotine exposure was similar to CC by the fifth day of the trial. These data are reinforced in the peer-reviewed literature comparing the design characteristics and nicotine flux of Vuse Original 4.8% and Vuse Alto Rich Tobacco 5% (PM0000973.PD3), which support that PM0000973.PD3 is the higher-powered device and can produce a nicotine flux that is similar to Marlboro Red (Talih et al., 2023).

- Together, the available evidence suggests that experienced ENDS users may achieve CC-like nicotine exposure with the new products in some populations.

Per the epidemiology review:

- Complete switching
  - The applicant submitted data from three applicant-sponsored studies: NTBM, TTM, and the Colorado Longitudinal Study. The NTBM and TTM were repeated cross-sectional surveys, while the Colorado Longitudinal Study was a longitudinal study with follow-up at six and twelve months after baseline. The applicant also submitted secondary analyses of Waves 1-3 of the PATH Study, a nationally representative longitudinal study of tobacco use. The analyses of complete switching from the Colorado Longitudinal Study and the PATH Study were not brand, product, or flavor specific. The applicant bridged the conclusions from all ENDS users to the new products; no data were provided on complete switching by adults who use the new products.
  - Applicant-submitted data from the PATH Study and the Colorado Longitudinal Study were used to evaluate transitions in tobacco use behavior (i.e., the transition to dual use or complete switching) in adult smokers. These analyses were not brand, product, or flavor specific. To increase sample size, analyses that evaluated some tobacco use behaviors among all closed ENDS users in the study were bridged to the new products. The applicant provided the justification that users of the new products are demographically similar to users of products such as Vuse Solo, and Vuse Solo users are demographically similar to users of closed ENDS overall.
  - Between Wave 1 and Wave 3 of the PATH Study, 1.5% of adults who were exclusively smoking at Wave 1 transitioned to exclusive ENDS use. An additional 5.3% of adult dual users of cigarettes and ENDS at baseline became exclusive ENDS users. In the Colorado Longitudinal Study, 4.6% of baseline dual users had completely switched to ENDS at the 6-month follow-up. Among those who were dual users at Month 6, 6.7% completely switched to ENDS by Month 12. All data on complete switching were adequately bridged from all ENDS users and no data were provided on complete switching rates among Vuse Alto users.
  - Among dual users, daily ENDS users were more likely to transition from dual use to exclusive ENDS use than were non-daily users. In the PATH Study Waves 1-3, the odds of complete switching from dual use were four times higher among those who used ENDS daily (14.6%) compared to those using ENDS less than daily (3.9%) (OR=4.2, 95% CI: 3.1-5.8; p<0.0001). In the Colorado Longitudinal Study, dual users' rates of complete switching were nearly twice as high among daily ENDS users from baseline to Month 6 (7.3%) than among non-daily users (4.1%).
- Dual use

- Dual use is common among users of Vuse Alto products. Based on data from the NTBM and TTM population surveys, over 64% of current established Vuse Alto users were current established cigarette smokers (64.5%). Among these dual users who were daily smokers, daily Vuse Alto users reported smoking fewer cigarettes per day (CPD) compared to non-daily Vuse Alto users (14.8 vs. 24.7 CPD).
- In a confirmatory analysis of PATH Study Wave 7 (2022-2023) Restricted Use File data, 8.24% (95% CI: 7.87, 8.63) of adults aged ≥21 years were current (past 30-day) ENDS users. Among those, 12.23% (95% CI: 10.38, 14.37) reported that their usual brand or the brand they last used was Vuse (referred to hereafter as "current Vuse users"). Nearly all of current Vuse users (96.36%, 95% CI: 93.00, 98.13) have ever smoked a cigarette, 3.64% (95% CI: 1.87, 7.00) have never been a cigarette smoker, and more than half (55.04%, 95% CI: 46.79, 63.03) are former established smokers (having smoked at least 100 cigarettes in their lifetime and have not smoked them within the past 12 months or are not currently smoking them at all). Among Vuse users who are former established smokers and provided the length of time since their last smoked cigarettes, most indicated they quit within the last 12 months (63.12%, 95% CI: 45.61, 77.75).
- In the analysis of PATH Study Wave 7, only the use of "Vuse" products could be identified, rather than "Vuse Alto" products specifically. To determine the proportion of these Vuse users who might be using the new products in particular, Epidemiology looked to sales data as an indicator. In an analysis of NielsenIQ Retail Measurement Service (RMS) data,[10] from the period spanning May 22, 2022 through June 17, 2023, Vuse Alto represented (b) (4) 1% of the total ENDS market share and (b) (4) % of the Vuse market share. Vuse Alto was the only Vuse product within the top 10 ENDS products by dollar sales, and none of the other Vuse sub-brands accounted for more than (b) (4) % of the market share by dollar sales. NielsenIQ RMS data tracks product sales when an item is scanned at the point of sale. The data tracks traditional retail channels, and excludes vape shops, online retailers, as well as other specialty stores that may sell ENDS products.
- The analysis of NielsenIQ RMS data demonstrated that Vuse Alto sales accounted for over (b) (4) % of "Vuse" product sales. Therefore, findings regarding adults currently using "Vuse" products in the PATH Study Wave 7 data are highly likely to be relevant to Vuse Alto products, including the new products.[11]

[10] The author's own analyses, calculations and conclusions, informed in part by the NielsenIQ Retail Measurement Service (RMS) data through NielsenIQ's RMS for the tobacco product category tobacco alternatives vapor for the time period May 22, 2022 through June 17, 2023 for Total US Expanded All Outlets Combined (xAOC) and convenience stores are those of the author and do not reflect the views of NielsenIQ. NielsenIQ is not responsible for, had no role in, and was not involved in analyzing and preparing the results reported herein, or in developing, reviewing, or confirming the research approaches used in connection with this report. NielsenIQ RMS data consist of weekly purchase and pricing data generated from participating retail store point-of-sale systems in all U.S. markets. See https://NielsenIQ.com/global/en/ for more information.

[11] Due to the high market share of the subbrand (b) (4) 2%), Vuse Alto, in these unique circumstances, FDA was able to use wave 7 of the PATH Study and NielsenIQ RMS data to confirm the findings of the applicant's cross-sectional studies. Because the subject products are tobacco-flavored ENDS products, for which a lesser showing of potential adult benefit may suffice, the evidence provided in the applicant's PMTAs would have been sufficient to demonstrate a benefit even in the absence of this confirmatory analysis.

3.4.1.3. Tobacco non-users (including youth)

Per the social science review:

- Although the survey samples lacked descriptive statistics (e.g., mean and standard deviation of age) that would have allowed social science to make more nuanced conclusions about the extent to which the young adult sample can be appropriately bridged to underage youth, current scientific literature suggests that young adult data in this PMTA can be used as a proxy for youth data (Sussman, 2019).
- Among non-user groups, mean perceived risk (full sample, M = 5.8-6.2; young adult sample, M = 5.4-5.9) and perceived addictiveness (full sample, M = 6.0-6.3; young adult sample, M = 5.4-6.2) for Vuse Alto with 1.8%, 2.4%, and 5% nicotine were above the midpoint of the 7-point scales. Both full sample and young adult sample non-users rated perceived risk and addictiveness as similar for Vuse Alto and other ENDS. Generally, both full sample non-user groups and young adult former tobacco users rated perceived risk and addictiveness as lower for Vuse Alto compared to CC. Young adult never users rated perceived risk and addictiveness as lower for Vuse Alto with 1.8% nicotine compared to CC, and similar for Vuse Alto with 2.4% and 5% nicotine compared to CC.
- Mean perceived appeal ratings for Vuse Alto with 1.8%, 2.4%, and 5% nicotine were below the midpoint of the 7-point scale (full sample, M = 2.1-2.3; young adult sample, M = 2.4-3.2). Generally, full sample and young adult sample non-users rated perceived appeal of Vuse Alto as similar to other ENDS, and similar to CC.
- The means for intentions to purchase Vuse Alto with 1.8%, 2.4%, and 5% nicotine concentration were well below the midpoint of the 10-point scale for non-user groups (full sample, M = 1.7-1.9; young adult sample, M = 1.9-2.8). Responses of 1 indicate “definitely would not purchase it to use,” thus the mean scores indicate that on average, non-users strongly intend not to purchase Vuse Alto. Additionally, non-user groups had significantly lower intentions to purchase Vuse Alto than current user groups. Young adult never users indicated similarly low purchase intentions as full sample never users. Compared to the full sample former users, young adult former users had significantly higher purchase intentions for Vuse Alto (full sample, M = 1.9; young adult sample = 2.6-2.8). Still, the means for intent to purchase among young adult former users indicate relatively strong intent not to purchase Vuse Alto.
- Among the new products with 1.8% nicotine, former tobacco users and never tobacco users in both the full sample and young adult sample tended to select Rich Tobacco with 1.8% nicotine (PM0000973.PD11) and Golden Tobacco with 1.8% nicotine (PM0000973.PD10) as flavors of most interest less often than other flavors with 1.8% nicotine (i.e., menthol and non-menthol non-tobacco flavored products).
- Similar results were found among the new products with 2.4% and 5% nicotine. Both former tobacco users and never users in the full sample and young adult sample tended to select Rich Tobacco with 2.4% (PM0000973.PD7) and 5% nicotine (PM0000973.PD3) and Golden Tobacco with 2.4% (PM0000973.PD6) and 5% nicotine (PM0000973.PD2) less often than other flavors with 2.4% and 5% nicotine (i.e., menthol and non-menthol flavored products).
- Generally, "curiosity/want to try it" was a main reason for interest in using Vuse Alto among both full sample and young adult sample non-user groups.

Per the BCP review:

- The abuse liability of the new products is lower than UB CC in current adult CC smokers with no prior ENDS experience. However, evidence suggests that inexperienced ENDS users achieve lower nicotine exposures from ENDS than what is typically obtained from a CC.
- Some literature suggests that youth who use pod-style ENDS (and are experienced with them) have nicotine exposures that are comparable to, or higher than, youth CC smokers and non-pod-ENDS users (Krishnan-Sarin et al., 2019). The new products contain nicotine salt concentrations similar to the pod-style ENDS tested in the literature (approximate range = 2-5% based on product labeling).
- No clinical studies of progression to regular use of the new products were conducted in non-tobacco users. Although the abuse liability of the new products is lower than CC, there is still some risk that nonusers, including youth, who initiate use of the new products may progress to regular ENDS use. However, the abuse liability of the new products does not exceed that of a CC among experienced ENDS users.

Per the epidemiology review:

- Initiation
  - In the 2018-2019 NTBM survey, 8.4% of adult established Vuse Alto users were never cigarette smokers and 2.6% were never tobacco users. Data on the prevalence of current use of these products in youth were not available.
  - The applicant also assessed overall initiation of ENDS use among never tobacco users in Waves 1-3 (2013-2016) of the PATH Study. Initiation of tobacco use with ENDS was uncommon. Only 0.2% of adult never tobacco users and 1.6% of former tobacco users initiated tobacco use with ENDS. No data were provided for the initiation of tobacco use with specific brands of ENDS.
- Youth
  - In the 2023 National Youth Tobacco Survey (NYTS), 8.7% of middle and high school current ENDS users identified Vuse as their usual brand. However, the "Vuse" brand can include products other than Alto (e.g., Solo, Vibe, Ciro) so the number of youth using the new products specifically may be lower.
  - The NTBM and TTM surveys that were analyzed by the applicant were comprised of adults of legal age to purchase tobacco products, and thus, do not include youth. Instead, the applicant proposed using information on young adults between the ages of 18-30 as a proxy for youth. Epidemiology considers this an appropriate strategy in the absence of youth data. Across both surveys, increasing age was associated with increasing use of closed ENDS (NTBM: OR=1.05, 95% CI: $p<0.0001$; TTM: OR=1.10, $p<0.0001$), suggesting that people of younger ages are less likely to use closed ENDS, like the new product. Although the prevalence of ENDS use did not decrease with increasing age in young adults, most adult Vuse Alto users are over age 30 (83.1% in NTBM).
- Former tobacco users
  - The applicant evaluated data from PATH Study Wave 1 to Wave 3 (2013-2016) to assess the likelihood of ENDS use among former tobacco users. No brand specific data were evaluated. In the PATH Study, 1.1% of former adult tobacco users reported exclusive use of ENDS a year later. Furthermore, evidence from the broader peer-reviewed literature suggests that prevalence of ENDS use

among former tobacco users (predominantly cigarette smokers) is low; generally 3-5% across studies.

- Flavors
  - Tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors. According to the 2023 NYTS data, among current middle and high school ENDS users, tobacco flavored ENDS were used by 6.4% (95% CI: 4.5%-9.0%), and significantly lags behind other flavored ENDS such as fruit flavor (63.4%, 95% CI: 59.8%-66.9%), candy, desserts, or other sweets (35.0%, 95% CI: 29.1%-41.5%), mint (27.8%, 95% CI: 22.0%-34.4%), and menthol (20.1%, 95% CI: 15.5%-25.8%).

3.4.1.4. Vulnerable populations (other than youth)[12]

Per the epidemiology review:

- The applicant did not provide data on use of the new products among any specific vulnerable subpopulations to examine potential differences relative to a general sample of tobacco users. Therefore, from an Epidemiology perspective, it is unknown whether the impact of the new products on product use behavior would differ for certain sociodemographic groups (other than youth) relative to the general samples of tobacco users studied.

Per the BCP review:

- The applicant did not provide data on use of the new products among any specific vulnerable subpopulations to examine potential differences relative to a general sample of adults who smoke. Therefore, from a BCP perspective, it is unknown whether the impact of the new products on abuse liability and/or product use behavior would differ for certain sociodemographic groups (other than youth) relative to the general samples of adult smokers studied.

Per the social science review:

- The applicant provided data for the overall sample and young adult (age 18-30 years) subsample, which the applicant stated are a subgroup of interest as they can inform on behaviors among underage youth. Social science did not identify concerns with other vulnerable populations.
- The applicant-provided information regarding impact on current tobacco users and nonusers is sufficient from a social science perspective.

3.4.1.5. Actions taken to mitigate risk of unintended use

Per the Office of Health Communication and Education (OHCE) consult:

- The applicant did not provide robust product-specific data on the degree to which its labeling, advertising, marketing, and promotion may influence youth perception, youth appeal, and the likelihood of youth initiation of tobacco use.
- The marketing plan information submitted by the applicant includes limited information on its target audience and provides a very high-level overview of its planned labeling, advertising, marketing, and promotion for the new tobacco products.
- The applicant states it intends to market its products to current adult smokers and vapers. The applicant references marketing practices aimed at adults ages 21 years

[12] This term refers to groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation.

or older and adults ages 18 years and older. The applicant states it does not intend to target its audience by other demographic characteristics (e.g., race/ethnicity, geographic region), psychographic characteristics, or behaviors other than current tobacco use.

- The applicant's marketing approach is very broad and would reach all adults ages 18+ (instead of only adults of the federal minimum legal age of sale) and a significant number of youth. The applicant does not indicate plans to use more sophisticated and cost-efficient marketing best-practices to reach adult smokers and vapers ages 21+, even where such targeting capabilities and controls are both available and considered standard practice in the media industry.
    - For example, when purchasing broadcast TV, a sophisticated plan can be developed, by TV network, to target adults ages 21+ with specific media passion points more likely to appeal to smokers, such as irreverent comedy, extreme sports, and horror/science fiction. Paid digital advertising allows marketers even more precise targeting capabilities, such as the ability to restrict advertising to only adults ages 21+ by using first- and second-party age-verified data. Additional data points can be layered on to further refine the target audience—for example, marketers can use credit card purchase data, key word search terms, and affinity-group membership (e.g., being a member of a frequent-buyer or rewards program) to identify adult smokers.
- OHCE recommended that any MGO letter for these products note measures to be implemented by the applicant including the marketing requirements as discussed in Section V of the OHCE consult, and restrictions related to digital advertising and use of TV/radio.

Per the social science review:

- The applicant described product features that mitigate risk of unintended use of the new products such as the incompatibility of the Vuse Alto power unit, cartridges, and USB charger with other ENDS components, and the lack of adjustable parameters on the power unit and cartridges.

3.4.1.6. Labeling and advertising

Per DPAL:

- Based on the information presented at this time, we have not concluded that the proposed labeling is false or misleading.[13]

Per the social science review:

- 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.
- The proposed labeling for the new products did not include potential modified risk claims.
- The applicant assessed label comprehension with a series of questions that measured participant knowledge about the new products after viewing images of the new products' packaging, labels, and available flavors and nicotine strengths.

[13] As presented during the Preliminary Assessment meetings for cycle 1 and cycle 2, DPAL did not have any deficiencies and thus did not find any false or misleading material.

- The mean proportions of correct responses were generally high for label comprehension questions for all current user and non-user groups (61%-97% across the likelihood of use studies). Compared to current users, non-users tended to have lower proportions of correct responses, though these differences were generally not significant.
- Never ever tobacco users were significantly more likely to respond, "Don't know" (30%; 95% CI: 27-33) to the statement "Vuse Alto pods come in two nicotine strengths" than all other groups when viewing images that included labeling for Vuse Alto cartridges with 2.4% and 5% nicotine.

3.4.2. Synthesis

As TPL, I agree with BCP and social science disciplines that the stated applicant intended user population for the new products is adult (ages 21+) current tobacco users, including current CC and ENDS users. In the applicant's submitted NTBM cross-sectional study (2018-2019), over 90% of participants who reported current established use of Vuse Alto also reported a prior history of CC use. Furthermore, a notable proportion (27.1%) of people who used Vuse Alto reported former established use of CC. While this pattern of use may indicate resumption of tobacco use by adults who quit CC, it is also likely that a significant portion of adults who use Vuse Alto products switched from CC to Vuse Alto products. As new information became available, including 2022-2023 results from the PATH Study Wave 7 and NielsenIQ RMS, additional analyses of current Vuse Alto users also confirmed the applicant's submitted findings from the NTBM study.

Per the epidemiology review, the applicant also provided longitudinal analyses based on the Colorado Longitudinal Study, and the PATH Study Waves 1-3. In the Colorado Longitudinal Study, about 5% of adults with dual use of ENDS and CC completely switched to ENDS at 6-month follow-up, and a further 7% of adults with dual use at the 6-month follow-up had completely switched by month 12. In the PATH Study analyses, about 1.5% of adults using CC exclusively in Wave 1 completely switched to ENDS by Wave 3, and 5.3% of adults with dual use of ENDS and CC at Wave 1 completely switched to ENDS by Wave 3. The findings from the Colorado Longitudinal Study indicated somewhat higher amounts of complete switching than those from the PATH Study. However, as TPL, I agree with the noted limitation that neither the applicant's Colorado Longitudinal Study findings, nor the analysis of PATH Study Waves 1-3 were able to provide estimates specific to the new products.

Regarding dual use of ENDS and CC, the applicant provided evidence that daily use of ENDS is associated with complete switching to ENDS. In the NTBM study, adults who used Vuse Alto daily reported lower CPD compared to non-daily Vuse Alto users. Although epidemiology noted the limitations of the applicant's analyses of the PATH Study Waves 1-3 (including changes in ENDS since data collection (2013-2016), and exclusion of a substantial number of individuals who did not have data across all three waves) these analyses also demonstrated that odds of complete switching to ENDS were significantly higher among adults using ENDS daily compared to non-daily use. This conclusion is consistent with more recent literature on dual use of ENDS and CC (Wang et al., 2021). Findings from the applicant's Colorado Longitudinal Study (2014-2016) also supported these conclusions, although significance testing was not provided in this analysis. Taken together, although these data do not reflect the current use patterns, these findings regarding dual use support

the conclusion that complete switching is more likely among adults who use the new products daily.

As discussed in Section 3.3, the abuse liability of the new products is above that of 4 mg nicotine gum and below that of CC among adults who use CC and lack experience with using ENDS, and increases to a level comparable to CC among adults who use CC and have ENDS use experience. The BCP review also notes that the use of a nicotine salt formulation, and nicotine flux comparable to that of CC is likely to provide adults who use CC a suitable substitute that can facilitate complete switching. Several published reviews and clinical studies in the literature support these conclusions, having found that ENDS are associated with complete switching. In particular, two distinct Cochrane reviews (Lindson et al., 2024; Lindson et al., 2023) and recent randomized clinical trials (Auer et al., 2024; Carpenter et al., 2023) have established a basis for concluding that ENDS, in general, can be used to completely switch away from CC or to facilitate significant reductions in CC smoking (i.e., fewer CPD). In particular, one of the Cochrane reviews noted that there is high-certainty evidence that nicotine-containing ENDS are more effective at promoting smoking cessation than NRT (Lindson et al., 2024). The magnitude of effect is likely to be comparable to, or even higher than, other modalities used for smoking cessation. These data indicate that ENDS, in general, have a benefit to public health by facilitating complete switching from CC in adults who use CC.

As TPL, I agree with the epidemiology and BCP conclusions that the new products are predominantly used by those with a history of CC use, including current use and former use, that may indicate complete switching, based on the evidence submitted in the applications. I also agree with the epidemiology conclusion that among adults using both CC and the new products, daily use of the new products increases the likelihood of complete switching.

As TPL, I also agree with the social science conclusions that the new products are most likely to be used by those currently using tobacco. In the likelihood of use studies, which assessed perceptions, appeal, and intent to use, people who currently use tobacco (i.e., current established CC use, current established non-CC tobacco use, current tobacco experimentation) reported the greatest intent to purchase the new products. Adults who currently used tobacco perceived risk and addictiveness of the new products to be similar to other ENDS, and lower than CC. Among current tobacco users who indicated any interest in purchase of Vuse Alto, “to stop smoking” was a main reason for interest in using the products. These findings demonstrated that the new products are appealing to adults who use CC and are interested in completely switching to ENDS.

The APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered an at risk population for various reasons, including that the majority of tobacco use begins before adulthood (U.S. Department of Health and Human Services, 2012) and thus youth are particularly susceptible to tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Almost 90 percent of adults who use cigarettes daily started smoking by the age of 18 (U.S. Department of Health and Human Services, 2014). Adolescents who

initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood (Apelberg et al., 2014). On the other hand, youth and young adults who reach the age of 26 without ever starting to use cigarettes will most likely never use cigarettes daily (U.S. Department of Health and Human Services, 2014). Because of the lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

The applicant did not provide direct data on youth use or perceptions of the new products. Instead, the applicant provided results from adults aged 18-30 to serve as a proxy for youth. Although the absence of youth data was a limitation for social science, both the social science and epidemiology disciplines were able to draw conclusions based on results from the sample of young adults and data from recent national surveys. Results from the 2023 NYTS indicated that 8.7% of middle and high school students reporting current (past 30-day) ENDS use identified Vuse as their usual brand. In addition, middle and high school students who currently use ENDS were more likely to report using flavors such as fruit; candy, dessert, or other sweets; mint; or menthol than tobacco flavor, which was only reported by 6.4% of students who currently use ENDS. These findings are indicative of low youth risk for the new products, which are tobacco flavored. In the applicant's NTBM study, over 80% of adults who used Vuse Alto products were over the age of 30. Although the NTBM study was conducted in adults of legal age to purchase tobacco products, this finding also supported conclusions of low risk to youth, as adults 18-30 comprised a small proportion of adults who used the new products. The applicant also provided evidence from the NTBM and TTM that increasing age was associated with increasing odds of using closed ENDS in particular. Although these associations were low in magnitude, these analyses align with the NTBM finding that most Vuse Alto users were over the age of 30.

As noted in the BCP review, the abuse liability of the new products is likely to be similar to that of CC among those with ENDS use experience. Therefore, nicotine levels of the new products may pose a risk of addiction to youth or young adults who do not use tobacco products and initiate tobacco use with the new products. However, the abuse liability of the new products is not likely to exceed that of CC, even among those who gain experience using the new products. Therefore, the risk of addiction of the new products is no higher than that of other currently available tobacco products such as CC.

The applicant's likelihood of use study findings indicated that non-users generally perceived similarly high risk and addictiveness for Vuse Alto, other ENDS, and CC, though Vuse Alto and other ENDS were generally rated slightly lower risk and addictiveness compared to CC. Appeal of Vuse Alto products was low among non-users and almost identical to appeal of other ENDS. Compared to current tobacco user groups, non-user groups had significantly lower intentions to purchase Vuse Alto. While purchase intent was low across user groups, the young adult subsample of current established cigarette smokers and former tobacco users did have significantly higher purchase intent than their full sample counterparts.

To further evaluate the new products' potential risks to youth, FDA examined the applicant's marketing plans and restrictions. The OHCE consult determined that the applicant provided a very broad marketing approach that would likely result in advertising

reaching youth and adults under 21. As TPL, I agree with OHCE's evaluation and conclude that the marketing restrictions recommended by OHCE, in Section V of the OHCE consult, are necessary to ensure that the new products sufficiently mitigate the risk to youth, especially with potential changes to the ENDS marketplace.

Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit adults who use CC who switch completely or significantly reduce their CC use would outweigh the risk to youth, provided the applicant follows marketing restrictions and postmarket requirements aimed at reducing youth exposure and access to the products. Accordingly, I recommend that if marketing of the new products is authorized, the MGO letter include the marketing requirements and recommendations specified in the OHCE consult.

Regarding product labeling and packaging, I agree with the social science review and conclude that the labels and statements do not contain misleading or false information.

Overall, as TPL, I conclude that the PMTAs provide sufficient evidence that the new products have the potential to benefit adults who smoke CC, and who switch completely to or significantly reduce their use of CC and pose a low risk to youth primarily due to their tobacco flavor.

3.5. TOXICANT EXPOSURE

3.5.1. Discipline key findings

The following discussion is based on key findings provided in discipline reviews.

3.5.1.1. Toxicity

Per the toxicology review:

- HPHC exposure: Overall, the new products' aerosol HPHCs were lower when compared to CC comparison data under both non-intense and intense puffing regimens. In comparison to CC smoke, HPHC levels for acetaldehyde, acrolein, crotonaldehyde, formaldehyde, and NNK were lower in the new product aerosols under both puffing regimens. Measurement supplied by the applicant show that acetyl propionyl, diacetyl, chromium, lead, and nickel aerosol constituent yields from the new products were lower than those reported for CC. While yields of ethylene glycol were within the range found for CC in published literature, (b) (4) and propylene oxide, which result from the thermal degradation of propylene glycol, were negligible compared to CC. In addition, aerosol yields of (b) (4), propylene glycol, acetaldehyde, acrolein, crotonaldehyde, formaldehyde, and NNK levels from the new products were within the range measured in aerosols from the 22 comparison ENDS under both non-intense and intense puffing regimens.
- Noncancer hazard: The noncancer hazard analyses indicate that the new products contain ingredients and ingredient subcomponents that are known respiratory toxicants and irritants. These ingredients include (b) (4) , as well as the (b) (4) subcomponents (b) (4) e and e (b) (4) , and the (b) (4) subcomponent (b) (4) Similarly, the exposure from an aerosol leachate, (b) (4) is of potential toxicological concern regarding respiratory hazards and potential changes

in liver metabolism. Several other ingredients and complex ingredients lack toxicological data, and their subcomponent composition is unknown or limited (i.e., (b) (4) , and (b) (4)). These ingredients are not well characterized regarding potential noncancer hazard and represent a limitation of the noncancer hazard assessment included in the toxicology review. Thus, while these ingredients were not included in overall noncancer hazard assessments or calculations, they are considered a source of uncertainty in the total estimation of noncancer hazard associated with the new products. Conclusions in future evaluations could change as additional information becomes available. Overall, the information submitted for the new products shows that the noncancer hazard risk to users of the new products is likely to be lower relative to CC from a toxicological perspective, although there is uncertainty as to how much lower.

- Overall cancer risk: The overall cancer risk evaluation included potential cancer hazards from all sources, including individual ingredients, HPHCs, and leachables found in the new products. The risk characterization process used by toxicology summarizes and integrates toxicity and exposure information to estimate and characterize overall cancer risk, both in quantitative assessments and qualitative descriptors.
    - The main metric of risk characterization is an ELCR calculation, which provides an extrapolated estimate for how many additional cases of cancer would be expected in a population exposed to a given toxicant concentration and intake level for an entire lifetime based on the toxicant's carcinogenic potency.
    - The ELCR approach is an objective way to consistently estimate cancer risk resulting from individual ingredients, HPHCs, and leachables measured in the new products, and it allows for a robust comparative analysis to other tobacco products assessed the same way.
    - All individual constituent ELCRs for a given product are added together to obtain a cumulative ELCR ($ELCR_c$) which was compared to the $ELCR_c$ for 1R6F Kentucky research cigarettes, which are representative of CC, and compared to the median $ELCR_c$ of the current CTP-authorized ENDS (Memorandum: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications; signed 06/03/2024).
- The new products contain ingredients, leachables, and HPHCs at levels that exceed or are equal to 1 case of cancer per 10^5 and, as such, could add to the cumulative cancer risk.
- Individual constituents of the new products are evaluated and placed into tiers as discussed in Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications (signed 06/03/2024), depending on the information available for the constituent.
    - Constituents included in Tiers 1 – 3 have been evaluated by IARC or EPA for carcinogenicity which increases toxicological certainty for these constituents contributing to cancer risk.
    - Placement into Tier 4 is primarily based on a weight of evidence analysis of existing data where there is either positive genotoxicity data or studies with

conflicting results that reduce toxicological certainty on whether constituents contribute to cancer risk.
    - For Tier 4 constituents, future chemical-specific studies and methodologies could provide data that facilitate updated chemical tiering.
- For the products under review, when the risk analysis is limited to Tier 1 – 3 constituents, all new products can be characterized as "lower concern" relative to 1R6F CC (i.e., less than 1.7% of the 1R6F $ELCR_c$). The associated $ELCR_c$ of all new products using Tiers 1 – 3 is also lower than the median $ELCR_c$ for CTP-authorized ENDS. The median $ELCR_c$ of the current CTP-authorized ENDS is 31 excess cancer cases per 100,000 users. The marketplace median, however, will change over time and reflects only those products authorized by February of 2024.
    - The $ELCR_c$s based on Tier 1 – 3 constituents are driven by NNK, acrolein, chromium, formaldehyde, and (b) (4) which are established HPHCs, classified by EPA/IARC as carcinogens and thus classified by Toxicology into Tiers 1 – 3.
    - However, limiting the assessment to only the most well studied and understood carcinogens (i.e., Tiers 1 – 3), when evaluating a new and emerging product portfolio, may result in an underestimation of cancer risks caused by a lifetime of exposure to the new product. Thus, it is important to understand and consider the risks represented by other constituents to which potential users of the new products will be exposed. These additional and potential cancer risks are due to constituents identified as Tier 4 mainly chemicals with one or more positive results in a genotoxicity assay or mixed and/or insufficient data that limit the confirmation or ruling-out of carcinogenicity. These chemicals may have carcinogenic potential but have not been formally evaluated by EPA or IARC to assess their carcinogenicity. If a Tier 4 chemical has previously been evaluated by EPA or IARC may be classified as EPA Group D or IARC Group 3.
- When the risk assessment includes Tier 1 – 4 constituents, the $ELCR_c$ for the new products fall between 1 – 10% of the 1R6F CC $ELCR_c$ indicating lower cancer risk relative to CC. Specifically PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11 are 2.8%, 1.1%, 4.7%, 1.8%, 7.2%, and 2.9% of the 1R6F CC ELCRc. The new products' $ELCR_c$s are also higher for PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11 and lower for PM0000973.PD3 when compared to the median $ELCR_c$ for CTP-authorized ENDS. The median $ELCR_c$ of the current CTP-authorized ENDS is 118 excess cancer cases per 100,000 users. The marketplace median, however, will change over time and reflects only those products authorized as of February 2024.
    - The $ELCR_c$s based on Tier 1 – 4 constituents are driven by NNK, (b) (4) acrolein, chromium, formaldehyde, (b) (4) (as identified in the Tier 1-3 assessment) as well as (b) (4) (b) (4) ol from (b) (4) and (b) (4), (b) (4).
    - Twenty-seven ingredients from PM0000973.PD2, PM0000973.PD6, and PM0000993.PD10 and twenty ingredients from PM0000973.PD3, PM0000973.PD7, and PM0000993.PD11 also exceeded the AET of 1.5 µg/day. Given these ingredients are either not genotoxic or without data to

support a positive (or negative) relationship with cancer outcomes (i.e., Tier 4E per Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed 06/03/2024), they were not included in the $ELCR_c$ assessments. These unknowns add to the uncertainty of the current risk characterization.

- The cancer risk assessment considering Tier 1 – 3 constituents indicates that if users completely switch from CC to the new products and assuming their nicotine consumption does not change when changing products, their risk of cancer is lower, but there is uncertainty about how much lower. Considering Tier 1 – 3 constituents, the new products are also associated with either higher (PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, and PM0000973.PD10) or lower (PM0000973.PD3 and PM0000973.PD11) risk relative to ENDS MGO marketplace, specifically regarding users that either initiate with this product (versus a marketed product) or switch from a currently marketed ENDS. When the $ELCR_c$ analysis takes Tier 1 – 4 constituents into account, the relative risk of the new products are likely to fall between 1 – 10 % of the 1R6F CC $ELCR_c$, and the calculated cancer risk of these products are either higher (PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11) or lower (PM0000973.PD3) than the median $ELCR_c$ for the ENDS MGO marketplace.
- Overall, for cancer risk assessment, the Tier 1 – 3 assessment represents the lower estimate of risk based solely on chemicals for which there is the greatest certainty of carcinogenicity, and the Tier 1 – 4 assessment represents the higher estimate of carcinogenicity, that includes constituents for which there is evidence of carcinogenic potential, but for which there is more uncertainty regarding that carcinogenic potential. Synergistic (and/or antagonistic) interactions between multiple constituents are a further uncertainty in this analysis that cannot be ruled out and the subsequent impact on cancer risk cannot be predicted at this time.

3.5.1.2. Biomarkers of exposure

Per the BCP review:

- The applicant did not conduct any clinical studies examining non-nicotine BOEs after use of the new products. The applicant cited a clinical study (CSD170501) which evaluated nicotine exposure associated with five-day ad libitum use of the Vuse Solo G2 4.8% ENDS (not subject to this PMTA review) and attempted to bridge findings for Vuse Solo G2 to the new products. CSD170501 was a randomized controlled switching open-label parallel cohort study in confined participants to determine the effects on BOEs of switching from UB CC to a Vuse product or tobacco abstinence for five days. These data showed that five days of complete switching from CC to Vuse Solo G2 use resulted in significant reduction of the majority of measured BOEs. However, these studies were not adequately bridged to the new products, mainly due to the differences between the two devices (e.g., different power delivery units, different coils). There are differences in machine-generated aerosol free nicotine between the two products, and the literature demonstrates that these differences can result in different levels of aerosol constituents and different use behaviors.
- One applicant submitted study (CSD190202) provides details about nicotine exposure; the new products PM0000973.PD2 and PM0000973.PD6 exposed

smokers to lower nicotine levels than UB CC over the 240-minute ad libitum testing session.

- Although the lack of product-specific or properly bridged BOE data for the new products is a limitation, BCP was able to make an overall conclusion regarding likely nicotine exposures among those who use the new products (see Section 3.3).

3.5.2. Synthesis

As TPL, I agree with the conclusions of the toxicology review that the new products' aerosols have lower levels of some HPHCs (e.g., acetaldehyde, acrolein, crotonaldehyde, and formaldehyde) compared to the CC, and noncancer and cancer risks of the new products are lower than CC. Although the potential noncancer hazard for some constituents are not well characterized and are considered a source of uncertainty, I agree with the toxicology review that the noncancer hazard risk to users of the new products is likely to be lower relative to CC.

Regarding cancer hazards, the toxicology review estimated the $ELCR_c$ of the new products. $ELCR_c$ estimates included e-liquid ingredients, subcomponents of e-liquid complex ingredients, aerosol leachates, and HPHCs. The $ELCR_c$ values reflect additivity of risks across all toxicants for each product. The new products' cancer risk was estimated based on two levels of hazard certainty. The Tier 1 – 3 assessment represents the lower estimate of risk based solely on chemicals for which there is the greatest certainty of carcinogenicity, and the Tier 1 – 4 assessment represents the higher estimate of carcinogenicity, that includes constituents for which there is evidence of carcinogenic potential, but for which there is more uncertainty regarding that carcinogenic potential. With uncertainty in hazard identification being the main difference between the Tier 1 – 3 $ELCR_c$ and the Tier 1 – 4 $ELCR_c$, the latter represents a conservative estimate which is the most appropriate when considering whether the new products are AAPH in this TPL review. $ELCR_c$ values calculated for the new products are compared to the $ELCR_c$ value for 1R6F CC and with the median $ELCR_c$ for CTP-authorized ENDS as of February 2024. However, the number of CTP-authorized ENDS is small and does not provide a robust ELCR assessment based on the small sample size, rendering this comparison incomplete for the purposes of this TPL review. Thus, for the purposes of this TPL review, the most appropriate toxicological assessment for the new products is Tier 1 – 4 $ELCR_c$ compared to CC.

In this case, the difference in $ELCR_c$s indicates that the main contributor(s) to overall cancer risk are predominately Tier 4 constituents: (b) (4) (b) (4) from (b) (4) . Using a more conservative $ELCR_c$ based on Tiers 1 – 4, the $ELCR_c$ for all new products is lower when compared to CC and either higher (PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11) or lower (PM0000973.PD3) than the median $ELCR_c$ for CTP-authorized ENDS.

The toxicology review identified several constituents that have some uncertainty as to their genotoxic hazard identification and associated risks. When considering those constituents (i.e., Tiers 1 – 4), the estimated $ELCR_c$ for the new products is between 1 – 10% of the 1R6F $ELCR_c$ indicating lower cancer risk relative to CC. Specifically for PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11, the ELCRc are

2.8%, 1.1%, 4.7%, 1.8%, 7.2%, and 2.9% of the CC $ELCR_c$. While the overall estimated $ELCR_c$ due to exclusive use of the new products is substantially lower than the estimated $ELCR_c$ for use of CC, these estimates are based on chemical exposure information and a reduction in exposure may not be directly proportional to a reduction in risk. Thus, there is uncertainty as to how much the cancer risk will decrease for a person who smokes CC and switches completely from CC to one of the new products. Although $ELCR_c$ for the new products are lower than 1R6F CC, the cancer risk associated with use of the new products may still be increased for people who have never used tobacco products or people who formerly used tobacco products.

It is also important to consider the potential cancer risks associated with switching from a CTP-authorized ENDS to the new products given that adults who currently use ENDS are one of the applicant's intended populations (see Section 3.1.1.). Based on the more conservative Tier 1 – 4 $ELCR_c$ assessment (which considers constituents with some uncertainty about their toxicological profile) the ELCRc for PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11 are above the median of the currently authorized ENDS marketplace. Whereas the $ELCR_c$ for PM0000973.PD3 is below the median of the currently authorized ENDS marketplace. Of note the median $ELCR_c$ of the current CTP-authorized ENDS is 118 excess cancer cases per 100,000 users. The marketplace median, however, will change over time and reflects only those products authorized as of February 2024. Nonetheless, these results must be interpreted while considering the limitations (i.e., small sample size of CTP-authorized ENDS) associated with the CTP-authorized ENDS $ELCR_c$ calculations. The sample size for the CTP-authorized ENDS calculation is small (i.e., twelve products as of February 2024) and does not represent the full ENDS market, nor does it represent the ENDS with the highest market share, particularly with a shifting ENDS marketplace; thus, this comparison is incomplete and not meaningful at this time. Although there may be a higher risk associated with completely switching from a CTP-authorized ENDS to the new products, as TPL, I believe that the comparison of the new products to CC provides a more compelling consideration in the APPH assessment at this time.

These toxicology cancer risk estimations assume that people who smoke CC (or use ENDS) will completely switch from CC (or marketed ENDS) to the new products. As TPL, I acknowledge that adults who dual use the new products with CC may not have the same reduction in cancer risk.

The applicant did not provide product-specific BOE data and did not adequately bridge the BOE data from tested products (Vuse Solo G2) in an applicant-provided clinical study, as the differences between the two devices can result in different levels of aerosol constituents. However, as discussed in Section 3.3.2, the new products' similar abuse liability to CC among adults who are experienced ENDS users, including those who use CC, and greater abuse liability than 4 mg nicotine gum may increase the likelihood of use of the new products for adults trying to switch from CC to ENDS and interested in quitting.

These data are consistent with the general literature on other ENDS and may indicate a likely relative health benefit associated with exclusive use of the new products compared to exclusive use of CC (see Section 3.6.). As TPL, I agree with toxicology and BCP conclusions that the data provided in the PMTAs demonstrate likely benefit for the new products if used

by adults who use CC and use the new products to switch completely, significantly reduce CC use, or quit all tobacco products.

3.6. HEALTH EFFECTS

3.6.1. Discipline key findings

The following discussion is based on key findings provided in discipline reviews.

3.6.1.1. Toxicology

Per the toxicology review:

- Nonclinical studies
  - Results from the in vitro toxicology studies provided by the applicant indicated that combined CC smoke fractions (i.e., total particulate matter [TPM] + gas vapor phase [GVP]) were positive for mutagenicity, cytotoxicity, and genotoxicity. By contrast, the new product and comparison ENDS aerosols were negative in all in vitro assays.
  - To support applicant-provided in vitro testing methods and results, the applicant provided a literature review of relevant in vitro and in vivo toxicity information. The applicant concluded that existing genotoxicity studies found in the literature indicate ENDS exposure have not yet demonstrated mutagenicity or genotoxicity in vitro and that these data are consistent with the results for the new tobacco products shown in the applicant's studies submitted with these applications.
  - The applicant did not conduct in vivo studies on the new products but instead bridged findings from in vivo studies using Vuse Solo G2 aerosols to the new products. Overall, data from in vivo studies indicated Vuse Solo G2 aerosols resulted in lower nonclinical toxicity and histopathological changes when compared to Newport Gold CC smoke. However, there are differences between the new and tested (i.e., Vuse Solo G2) products which can result in different levels of aerosol constituents, meaning these results cannot be bridged to the new products.
  - In reviewing the original applications, the toxicology review assessed nonclinical genotoxicity data based on in vitro exposure with whole CC smoke and aerosols (new products). However, toxicology has identified limitations with genotoxicity assay results when whole smoke or aerosols (i.e., complex mixtures) are used as test articles. The $ELCR_c$ approach specifically addresses issues regarding the presence of carcinogens or potential carcinogens in the aerosol of the new products. As such, the individual constituent hazard identifications, exposures, and resultant $ELCR_c$ estimates calculated in the second cycle review are used in aggregate to update the initial toxicology review conclusions regarding nonclinical studies that assessed genotoxicity based on whole smoke as well as qualitative HPHC conclusions.
- Clinical data with toxicity endpoints
  - The applicant did not conduct clinical studies on the new products but instead referenced clinical studies using the comparison products Vuse Solo, Vuse Vibe, and Vuse Ciro. The applicant provided information to bridge findings from Vuse Solo G2 to the new products based on similar reductions in aerosol constituents compared to CC. However, comparison product findings (i.e., Vuse Solo G2)

provided by the applicant were not adequately bridged to the new products in these applications, mainly due to the differences between the two devices (e.g., different power delivery units, different coils). Therefore, the clinical data submitted by the applicant indicating reduced urinary BOE are not applicable to the new products from a toxicology perspective.

- Toxicant and study integration
  - Overall, the toxicological evaluation of the information provided in the PMTAs shows that noncancer hazards and cancer risks to exclusive users of the new products are likely to be lower relative to the risks of exclusive CC use.

3.6.1.2. BIMO inspection findings

Per the BCP review:

- FDA's Office of Compliance and Enforcement completed a Bio Research Monitoring Program (BIMO) review for two of the applicant's research sites and BCP reviewed the findings in the BIMO report. The results of the BIMO inspections revealed issues that may impact the reliability of the data submitted for protocol CSD190202, which was reviewed during cycle 1. Some of the issues noted at Site 1 included inaccurate recordkeeping and inaccurate and/or inadequate investigational product control and accountability records. At Site 2, similar issues were discovered including inadequate recordkeeping and an instance of protocol noncompliance. BCP considered these findings in evaluation of the study data. In addition to abuse liability data found in CSD190202, the applicant provided machine-generated aerosol nicotine data, a comprehensive bridging document (i-1-al-bridging.pdf) that referenced studies from other Vuse products (e.g., Vuse Solo G2) within the same nicotine concentration as the new products, and a puff topography study (CSD190203) that allowed for evaluation of the abuse liability of the new products. Since the conclusions on abuse liability are confirmed through multiple lines of evidence, BCP determined that the issues identified are limitations to CSD190202, but do not change BCP's overall conclusion based on the totality of evidence regarding the abuse liability of the new products.

3.6.1.3. Addiction as a health endpoint

Per the BCP review:

- Data from the PK and subjective effects study, (CSD19202), suggest that the abuse liability of the new products is lower compared to that of CC in ENDS naïve CC smokers. Although subjective effects data from the abuse liability assessment show that the new products are rated lower than UB CC, the new products showed favorable responses for liking, intent to use again, satisfaction, relief, and urge to smoke, suggesting that cigarette smokers find the new products reinforcing and showed greater liking and craving relief compared to nicotine gum. The applicant also submitted a randomized controlled switching study in inexperienced ENDS users with Vuse Solo Original G2 4.8% which demonstrates that nicotine exposure increases with as users become more experienced with Vuse Solo products. A study from peer-reviewed literature comparing the design characteristics and nicotine flux of Vuse Original 4.8% and Vuse Alto Rich Tobacco 5% concluded that Vuse Alto Rich Tobacco 5% (PM0000973.PD3) is the higher-powered device and can produce a nicotine flux that is similar to Marlboro Red (Talih et al., 2023). These data suggest

that the abuse liability of the new products is likely comparable to CC in adults who smoke when users gain experience with ENDS devices. Therefore, current CC smokers are likely to maintain their nicotine addiction severity following use of the new products.

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

Per the medical review:

- Overall, the applicant provided clinical study data to evaluate the short and long-term health effects of the new products. Based on the provided information, no significant health concerns were identified. There are currently no published data for the health effects of the new products.
- No definitive health conclusions can be drawn regarding the new products and the impact on human health based on review of the clinical data and health effects literature submitted by the applicant. Several clinical study limitations preclude concluding that use of the proposed new products is not without potential human health risks, especially during long-term, chronic product exposure. However, the totality of the health effects data, including clinical study data, published literature, and consumer reported adverse experiences, provide information consistent with previously reported and expected health effects associated with ENDS use.
- There was an acute increase in heart rate and blood pressure observed following the use of the new products PM0000973.PD2 and PM0000973.PD6 in study CSD190202. This transient effect is generally seen in published clinical studies involving use of similar ENDS products. Published literature is limited on the effect of these acute changes in heart rate and blood pressure on long-term health outcomes.
- The applicant submitted clinical study, CSD170501, evaluated BOE and BoPH in smokers switched to short-term use of other manufacturer products or abstinence. This study was used to support the applicant's statement that smokers who switch to the tested products likely decrease their exposure to harmful tobacco smoke constituents, which likely decreases their health risk. None of the new products were evaluated in this study, and the applicant states that BoE data from this study can be extrapolated to the new products because aerosol constituent yields for study products are similarly and substantially reduced relative to CC. In addition, no data on BoPH, nor on actual health outcomes related to the selected BOPH, are included for the new products; the clinical relevance of the bridged BoPH reduction study data remains unclear.
- The literature is unclear if specific reductions in exposure to harmful constituents leads improve tobacco-related health outcomes or decrease disease risk. Longitudinal data on health outcomes of chronic ENDS use remains scarce, and it is not clear if reduction of BoPH translates to reduced health risk. There continues to be a significant knowledge gap in the body of published literature regarding empirical morbidity and mortality data to fully characterize the range of potential short and long-term health effects of ENDS use and aerosol exposure in users and nonusers. Based on the information reviewed, including the clinical study, published literature, and adverse experiences, the short-term health effects of the new products are expected and consistent with those reported for this class of products.

Per the epidemiology review:

- The applicant did not submit any observational health effects studies.
- There are currently no published data for the health effects of the new products, and few observational studies have been published on the short- and long-term health effects of ENDS use.
- Some published literature suggests that ENDS use compared to never tobacco use may be associated with a higher likelihood of some health outcomes such as cardiovascular disease, respiratory disease, and oral health (Giovanni et al., 2020; Osei et al., 2020; Osei et al., 2019). Although many of these studies utilized cross-sectional surveys to examine these relationships, the timing of ENDS use and disease onset cannot be established with certainty.
- Biomarker data from observational studies generally show that ENDS users have higher exposure to nicotine, some volatile organic compounds (VOCs), and tobacco-specific nitrosamines (TSNAs) than do non-tobacco users (Goniewicz et al., 2018; Rubinstein et al., 2018). Some biomarker data from observational studies have also found that dual users can have higher levels of certain biomarkers of exposure than exclusive cigarette smokers (Goniewicz et al., 2018; Rostron et al., 2019).
- A meta-analysis found that compared to heavy smokers, those who reduce their cigarettes per day by at least 50% had a significant reduction in lung cancer (Chang et al., 2021). However, such reductions in cigarette smoking have not been found to lower the risk of all-cause mortality, all-cancer risk, or other smoking/tobacco related cancers (Chang et al., 2021). These findings suggest that dual users who are able to reduce the number of cigarettes they smoke by at least 50% may be able to reduce their risk of lung cancer.
- Complete switching likely reduces exposure to tobacco related toxicants. In an observational study where smokers completely switched to ENDS for two weeks, total nicotine and some PAH metabolite levels did not change, but levels of all other biomarkers, including VOCs and TSNAs, significantly decreased after one week of using ENDS (Goniewicz et al., 2017).

3.6.1.5. Likelihood and effects of product misuse

Per the medical review:

- The new products are closed systems consisting of a rechargeable power unit and disposable cartridge that is not intended to be opened. The applicant states that the cartridges are blister packaged and have a tamper evident seal, so health risk is likely mitigated for accidental exposure in children. Further, there have been few reports of accidental exposure for these products in the applicant-submitted clinical study or in FDA reports.

Per the BCP review:

- The new products are closed-system cartridge-style ENDS. The new product settings are non-adjustable, and the e-liquid is enclosed in a pod, thereby reducing chances that users may manipulate ENDS product settings and e-liquid constituents, including nicotine levels, which may influence exposure to nicotine and other HPHCs in the aerosol.

3.6.1.6. Adverse experiences

Per the medical review:

- Of the four studies submitted by the applicant, two studies (CSD 190202 and CSD190203) evaluated the new products. AEs for these two studies were generally mild in severity, and the most frequently reported events in both studies were generally expected and commonly reported AEs in ENDS users (e.g., headache, nausea). One subject reported decreased exercise tolerance and was withdrawn from CSD190203. This AE that was deemed moderate in severity, possibly related to the study product, and symptoms resolved after discontinuation of the product.
- For study CSD190203, transient increases in mean maximal changes in blood pressure and heart rate were noted following use of the new products. Acute increases in blood pressure and heart rate have been reported in the literature in studies involving the use of similar ENDS. Published data on how these acute cardiovascular changes impact long-term health outcomes of ENDS users are limited.
- All AEs in the submitted clinical studies were reported as resolved and no serious adverse events or deaths were reported. Overall, there were few clinically significant findings in laboratory values, vital signs, physical exams, and ECG assessments and no permanent health effects were reported. However, several study limitations including generally healthy subjects, small sample sizes, and short durations of exposure limit the ability to draw conclusions on health risks of the new products.
- Information in the FDA Safety Reporting Portal (SRP) is limited, which makes it challenging to identify potential trends in adverse events for the new products and draw conclusions regarding health risk. The applicant did not provide consumer reports which would have provided additional useful information on health effects and risks to consumers of the new products.

Per the engineering review:

- No engineering-related adverse experiences from health effects were reported to FDA.

3.6.2. Synthesis

As TPL, I agree with the conclusions of the toxicology, BCP, and epidemiology reviews that adults who currently smoke CC and either completely switch to the new products, or significantly reduce their CC smoking, will likely benefit from reduced exposure to HPHCs. I also agree with the BCP review conclusion that among people who smoke CC and are inexperienced with ENDS use, the new products are associated with a lower exposure to nicotine than CC.

The applicant submitted data from nonclinical studies and clinical studies with toxicity endpoints. Importantly, in vivo and clinical studies were not conducted using the new products but instead the applicant provided information to bridge findings from studies using an ENDS comparison product (Vuse Solo G2). However, there are differences between the new and tested (Vuse Solo G2) products which can result in different levels of aerosol constituents. FDA determined results from the comparison product studies were not adequately bridged and not applicable to the new products. Results from in vitro toxicology studies provided by the applicant indicated that CC smoke fractions were positive for mutagenicity, cytotoxicity, and genotoxicity. Results from testing of the new products and comparison ENDS aerosols were all negative for mutagenicity, cytotoxicity, and genotoxicity.

However, new product aerosols contain constituents known to be genotoxic and/or carcinogenic which is incongruent with the applicant's in vitro hazard ID results. As noted above (3.5.1.1.), an $ELCR_c$ approach was used to address issues regarding the presence of carcinogens or potential carcinogens in the aerosol of the new products. The individual constituent hazard identifications, exposures, and resultant $ELCR_c$ estimates calculated in the toxicology review are used in aggregate to update the initial toxicology review conclusions regarding nonclinical studies that assessed genotoxicity as well as qualitative HPHC conclusions. $ELCR_c$ assessments in the toxicology review determined that cancer risks to users of the new products are likely to be lower relative to CC. Moreover, the toxicological evaluation of information provided shows that both noncancer hazards and cancer risks to users of the new products are likely to be lower relative to CC indicating adverse health effects may also be lower. As TPL, I agree with the conclusions of the toxicology review that noncancer and cancer risks are likely to be lower among adults who exclusively use the new products compared to those who exclusively smoke CC.

As noted above (3.5.1.2), the applicant submitted a randomized clinical study of short-term urinary BOE changes among adults who smoke CC and switch to ENDS (CSD170501). This study was conducted using Vuse Solo G2, Vuse Vibe, and Vuse Ciro ENDS (not subject to this PMTA review). The applicant attempted to bridge results for Vuse Solo G2 products to the new products. The study (CSD170501) generally concluded that switching from CC to ENDS is associated with significant reductions in BOEs for multiple HPHCs. As noted in the BCP review, the applicant did not appropriately bridge the results for Vuse Solo G2 to the new products because of the differences between the two devices (e.g., different power delivery units, different coils) that impacts users' exposure to aerosol constituents.

BIMO inspections for study CSD190202 identified recordkeeping issues and one instance of protocol noncompliance in this study. However, as TPL, I agree with the conclusions of the BCP review that these limitations do not preclude drawing conclusions regarding likely nicotine exposures among those who use the new products (see Section 3.3). As noted in the epidemiology review, published literature has generally identified some health risks associated with ENDS use compared to never-use of tobacco products (Giovanni et al., 2020; Osei et al., 2020; Osei et al., 2019), but have also found significantly reduced exposures to tobacco-related toxicants (e.g., TSNAs, VOCs, and nicotine) among people who smoke cigarettes and completely switch to ENDS (Goniewicz et al., 2017; Goniewicz et al., 2018). Studies also generally indicate that reducing smoking by 50% or more is associated with significant reductions in some health risks such as lung cancer, but no significant change in all-cause mortality (Chang et al., 2021). Studies examining dual use of ENDS and CC without significant reductions in smoking have concluded that some BOEs (e.g., biomarkers of acrolein, acrylonitrile, NNK, nicotine) may be higher than those in people exclusively smoking CC (Goniewicz et al., 2018; Rostron et al., 2019). However, based on the new products' intended user population of adults who currently smoke CC or use ENDS, the large number of adults who currently smoke CC (11.5% or 28.3 million adults 18 or older in 2021), and the current lack of product-specific evidence of increased health risks among adults who dual use CC and the new products, the health benefits of reduced toxicant exposure among adults who switch or significantly reduce CC smoking likely far outweighs the health risks to adults who smoke and do not significantly reduce CC smoking or switch to the new products (Cornelius et al., 2023). Therefore, despite the limitation noted in the BCP review, I

agree that findings from the toxicology and epidemiology reviews support overall conclusions regarding potential health effects of the new products.

As TPL, I agree with the conclusions of the medical and engineering reviews regarding AEs reported by the applicant or directly reported to the FDA SRP. As noted in the medical review, observed AEs in submitted studies were generally mild, and the single moderate severity AE reported resolved after discontinuation of the product. However, the applicant's switching studies did not assess the effects of long-term use and the impact of dual use which would be more likely to occur in real-world conditions. There are limited published data about the long-term health effects of ENDS, in general, from large clinical studies or long-term epidemiological studies. In addition, the study design limitations (e.g., relatively small sample size, short exposure periods) in the published literature make it difficult to draw definitive conclusions related to health effects of ENDS, specifically the new products. Therefore, the long-term effects from dual use of the new products could not be evaluated. However, based on these distinct lines of evidence for the health effects and patterns of ENDS use, I agree that adults using CC who switch to these new products (either completely or partially with a significant reduction in CC consumption) will likely benefit from reduced exposure to HPHCs relative to continued CC smoking alone.

As noted above (3.4.2), in the applicant's NTBM study, about 27% of all adults who currently use Vuse Alto products were former established smokers. Therefore, it is highly likely that some adults who smoke CC will switch to the new products or use the new products to significantly reduce their CC smoking. It is also likely that people who do switch (or significantly reduce CC smoking) will do so after a transition period of dual use. However, the new products are also likely to result in some adults who neither completely switch nor significantly reduce their CC smoked per day. Any potential health benefits of complete switching or significant CC reduction are unlikely to be observed in those who dual use without significantly reducing CC use.

As TPL, I agree with the conclusions of the medical and BCP reviews that the new products have a lower likelihood of product misuse, including manipulation of the products. The new products have no user-adjustable settings and include a disposable e-liquid cartridge. These features are likely to mitigate accidental exposures to e-liquid and reduce the likelihood of increased exposures to nicotine and HPHCs that may occur through manipulation of product settings.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

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

3.7.1.1. Population health impact (PHI)

Per the epidemiology review:

- The applicant used the Dynamic Population Modeler (DPM)(+1), a statistical model to estimate the effect of changes in tobacco use patterns across multiple age cohorts. The outcome was the difference in mean number of survivors—from age category 13-18 years to the end of the age category 68-72 years—for a

counterfactual scenario where Vuse Alto products are available in the marketplace compared to a base case without Vuse Alto products' availability.

- Model inputs came from the 2018 National Survey on Drug Use and Health (NSDUH) data (smoking initiation) and 2015-2017 NSDUH (cessation). Gender- and age-specific mortality rates for never, current, and former cigarette smokers were calculated based on data from the Kaiser-Permanente Cohort Study and 2000 U.S. Census. It was assumed that exclusively using Vuse Alto compared to cigarette smoking would result in tobacco-related mortality risk reductions of 90% or 95%. Probabilities for all primary transitions were based on the likelihood of use testing specific to Vuse Alto (Section H.5.2.3 of the PMTAs).
- The model suggests that that the use of Vuse Alto among tobacco users and nonusers would be projected to increase survival to age 72 for about 405,000 individuals in the U.S. population over a 60-year period.
- There are some limitations to the inputs used in this model that may overestimate the population health benefit. First, the model used likelihood of use data rather than prevalence data observed in real-world surveys (i.e., the TTM and NTBM). Secondly, the model did not allow for periods of sustained dual use, which is a common use pattern before complete switching occurs. Finally, the main analyses are based on an optimistic risk reduction estimate (i.e., the assumption of a 95% lower excess relative risk compared to cigarettes). Despite these weaknesses, the population modeling approach presented in the applications is sufficient from the epidemiological perspective.

3.7.2. Synthesis

As TPL, I agree with the conclusions of the epidemiology review regarding the population health impact of the new products. The model does not raise concerns in term of model structure or tobacco use transitions.

The applicant's submitted population model, based on the DPM(+1) approach, predicts significant net population health benefit over a 60-year period. The applicant obtained certain model inputs (e.g., smoking initiation, cessation, and gender- and age-specific mortality estimates by smoking status) from population health survey sources (e.g., NSDUH, Kaiser-Permanente Cohort Study). This approach is appropriate for parameterizing the use of other tobacco products, such as CC, in a model forecasting the public health impacts of products such as ENDS. The applicant derived model inputs regarding use of the new products from their own product-specific LOU studies. In general, this use of observational and product-specific data is also appropriate for population health modeling. However, as noted in the epidemiology review, the applicant's submitted observational surveys of actual use, such as the TTM and NTBM, would have provided greater model fidelity than the LOU studies that were used to predict transitions to the new products.

The applicant also utilized potentially liberal excess relative risk (ERR) estimates for ENDS of 0.05 and 0.10 (i.e., assumptions that ENDS have 5% or 10% of the mortality risk of CC) as model inputs, based on a well-known estimate of 95% reduced mortality risk compared to CC that was promoted by Public Health England in the United Kingdom (McNeill et al., 2015). The true lifetime mortality risk reduction associated with complete switching from CC to ENDS is still unknown, and these estimates may overestimate the mortality benefits of complete switching from CC to ENDS within the model. However, as noted in the toxicology

review findings described above (3.5.1.1), the estimated $ELCR_c$s of the new products compared to those of the 16RF comparison CC provide some support for the use of an ERR estimate of 0.10 as a model input.

The primary finding of the model was that the new products would increase survival to age 72 for about 405,000 people in the United States over a 60-year period. Despite limitations due to the choice of model inputs described above, the direction and magnitude of these findings are consistent with other published findings using a range of modeling approaches and inputs (Levy et al., 2021; Mendez et al., 2021; Vu et al., 2023; Warner et al., 2019). Therefore, as TPL, I agree that these population health impact models provide evidence to support an APPH finding for the new products. The APPH determination will be made based on the totality of information submitted and evaluated.

3.8. STATUTORY REQUIREMENTS

3.8.1. Public health conclusion

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

3.8.2. Tobacco product manufacturing practices[14]

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.

3.8.3. Labeling

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

3.8.4. 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.

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

4.2. ENVIRONMENTAL CONCLUSION

A finding of no significant impact (FONSI) was signed by Luis G. Valerio, Jr. on July 9, 2024. The FONSI was supported by an Environmental Assessment (EA) prepared by FDA on July 9, 2024.

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, which includes youth, young adults, and other vulnerable populations. In 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 from adult users of more harmful tobacco products completely switching).

FDA reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate that marketing of the products would be APPH. The applications demonstrate that the new products have the potential to benefit adults who smoke CC and completely switch to the new products, or significantly reduce their smoking of CC, and that such benefit outweighs the risk to youth. We conclude that the marketing of the new products, subject to certain marketing restrictions and postmarket requirements, is APPH.

FDA's evaluation of these PMTAs determined that they contain sufficient information to characterize the new products' composition and design, and that there are adequate process controls and quality assurance procedures to help ensure the new products are manufactured consistently. The applicant provided the target specifications, range limits, and test data necessary to characterize the new products' design; adequately characterized the components and sub-components of the new products; and provided a description of operation and validation of function for various protection mechanisms for the new products. The new products were compared to CC and ENDS because the applicant identified that the new products are intended for adults who currently smoke CC and adults who currently use ENDS.

FDA's conclusions regarding the adult benefits of the new products are based on our evaluation of their abuse liability; cancer and noncancer risks; adult perceptions about the new products, including those who do not use tobacco; and adult and youth use behaviors. Importantly, based on the information provided in the PMTAs, the new products' abuse liability (i.e., ability to promote continued use, dependence, or addiction) in ENDS-naïve adults is lower than that of CC and higher than that of 4 mg nicotine gum. With ENDS experience, adults who use CC might reach nicotine levels that are higher than those observed in the applicant's submitted study, and more comparable to CC. Therefore, the new products' abuse liability is likely similar to that of CC in ENDS-experienced adults. The new products have a nicotine salt formulation, which is known to be associated with

higher nicotine exposures that are comparable to CC. A recently published study has also demonstrated that the nicotine flux (i.e., the nicotine emission rate) of the tested Vuse Alto product (Rich Tobacco, 5% nicotine) is similar to CC (Talih et al., 2023). Their similar nicotine delivery to CC suggests that these new products may be a more substitutable replacement for CC and facilitate complete switching/CC cessation more than ENDS with lower nicotine delivery or nicotine gum. Because the new products have an abuse liability similar to CC, it is likely that adults who completely switch to the new products will also maintain ENDS use without reinitiating CC use. The nicotine levels may pose an addiction risk for non-tobacco users. However, this risk is no higher than that of other currently available tobacco products (such as CC) because the abuse liability of the new products is not likely to exceed that of CC even among those who gain experience using the new products.

The toxicological evaluation of the new products indicates that the noncancer hazard risk to users of the new products is likely to be lower relative to CC. In addition, the new products' cumulative estimated lifetime cancer risk ($ELCR_c$) predicts that people who exclusively use the new products will have lower cancer risks than people who smoke CC. When compared to the median for CTP-authorized ENDS as of February 2024, the new products' $ELCR_c$ are a mixture of higher (i.e., PM0000973.PD2, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11) and lower risk (i.e., PM0000973.PD3). However, based on the small number of CTP-authorized ENDS, Tiers 1-4 $ELCR_c$ comparison to CC is considered an appropriate toxicological assessment for the new products. Based on the chemical evaluation of the new products' aerosols, the new products have lower levels of many carcinogenic HPHCs (e.g., carbonyls, volatile organic compounds (VOCs), metals) compared to CC. These findings, taken together with abuse liability findings, suggest that these new products will benefit adults who smoke CC and completely switch to the new products, or significantly reduce CC, as compared to those who continue to use CC exclusively.

Regarding tobacco use behavior, the applicant submitted data from two repeated cross-sectional surveys and a 12-month longitudinal study. In one of the applicant's cross-sectional studies (conducted in 2018-2019), about 92% of participants who reported current established use of Vuse Alto also reported a prior history of CC use and about 27% reported former established use of CC. Since the applicant's submission, data from PATH Study Wave 7 (2022-2023) were released. Epidemiology found that the findings of the applicant's cross-sectional studies were consistent with analysis of PATH Study Wave 7.

Longitudinal transitions in tobacco use behavior in adults who use CC (i.e., the transition to dual use or complete switching) were evaluated using the Colorado Longitudinal Study and the PATH Study Waves 1-3. The results of these analyses indicated that complete switching does occur among adults using CC or among adults with dual use of ENDS and CC, although estimates of the magnitude of switching over a given period differed. The applicant also found that among adults with dual use of ENDS and CC, daily use of ENDS is a strong predictor of both complete switching and significant reduction in CC use. However, these analyses were not brand, product, or flavor-specific, and conclusions regarding complete switching were bridged from all ENDS users. Furthermore, the magnitude of estimates concerning complete switching are lower than those typically seen in the current literature. Therefore, no data were provided on complete switching by adults who use the new products.

In the likelihood of use studies, which assessed perceptions, appeal, and intent to use, people who currently use tobacco (i.e., current established CC use, current established non-CC tobacco use,

current tobacco experimentation) reported the greatest intent to purchase the new products. In support, analyses reviewed by epidemiology demonstrated that the new products are widely used by adults who use ENDS. Additionally, among current tobacco users who indicated any interest in purchasing Vuse Alto, "to stop smoking" was a main reason for interest in using Vuse Alto.

Taken together, use behavior findings demonstrated that the new products are widely used by adults who use tobacco products such as CC, or formerly used tobacco products such as CC. Most adults who initiate use of the new products are expected to currently use CC. Additionally, many adults who use the new products are expected to be former CC users, which may be indicative of complete switching. However, for these new products, the behavioral findings alone are not sufficient to demonstrate the potential adult benefit of the new products. Rather, it is the balance of findings concerning abuse liability, toxicant exposure, use behavior, and likelihood of use that demonstrate the potential adult benefit of the new products.

In terms of the risks to non-users, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. However, the risk of the new products to youth are likely to be low compared to other ENDS. Surveillance via the National Youth Tobacco Survey has consistently indicated that use of tobacco-flavored ENDS accounts for a small fraction (6.4% in 2023) of middle and high school student ENDS use compared to other flavors (e.g., fruit, candy, mint). This surveillance has also demonstrated that, among youth who used ENDS in 2023, 8.7% reported using "Vuse" products as their usual brand. The applicant's likelihood of use study findings indicated that those who did not use tobacco generally perceived similarly high risk and addictiveness for Vuse Alto, other ENDS, and CC, though Vuse Alto and other ENDS were generally rated slightly lower risk and addictiveness compared to CC. Appeal of Vuse Alto products was low among those who did not use tobacco and almost identical to appeal of other ENDS. Those who did not use tobacco were also less likely to select "Rich Tobacco" or "Golden Tobacco" as flavors of most interest compared to menthol and fruit flavors. Compared to groups currently using tobacco, groups who did not use tobacco had significantly lower intentions to purchase Vuse Alto. While purchase intent was low across groups that used tobacco, the young adult subsample of those with current established CC use and former tobacco use did have significantly higher purchase intent than their full sample counterparts. Given this, and the strong evidence regarding the impact of youth exposure to marketing on youth appeal and initiation of tobacco use, a marketing authorization for the new products should include marketing restrictions and postmarket requirements to help ensure that youth exposure to tobacco marketing is limited. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit adults who use CC who switch completely or significantly reduce their CC use would outweigh the risk to youth, provided the applicant follows marketing restrictions and postmarket requirements aimed at reducing youth exposure and access to the products.

The applicant proposed a (b) (4) shelf life for the new products. The applicant did not provide sufficient data for chemical and microbial stability that would allow FDA to evaluate whether all new products are stable over the proposed shelf life of (b) (4). However, the lack of microbial and chemical stability data for (b) (4) does not preclude a finding that the marketing of the new products is APPH. Overall, the applicant provided adequate chemical stability, leachables, and microbial stability data and bridging rationale to support a shelf life of (b) (4) for PM0000973.PD2 and PM0000973.PD3, and a shelf life of (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11. Therefore, based on the data provided

by the applicant, any marketing authorization for the new products should limit the shelf life of the new products accordingly, while also allowing for shelf life to be extended with postmarket submissions of additional stability data.

Although engineering noted two limitations regarding potential unintentional activation and dry puffing these limitations do not preclude a finding that marketing of the new products is APPH. First, the new products are airflow activated, and therefore pose some risk of overheating, fires, and explosions from unintentional activation and dry puff conditions. Sustained or repeated pressure differential can cause continued activation and overheating of the heating element, particularly under low e-liquid levels that can lead to dry puff conditions. Although the applications did not adequately address the potential unintentional activation of the new products, this limitation is acceptable from engineering's perspective because the product-specific design and protection mechanisms (e.g., battery short circuit protection (UL 1642) and 5-second maximum puff duration) may mitigate these risks. Users can also remove the cartridge from the power unit to prevent unintentional activation, which further mitigates the risk. Currently, there is limited information available in published literature on the risks of unintentional activation of ENDS, so there are not sufficient data to be able to determine the acceptable level of mitigation from an engineering perspective. Notably, as of the date of the TPL, there have been no AEs reported to the FDA Safety Reporting Portal (SRP) associated with the unintentional activation of the new products. Therefore, given the above, this limitation of evidence can be addressed through the manufacturer's postmarket reporting obligations that will allow FDA to monitor and assess reported adverse events of overheating, fires, and explosions associated with unintentional activation and dry puff conditions.

Second, the new products may increase exposure to HPHCs under dry puff conditions because operation of the new products under low e-liquid levels could cause thermal decomposition of the e-liquid or heating element. The lack of HPHC aerosol data or thermal profile of the heating element under dry puff conditions is a limitation. However, this limitation does not preclude a finding that marketing of the new products is APPH. The design features and control mechanisms of the new products (e.g., ceramic wick, battery short circuit protection, and 5-second maximum puff duration) may mitigate the risks associated with dry puffing. Additionally, the potential impact of increased HPHC exposure from dry puff conditions can be weighed against other evidence submitted by the applicant. The applicant provided HPHC aerosol yields of the new products under non-intense and intense puffing conditions, showing lower levels of HPHCs compared to CC. This information offsets the risk of increased exposure to HPHC aerosols from dry puffing, which is expected to be limited to infrequent and brief exposures near the end-of-life of the new products. Furthermore, a review of adverse experiences (AEs) submitted to the FDA SRP do not show any cases of AEs in the new products specifically attributed to the risks related to unintentional activation and dry puffing.

Based on my review of the subject PMTAs and the available evidence, I find that permitting the marketing of the new products, as described in the applications and specified in Appendix, Table 3, 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 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 marketing granted orders.

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

Marketing granted orders should be issued for the new products that are the subject of this review, as identified on the cover page of this review. The orders should limit shelf life to (b) (4) for PM0000973.PD2 and PM0000973.PD3, and to (b) (4) for PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, and PM0000973.PD11. The order letter for the new products should note that these shelf lives may be extended to (b) (4) with additional stability data submitted in postmarket reports.

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7. APPENDIX

Appendix A. New products

Table 3. New products subject to Granted Orders

Common Attributes of PMTAs[15,16,17,18]	
Submission Date	September 4, 2020
Receipt Date	September 4, 2020
Applicant	R.J. Reynolds Vapor Company
Product Manufacturer	R.J. Reynolds Vapor Company
Product Category	Electronic Nicotine Delivery Systems (ENDS) (VAPES)
Attributes	**New Tobacco Product**
STN	**PM0000973. PD1**
Product Name	Vuse Alto Power Unit
Product Subcategory	ENDS Component
Package Type	Carton
Product Quantity	1 Power Unit
Characterizing Flavor (CF)	Unflavored
Nicotine Source	None
Additional Property	Length: 89.4 mm, Diameter: 19.2 mm, Wattage: 6.5 W, Battery capacity: 370 mAh
STN	**PM0000973.PD2**
Product Name	Vuse Alto Pod Golden Tobacco 5%
Product Subcategory	Closed E-Liquid
Package Type	Cartridge
Product Quantity	1 Cartridge
Characterizing Flavor (CF)	Tobacco
Nicotine Source	Tobacco
Nicotine Concentration	57.8 mg/mL
PG/VG Ratio	45/55
E-Liquid Volume	1.8 mL
Additional Property	Length: 46.1 mm, Diameter: 19.0 mm

[15] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.
[16] Product name is brand/sub-brand or other commercial name used in commercial distribution.
[17] Effective April 14, 2022, FDA's authority to regulate tobacco products was extended to include tobacco products containing nicotine from any source. Therefore, nicotine source should be included in future submissions.
[18] Attributes in Appendix A may display converted values.

Attributes	New Tobacco Product
STN	**PM0000973.PD3**
Product Name	Vuse Alto Pod Rich Tobacco 5%
Product Subcategory	Closed E-Liquid
Package Type	Cartridge
Product Quantity	1 Cartridge
Characterizing Flavor	Tobacco
Nicotine Source	Tobacco
Nicotine Concentration	57.8 mg/mL
PG/VG Ratio	45/55
E-Liquid Volume	1.8 mL
Additional Property	Length: 46.1 mm, Diameter: 19.0 mm
STN	**PM0000973.PD6**
Product Name	Vuse Alto Pod Golden Tobacco 2.4%
Product Subcategory	Closed E-Liquid
Package Type	Cartridge
Product Quantity	1 Cartridge
Characterizing Flavor	Tobacco
Nicotine Source	Tobacco
Nicotine Concentration	27.4 mg/mL
PG/VG Ratio	48/52
E-Liquid Volume	1.8 mL
Additional Property	Length: 46.1 mm, Diameter: 19.0 mm
STN	**PM0000973.PD7**
Product Name	Vuse Alto Pod Rich Tobacco 2.4%
Product Subcategory	Closed E-Liquid
Package Type	Cartridge
Product Quantity	1 Cartridge
Characterizing Flavor	Tobacco
Nicotine Source	Tobacco
Nicotine Concentration	27.4 mg/mL
PG/VG Ratio	47/53
E-Liquid Volume	1.8 mL
Additional Property	Length: 46.1 mm, Diameter: 19.0 mm
STN	**PM0000973.PD10**
Product Name	Vuse Alto Pod Golden Tobacco 1.8%
Product Subcategory	Closed E-Liquid
Package Type	Cartridge
Product Quantity	1 Cartridge
Characterizing Flavor	Tobacco
Nicotine Source	Tobacco
Nicotine Concentration	20.6 mg/mL
PG/VG Ratio	48/52
E-Liquid Volume	1.8 mL
Additional Property	Length: 46.1 mm, Diameter: 19.0 mm

Attributes	New Tobacco Product
STN	**PM0000973.PD11**
Product Name	Vuse Alto Pod Rich Tobacco 1.8%
Product Subcategory	Closed E-Liquid
Package Type	Cartridge
Product Quantity	1 Cartridge
Characterizing Flavor	Tobacco
Nicotine Source	Tobacco
Nicotine Concentration	20.5 mg/mL
PG/VG Ratio	48/52
E-Liquid Volume	1.8 mL
Additional Property	Length: 46.1 mm, Diameter: 19.0 mm

Appendix B. Amendments and additional submissions received

Table 4. Amendments

Submit Date	Receipt Date	Applications being amended	Reviewed	Brief Description
April 17, 2021	April 17, 2021	All	Yes	Updated product images and interim stability reports
August 24, 2021	August 24, 2021	All	Yes	Final 24-month stability report
September 21, 2021	September 21, 2021	All	No	Request to add four new PMTAs[7]
June 20, 2022	June 20, 2022	All	Yes	Interim packaging stability study report data
June 30, 2022	June 30, 2022	All	Yes	Response to FDA's June 17, 2022, Inspection Request letter
July 13, 2022	July 13, 2022	PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, PM0000973.PD11	Yes	Notification of additional manufacturing site
September 2, 2022	September 2, 2022	All	Yes	Notification of additional manufacturing site

Submit Date	Receipt Date	Applications being amended	Reviewed	Brief Description
September 14, 2022	September 14, 2022	All	Yes	Response to FDA's September 1, 2022, Inspection Request letter
October 3, 2022	October 3, 2022	All	Yes	Response to FDA's September 26, 2022, Inspection Request letter
January 13, 2023	January 13, 2023	PM0000973.PD2, PM0000973.PD3, PM0000973.PD6, PM0000973.PD7, PM0000973.PD10, PM0000973.PD11	Yes	Notification of additional manufacturing site
August 16, 2023	August 16, 2023	All	Yes	Response to FDA's May 19, 2023, Deficiency letter
September 22, 2023	September 22, 2023	All	Yes	Corrections to applicant's August 16, 2023, response to FDA's May 19, 2023, Deficiency letter and response to FDA's June 14, 2023, Correction letter