FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[1]	
Submission tracking numbers (STNs)	PM0000551, PM0000553, PM0000560
Common Attributes	
Submission date	October 10, 2019
Receipt date	October 17, 2019
Applicant	R.J. Reynolds Vapor Company
Product manufacturer	R.J. Reynolds Vapor Company
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component, Closed E-Cigarette
Cross-Referenced Submissions	
All STNs	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	None
Recommendation	
Issue marketing granted order for the new products that are the subject of this review.	

Technical Project Lead (TPL):

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Date: 2021.10.12 10:35:33 -04'00'

Berran Yucesoy, PhD, ATS, DABT
Deputy Director
Division of Nonclinical Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2021.10.12 10:53:11 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

[1] Tobacco product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application.

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1. EXECUTIVE SUMMARY

Based on the information provided in the application and other scientific data, as described in this Technical Project Lead 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*).

FDA's evaluation of these premarket tobacco product applications (PMTAs) determined that there are adequate process controls and quality assurance procedures to help ensure both the device and e-liquids are manufactured consistently. Based on the information provided in the PMTAs, the new products' abuse liability—i.e., ability to promote continued use, addiction, or dependence—is lower than combusted cigarettes and is similar to, or lower than, that of other ENDS. The overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in aerosol HPHCs of the new products compared to cigarettes, as evidenced by results of nonclinical studies. Further, significant reductions in blood and urinary biomarkers of exposure (e.g., volatile organic compounds (VOCs), tobacco-specific nitrosamines (TSNAs), and polycyclic aromatic hydrocarbons (PAHs)) after switching from cigarettes to the new products indicate that exposure to carcinogens and other toxicants present in cigarette smoke was greatly reduced in smokers who switched completely to the use of the new products. In the applicant's analysis, among all user groups (current established cigarette users, current established non-cigarette tobacco users, former tobacco users, and never tobacco users), current established cigarette users indicated the highest intentions to purchase Vuse Solo products, and the most preferred flavor among these individuals was the tobacco (original) flavor compared to non-tobacco flavors (e.g., mint, nectar, and tropical). Therefore, the applicant has demonstrated that current adult smokers are particularly interested in the new products to assist in intended switching, and these products have the potential to benefit that group as compared to continued exclusive cigarette use.

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. Existing evidence consistently indicates that use of tobacco-flavored ENDS is less common compared to non-tobacco flavored ENDS among youth. In addition, the applicant's study findings demonstrated low intention to purchase the new products among adult never and former established tobacco users. Nonetheless, given the strong evidence regarding the impact of youth exposure to marketing on youth appeal and initiation of tobacco use, a marketing authorization 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 smokers who switch completely or significantly reduce their cigarette use would outweigh the risk to youth, provided the applicant follows post-marketing requirements aimed at reducing youth exposure and access to the products.

Regarding product stability, the applicant stated that the shelf life of the new products is (b) (4) . The applicant provided chemistry data to support that the new products are chemically stable over (b) (4) . However, the applicant did not provide microbial data that would allow FDA to evaluate whether the products are microbially stable over (b) (4) . The applicant instead provided data that supports microbial stability of the products over (b) (4) . Because the microbial stability data for (b) (4) is acceptable and indicates that the products are low-risk for microbial growth over a (b) (4) period and because there are no other stability concerns, the lack of microbial data for (b) (4) does not preclude an APPH finding for the products.

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

2. BACKGROUND

2.1. NEW TOBACCO PRODUCTS

The applicant submitted information for the three new tobacco products listed on the cover page and with more detail in the Appendix, sold under the brand names Vuse and Vuse Solo. Briefly, a complete Vuse Solo ENDS is composed of a rechargeable Power Unit (device) (PM0000551), a prefilled replacement cartridge containing the e-liquids, and an accessory USB charger for the power unit. The power unit and cartridge settings are not adjustable by the user. There are two cartridge designs: generation 1 (G1) (PM0000553) and generation 2 (G2) (PM0000560). The primary differences between the two designs are the outer tube material (G1 stainless steel, G2 (b) (4)) and the placement of the authentication/memory chip. Each cartridge design contains e-liquids in original (tobacco) flavor.

2.2. REGULATORY ACTIVITY

On October 17, 2019, FDA received 3 PMTAs from R. J. Reynolds (RJR) Vapor Company. FDA issued an Acceptance letter to the applicant on October 30, 2019. FDA issued a Filing letter to the applicant on November 22, 2019. FDA issued a Deficiency letter to the applicant on May 19, 2020.

Refer to the Appendix, Table 4 for a complete list of amendments received by FDA.

2.3. SCOPE OF REVIEW

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

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Engineering	Ryan Andress	5/18/2020	Ryan Andress	10/12/2021
Chemistry	Jikun Liu	5/19/2020	Jikun Liu	10/07/2021
Microbiology	David Craft	5/18/2020	Aimee Cunningham	10/12/2021
Toxicology	Steven Yee	5/18/2020	Thomas Hill	10/08/2021
Behavioral & Clinical Pharmacology	Mollie Miller	5/18/2020	Allison Kurti	10/12/2021
Medical	Lester Lacorte	5/19/2020	Lester Lacorte	10/08/2021
Epidemiology	Blair Coleman	5/19/2020	Jamal Jones	10/12/2021
Social Science	Katherine Margolis	5/18/2020	Andrea Ruybal	10/12/2021
Environmental Science	William Brenner	5/18/2020	Yasmin Termeh-Zonoozi	10/06/2021
OCE – Manufacturing/Lab	Lara Williams	5/19/2020	N/A	N/A
OCE – BIMO	Tara C. Singh	5/19/2020	N/A	N/A

Table 2. Consultations

Discipline or Office	Reviewer(s)	Review Date
Statistics	Ruben Montes de Oca	5/19/2020
OCE – DPAL	Julie Nguyen	5/19/2020
Tobacco Product Surveillance Team (TPST)	Susan Rudy	3/04/2021
OHCE	Emily Talbert	10/12/2021

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

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

- Newport Gold data was chosen as cigarette comparison data. The applicant stated that the reason to use this data was because Newport Gold was the only RJR cigarette that had received a marketing order at the time of testing. Newport Gold was used for the HPHC comparative analysis studies, in vitro toxicity studies, and in vivo inhalation studies. The chemistry review found Newport Gold as an appropriate combusted tobacco comparison product as the applicant provided adequate data and rationale to support their chosen comparison product. However, since it may not represent the U.S. cigarette market, the chemistry review introduced additional datasets from other combusted tobacco comparison products (3R4F research cigarette and the FDA 50 cigarettes) for comparative HPHC analysis to comprehensively elucidate the differences in product characteristics between the two different categories of tobacco products.
- Data from three closed ENDS market comparison products were chosen to cover a range of aerosol deliveries and flavors (tobacco, menthol, and fruit) and because of their significant market share among closed ENDS at the time studies were initiated. In comparative HPHC analysis studies, the new products were compared against select ENDS market comparison product data (Blu PLUS+ Classic Tobacco, Magnificent Menthol, and Cherry Crush; Logic Pro Tobacco, Menthol, and Cherry; and Mistic 2.0 Tobacco, Menthol, and Strawberry Splash) and for in vitro toxicity studies, comparisons were made against Blu PLUS+ Classic Tobacco, Magnificent Menthol, and Cherry Crush. The chemistry review concluded that the applicant's rationale for the selection of ENDS comparison data is reasonable.
- The engineering review indicates that the applicant provided draw resistance and aerosol mass-based particle size distribution data for Vuse Vibe and Vuse Ciro products as market comparison data.
- The behavioral and clinical pharmacology (BCP) review indicates that the applicant used data from usual brand (UB) cigarettes or Newport Gold Non-menthol King cigarettes (CSD170304) as comparison data in clinical studies that provided data on abuse liability and BOE. While 4mg NRT (nicotine replacement therapy) gum was used as a comparison product in three clinical studies (CSD170401, CSD1303, and CSD1304) that provided data on abuse liability and biomarkers of exposure (BOE) associated with using the new products, blu PLUS Classic Tobacco, Logic Pro Tobacco, Mistic 2.0 POD MOD products were used as comparison ENDS in another

clinical study (CSD170304) that provided data on abuse liability of the products in PM0000553 and PM0000554. From a BCP perspective, the comparison products are appropriate comparisons for the new products.

- The previous version of Vuse Solo G1 Original product was used in four of the clinical studies (CSD1302, CSD1303, CSD1304, and CSD1503). Per chemistry and engineering reviews, the applicant provided sufficient information to determine that ingredients, aerosol constituent levels, and design parameters of the previous version are comparable with the Vuse Solo G1 product in the PMTA.

3.1.2. Synthesis

As TPL, I agree with chemistry and engineering reviews that the applicant's rationale for the selection of cigarette and ENDS as comparison products of the new products is appropriate and the applicant provided adequate data to support the comparison between the new products and their chosen comparison products. In addition, selection rationale for cigarette and ENDS market comparators are reasonable and the information provided by the applicant demonstrates that product composition and design parameters for the previous versions of the Vuse Solo G1 original product used in submitted clinical studies are comparable with their current versions in the PMTAs. I also agree with the BCP review that comparison data used in the BOE and abuse liability studies are appropriate.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

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

3.2.1.1. Product design and composition

Per the chemistry review:

- The new product e-liquids contain nicotine salt formulations (nicotine lactate and nicotine levulinate), which may be easier (i.e., less irritating) to inhale at high nicotine concentrations[1-3], thereby facilitating initiation and use of ENDS with high amounts of nicotine. Chemistry deferred to toxicology, medical, BCP, and social science disciplines for the evaluation of toxicological and sensory effects of the nicotine salts in the new products. As discussed in Sections 3.3-3.6, based on clinical and nonclinical studies provided by the applicant, these disciplines did not find any potential concerns regarding the impact of nicotine salts in the new products.

Per the engineering review:

- For the previous version of Vuse Solo G1, used in clinical studies CSD1302, CSD1303, CSD1304, and CSD1503, the applicant did not provide specifications for air flow rate, coil temperature, power delivery unit wattage operating range, inhaled aerosol temperature, and e-liquid viscosity. Although these design parameters may affect HPHC yields and related toxicities[4-10], chemistry and toxicology disciplines concluded that, given the magnitude and statistical significance of the decreases in HPHC yields in the Vuse Solo aerosol compared to combusted tobacco products and comparable HPHC levels with ENDS market comparison data, it is unlikely that the absence of these design parameters will raise concerns.
- For the previous version of the new products in PM0000553, used in clinical studies CSD1302, CSD1303, CSD1304, and CSD1503, the wick material is different than the

wick material used in the new product according to the material safety data sheet. The difference in wick material may affect wicking rate[6,11] and, therefore, the impact of wick material on HPHC yields is deferred to chemistry for evaluation. Chemistry concluded that changes in aerosol constituent levels of the prior and current versions of the new products are comparable.

- For all PMTAs, the air flow rate is uncontrolled and may affect HPHC yields.[4] The impact of uncontrolled air flow rate on HPHC yields is deferred to chemistry for evaluation. Chemistry concluded that the HPHC yields of the new products are significantly lower than the combusted cigarettes despite any potential effect of the air flow rate.
- For PM0000553, the Design Failure Mode Effects Analysis shows an increased risk for e-liquid exposure when external force is applied. There is an occasional probability of occurrence of the external tube separating from the mouth end cap. Oral, dermal, or ocular exposure to e-liquids containing nicotine can cause adverse health effects, including seizures, anoxic brain injury, vomiting, and lactic acidosis, and may be fatal.[12] Engineering defers the health impact of e-liquid exposure to medical for evaluation. Medical concluded that the health risk of fluid leakage and subsequent exposure to leaked chemical constituents cannot be ascertained or quantified, particularly since exact quantities of constituent exposure from potential e-liquid leakage is unknown. However, although the possibility of accidental exposure remains, these concerns have been reduced by the product design (i.e., closed pod-based non-refillable system). In addition, post-market manufacturer reporting obligations will allow FDA to monitor and assess any issues with accidental exposure.
- For PM0000553, the applicant does not provide a target specification for cartridge resistance. Cartridge resistance may affect HPHC yields[11, 13] and, therefore, engineering deferred the impact of cartridge resistance on HPHC yields to chemistry for evaluation. Chemistry concluded that it is unlikely that product characteristics negatively impact the aerosol constituent levels of the new products as the aerosol constituent levels are significantly lower than the combusted cigarette.

Per the microbiology review:

- Stability data indicate that the new products in the PMTAs are low-risk for microbial growth over a (b) (4) time period (see 3.1.2.3 for details).

3.2.1.2. Manufacturing

- FDA has conducted an inspection of the applicant's manufacturing facility at 7855 King-Tobaccoville Road, Tobaccoville, NC 27050 in February 2020. From the chemistry, engineering, and microbiology perspectives, the applicant demonstrates that the new products are manufactured in a consistent manner that minimizes variability in product quality.

3.2.1.3. Product stability

Per the chemistry review:

- The analytical methods used in the stability studies were fit for purpose and fully validated.
- The aerosol yields of nicotine, propylene glycol (PG) and vegetable glycerin (VG) from the new products fell within their acceptance limits (b) (4) % of T0 aerosol

constituent levels) over (b) (4) . From a chemistry perspective, the new products are chemically stable within the applicant-proposed (b) (4) shelf life.

- Variation in atmospheric CO_2 levels caused the variation in the measured air pH but did not affect the aerosol emissions of the new products in the stability studies.

Per the microbiology review:

- The microbial stability data is necessary for the proposed shelf life as bacterial communities change as a function of storage time.[14, 15] Increased microbial growth over time can impact stability of the product and may result in an increased risk to public health as the product sits in storage. Microbial stability study data (total aerobic microbial counts (TAMC), total yeast and mold counts (TYMC), and water activity (a_w)) were provided for the new finished products at times (b) (4) . The data provided indicates that the products are low-risk for microbial growth over a (b) (4) time period. However, the applicant's proposed shelf life is (b) (4) . The applicant also provided bulk e-liquid a_w data at time (b) (4) and at (b) (4) . However, FDA only considers finished product data (in this case, up to (b) (4)) because further manufacturing from a bulk e-liquid into the finished product could affect microbiological stability (i.e., possible introduction of contaminants during filling, or use of a different container closure system). Therefore, the data provided are sufficient to demonstrate the microbial stability of the products over (b) (4) , but not sufficient to demonstrate the microbial stability of the products over the applicant-proposed shelf life of (b) (4) .

3.2.1.4. Product test data

Per the chemistry review:

- The aerosol HPHC yields of the new products are tested using the power unit in PM0000551. There are significant reductions in HPHCs from the new products' aerosols compared to cigarette comparison data under intense and non-intense regimens.
- The intense and non-intense aerosol yields of some constituents (e.g., PG, VG, acetaldehyde, and formaldehyde) from the new products are increased compared to ENDS market comparisons. However, aerosol levels of these HPHC are significantly below the levels present in cigarette smoke.
- The discrepancy between the intense aerosol formaldehyde yields of (b) (4) and (b) (4) may be caused by different carbonyl methods used, high method variation in the determination of low formaldehyde yields, unstable coil temperature in the intense aerosol testing, occurrence of dry-puff phenomenon, and device manufacturing variability. The amount of formaldehyde only accounts for less than 0.5% of total aerosol constituent weight, and the aerosol level of formaldehyde is lower than that of the levels in cigarette smoke. The variation of aerosol formaldehyde will not impact the stability of the new products.
- The e-liquid ingredients and aerosol constituent yields of the current new product in PM0000553 differ from their previous version. Chemistry deferred to BCP discipline to determine whether the test results of the prior version of the new product in clinical studies CSD1302 – CSD1304 and CSD1503 can be bridged to the current version. BCP concluded that nicotine yield comparisons for the predecessor used in these clinical studies and the new product in PM0000553 are sufficiently comparable to support bridging.

Per the engineering review:

- The power unit (PM0000551) contains a rechargeable lithium battery and printed circuit board assembly (PCBA) and is packaged with a universal serial bus (USB) charger. The battery is certified to IEC 62133:2012, UN38.3, and UL 1642 standards. The applicant controls battery cycle life by limiting the power unit to (b) (4) cycles, which is below the battery vendor specification. Charging and output power is controlled by the PCBA. The applicant provides power, temperature, and functionality test data to show that specifications have been met. The new products do not have user settings and cannot be modified by the user.
- The replacement cartridges are closed systems and contain e-liquid and a heater wick assembly. The cartridges have a proprietary snap-fit connection, unique to Vuse Solo ENDS, and a cartridge authentication system. The heater is pressure activated and will remain on for up to 4 s of puff time, with a minimum (b) (4) between activations. Additionally, the replacement cartridges are factory programmed to have (b) (4) s of puff time stored in the microchip memory. These design features prevent product tampering and may mitigate dry puffing.
- For the new products, measured wet bulb aerosol temperatures do not exceed 44°C, however, dry bulb aerosol temperatures up to 90°C were reported. 60°C saturated air is the hottest air that can be breathed without injury[16], but wet bulb temperatures up to 50°C can be tolerated for up to one hour.[17] Therefore, engineering deferred the health impact of aerosol dry bulb temperatures above 60°C to medical for evaluation. From a medical perspective, based on published literature and the lack of consumer reports for the adverse experiences (AEs)[2], the health risk of thermal and aerosol inhalation injury appears to be low.
- For the new products, coil temperature is uncontrolled and, in general, increases with each puff. Heater coil temperature is generally correlated with carbonyl emissions[18-20] and, therefore, the impact of uncontrolled coil temperatures on HPHC yields is deferred to chemistry for evaluation. Chemistry concluded that it is unlikely that product characteristics negatively impact the aerosol constituent levels of the new products as the aerosol constituent levels are significantly lower than the combusted cigarette.
- For the new products, the measured maximum surface temperatures, including the mouth end cap, external tube, and power unit, are at or below 40°C and are appropriate from an engineering perspective.
- Based on the information provided in the PMTAs for the device and replacement cartridges, adequate manufacturing processes and controls were used to ensure that the new products meet manufacturer's specifications and they will operate consistently throughout the life of the product.

3.2.2. Synthesis

As TPL, I agree with engineering, chemistry, and microbiology conclusions that these PMTAs contain sufficient information to characterize the product design and adequate manufacturing processes and controls to help ensure that the new products will operate consistently throughout the life of the product and according to the manufacturer's specifications. I also agree with these discipline reviews that there is sufficient information for product design and manufacturing and the new products contain significantly lower

[2] *Adverse experiences* refer to any adverse report (experience or effect or event) associated with the use of the new products.

levels (*greater than 65% decreases in aerosol HPHCs such as aromatic amines, carbonyls, and TSNAs*) of measured HPHCs when compared to combusted comparison data.

Per the microbiology review, the microbial stability data (TAMC, TYMC, and a_w) for the finished new products support microbial stability for (b) (4) . However, the applicant's proposed shelf life is (b) (4) . To determine the stability of these products for the entire shelf life, microbiology would need additional data beyond (b) (4) . I agree with this conclusion. However, because the stability data for (b) (4) is acceptable and indicates that the products are low-risk for microbial growth over a (b) (4) period and because there are no other stability concerns, the lack of microbial stability data for (b) (4) does not preclude an APPH finding for the new products.

3.3. ABUSE LIABILITY

3.3.1. Discipline key findings

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

3.3.1.1. Current tobacco users

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. In ENDS naïve exclusive smokers, the abuse liability of the new products in PMTAs is lower than that of combusted cigarettes. For PM0000560, the abuse liability is slightly greater than 4mg NRT gum, evidenced by similar nicotine uptake and subjective effects after acute use, which may increase the likelihood of its use and adherence compared to NRT in smokers interested in quitting combusted cigarette smoking. Overall, the low abuse liability of the new products among adult naïve ENDS users suggests a low likelihood of initiation with any of the products in the PMTAs among adult current tobacco product users.
- The abuse liability of the new product in PM0000553 is lower than the abuse liability of combusted cigarettes following acute use (CSD170304 and CSD1303), and after five days of complete switching from combusted cigarettes to PM0000553 (CSD1304). The abuse liability of PM0000553 is similar to, or lower than, that of other ENDS device comparisons evaluated (CSD170304). Similarly, the abuse liability of the new product in PM0000560 is lower than the abuse liability of combusted cigarettes following acute use (CSD170401 and CSD1502), and after five days of switching from combusted cigarettes to PM0000560 (CSD170501). Although PM0000560 was not explicitly compared to other ENDS like PM0000553, BCP determined that the new product in PM0000553 could be bridged to the new product in PM0000560.
- The abuse liability of the new products following extended use cannot be determined as the switching studies were conducted over five-day in-clinic studies among exclusive smokers who used the new products over a short-term period. The

abuse liability of these new products used long-term in one's naturalistic environment was not evaluated. However, previous research has shown experienced ENDS users can achieve comparable nicotine uptake from ENDS relative to combusted cigarettes. Therefore, extended use of the new products may permit users to obtain higher nicotine uptake than what was observed in the applicant's clinical studies. Although more extended use may facilitate switching, long-term use of the new products was not explicitly examined by the applicant.

3.3.2. Synthesis

Per the BCP review, the evaluation of nicotine pharmacokinetic (PK) and subjective effects indicate that the abuse liability of the new products is lower than cigarettes in ENDS naïve exclusive smokers. Based on (a) existing literature showing that inexperienced users may obtain less nicotine from ENDS than experienced users, and (b) applicant-submitted information indicating low abuse liability of the new products under acute use conditions, it is possible that a naïve/non-user may not be able to achieve nicotine levels that would sustain ongoing use and the development of dependence. However, evidence shows that experienced ENDS users can attain higher Cmax plasma nicotine concentrations than inexperienced users,[21, 22] and these levels can even reach similar levels to those of cigarette smokers.[23, 24] Therefore, extended use of the new products may result in higher nicotine uptake than seen in the applicant's clinical studies and this may facilitate switching among current smokers. However, long-term use was not explicitly examined. In addition, as compared to non-daily ENDS use, daily use of the new products with concomitant reduction in cigarettes per day (CPD) may result in equivalent or lower nicotine dependence compared to exclusive cigarette smoking.

Although conclusions on long-term health benefits cannot be made at this point, as TPL, I agree with the BCP conclusion that based on the findings across all clinical studies included in the PMTAs, the abuse liability of the new products is lower than combusted cigarettes and are similar to, or lower than, that of other ENDS comparisons evaluated. However, with experience, users might reach higher nicotine levels to satisfy the withdrawal and craving symptoms. This is potentially beneficial for smokers trying to switch to ENDS as they are more likely to have satisfactory results and not resume cigarette smoking. In addition, slightly greater abuse liability of the new products than 4mg NRT gum may increase the likelihood of use of these products compared to nicotine gum among smokers interested in quitting. The nicotine levels may pose an addiction risk for non-tobacco users; however, the risk is no higher than other currently available tobacco products due to relatively low abuse liability of the new products.

3.4. USER POPULATIONS

3.4.1. Discipline key findings

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

3.4.1.1. Intended user population

Per the BCP and epidemiology reviews:

- The applicant states that use of the new products is likely to be higher among current tobacco users (in particular, current cigarette smokers) than among non-users of tobacco.

Per the social science review:

- The applicant notes that the mean projected product use rate among adult current established combusted cigarette users for the new products is 9.1%. However, due to limitations identified with the algorithm study in cycle 1 review (e.g., it was not validated with ENDS or the new products, the algorithm overestimated combusted cigarette purchases), this is likely an overestimation and the results of the study should be taken with caution.
- In another study, the applicant provided data on predicted product use, intentions to use the products based on main reasons for interest, and behavioral intentions regarding how the products will be used. Based on this information, the likely users of the new products include current established combusted cigarette users. In this study, 66.8% of current established tobacco users were interested in the new products. Although it is unclear which products they typically use (i.e., combusted cigarettes and ENDS, only combusted cigarettes, other tobacco products), many questions asked respondents about intentions to quit or reduce smoking.

3.4.1.2. Current tobacco users

Per the social science review:

- The applicant's algorithm study was not validated with ENDS or the new products and as such may overestimate product purchase of combusted cigarettes. However, among adults, the projected product use rate was highest among current established combusted cigarette users (9.1%), followed by current established non-combusted cigarette tobacco users (2.2%).
- Among adult current combusted cigarette users sampled, 45% said they intended to stop smoking completely and use the new products instead. However, the applicant's analysis of data from the Population Assessment of Tobacco and Health (PATH) Study (across Waves 1-3) indicated that 1.5% of adults who were exclusive combusted cigarette users transitioned to exclusive ENDS use. It is plausible that the discrepancy in values between behavioral intention and complete switching may be due to the fact that the applicant study assessed intention to completely switch for the new products while the PATH Study assessed complete switching for general ENDS. The discrepancy may also be attributed to the moderate relationship between behavioral intention and future tobacco use behavior due to the addictive nature of tobacco products.[25, 26]
- Among current combusted cigarette users with intentions to purchase the Vuse Solo products, 28.6% preferred "original"[3]/tobacco flavored, 23.2% preferred menthol flavored and interest in non-tobacco/non-menthol flavored products[4] varied from 6.4% to 14.7% depending on the specific flavor. Overall, 51.9% preferred original or menthol and 47.6% preferred the non-tobacco and non-menthol flavored products.
- Regarding main reasons for interest in the new products, few statistical differences were observed across product flavors in 84 different comparisons that compared

[3] "*Original*" refers to the applicant-provided characterizing flavor for PM0000553 and PM0000560 which are tobacco-flavored.
[4] FDA uses the term '*tobacco-flavored products*' to reflect products which are sometimes referred to as "*non-flavored*" or "*unflavored*" in the published literature. FDA uses the term '*non-tobacco flavored products*' for all other products.

each flavor to all other flavors across all reasons for use. Combusted cigarette users with any purchase intent who selected original (26.4%) as their most preferred flavor were more likely to report intentions to use these flavors to stop smoking, compared to users who selected mint flavor (12.7%). There were no significant differences among other flavors and interest in each flavor to help quit smoking ranged from 16.1-23.7%.

- The main reasons for interest in purchasing the new products among combusted cigarette users were to either reduce combusted cigarette usage (14.6-19.7%) or to stop smoking all together (12.7-26.4%). Other common reasons included curiosity (8.8-16.4%) and enjoyable flavors (3.3-14.3%). Percentages varied based on specific flavor.
- Most respondents indicated that their intended behavioral change with the new products was to switch to the product (38.5-52.8%) or to dual use (combusted cigarettes and the new products, 39.7-52.8%) with the intention of using fewer combusted cigarettes.
- The mean rating for likelihood of switching back to combusted cigarettes after adopting the new products among adult current established users was 4.3 (95% CI, 4.1- 4.5) on a 1 (not at all likely to switch back to cigarettes) to 10 (very likely to switch back to cigarettes) scale. Among those likely to quit combusted cigarettes, the mean rating for likelihood of switching back after adopting the new products was 3.9 (95% CI, 3.5-4.3).

Per the epidemiology review:

- Evidence from observational studies submitted in the PMTAs, as well as evidence from the peer-reviewed literature, suggests that adult use of closed ENDS, and the subject new products in particular, is predominately non-daily and concurrent use with cigarettes is common.

Dual or poly use

- Per the BCP review, the applicant-submitted survey data show that approximately 2-5% of adult exclusive combusted cigarette smokers or dual cigarette and ENDS users switched completely to ENDS use at subsequent waves, suggesting a high likelihood of dual tobacco use with the new products. However, this estimate is based on use patterns of ENDS in general because the applicant did not conduct longitudinal studies on use patterns with the new products.[5]
- From an epidemiology perspective, the applicant did not provide any prospective data to assess long-term trajectories of use, so it is unclear to what extent dual use is a transient state along a pathway to switching versus a permanent state.

[5] Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be overcome by a sufficient benefit to adult users, and as the known risks increase, so too does the burden of demonstrating a substantial enough benefit. In the case of a new non-tobacco flavored ENDS product, the risk of youth initiation and use is substantial, given the clearly documented published evidence. In contrast, the risk of youth initiation for tobacco-flavored ENDS products is less substantial, thus the level of evidence demonstrating benefit to adult smokers may not need to be as high.

Switching

- Per the BCP review, survey data suggest that, while a small proportion of adult tobacco users are likely to switch completely to the new products, daily and exclusive users have an increased likelihood of switching completely compared to non-daily and dual-users.
- Per the epidemiology review, the applicant examined the association between ENDS use ("original"/tobacco flavor vs. all other flavors) and smoking status (current vs. former smokers). The extent to which the new products (or ENDS in general) facilitated cessation was unknown, and therefore the conclusion made by the applicant that the availability of flavors may help smokers completely switch was unsupported by the data. The applicant used longitudinal studies to examine tobacco use transitions from exclusive cigarette smoking to exclusive ENDS use in the first cycle review. Rates of switching from combusted cigarette use to exclusive ENDS use reported in the application (1.5-6.7%) were comparable to rates in the published literature (3.4-5.9%).[27-29] However, the applicant did not provide information that examined the role of flavors on tobacco use transitions. Additionally, the applicant did not provide evidence on tobacco use transitions overall or the role of flavors on tobacco use transitions for cycle 2 of PMTA review. In the absence of product-specific (longitudinal) data on switching in this PMTA, it may be reasonable to infer that switching rates for this product would be somewhere within the range found in the published literature and presented in the PMTA. However, based on the applicant's analysis and available evidence showing higher preference of original flavored ENDS among adult smokers, the new products could help current adult smokers in quitting or reducing cigarette smoking.

Cessation

Per the BCP review:

- Existing studies have shown that daily ENDS use is associated with significant reductions in combusted cigarette use; however, non-daily ENDS use does not appear to be associated with these reductions.
- Published literature and survey data show that some closed ENDS (e.g., cig-a-like) may deliver sufficient nicotine to effectively replace some cigarettes.
- The new products in PM0000553 (used in CSD1303) and PM0000560 (CSD170401) were associated with slightly greater abuse liability than 4mg NRT gum, which may increase the likelihood of use and adherence of these three products compared to nicotine gum among smokers interested in quitting cigarette smoking.

3.4.1.3. Tobacco non-users (including youth)

Per the BCP review:

- Due to the lower abuse liability of these products compared to cigarettes, former and non-tobacco users (including youth) who initiate use of the new products are less likely to progress to regular use of the new products.
- Overall, the applicant submitted two human abuse liability studies (CSD1303 and CSD170401) and four nicotine PK studies (CSD1502, CSD1503, CSD170303, and CSD170304) that collectively indicate lower abuse liability for the new products in PMTAs relative to combusted cigarettes. Although tobacco non-users including youth were not included in the applicant-submitted clinical studies, the comparably

low abuse liability of the new products relative to combusted cigarettes suggests initiation and sustained use of the new products among tobacco non-users is likely to be lower than initiation and sustained use of tobacco products with greater abuse liability (e.g., combusted cigarettes).

Per the social science review:

- The applicant study findings indicate that among most adult non-tobacco users, both former (84.3%) and never users (74.7%), indicated they were not interested in the new products. Additionally, according to an algorithm created by the applicant, adult never tobacco users had a projected product use rate of 0.4%. While findings indicated that those susceptible to combusted cigarette use had a significantly higher projected product use rate than those not susceptible, these projected product use rates are low, which is consistent with previous literature.[30] The mean projected product use rate among former adult tobacco users was 1.4% and 1.8% among current tobacco experimenters. Based on the respondent data, the applicant concludes that adult never users are not likely to become users of the new products.
- The applicant examined intentions to purchase Vuse Solo products on a 1 (definitely would not purchase it to use) to 10 (definitely would purchase it to use) point scale. Current established cigarette users (4.6; 95% CI 4.5 – 4.8) indicated the highest intentions to purchase. Current established non-cigarette users (3.6; 95% CI 3.3 – 3.9), former established tobacco users (1.9; 95% CI 1.8 – 2.0), and never established tobacco users (2.5; 95% CI 2.4 – 2.6) reported low intentions to purchase.
- In 2020, approximately 19.6% of high school students and 4.7% of middle school students reported current use of ENDS.[31] Additionally, longitudinal research using 2013-2015 PATH data indicated that 42.2% of past 30-day youth ENDS users remained past 30-day ENDS users one year later.[29] These published findings indicate risk of ENDS use among youth. However, youth are less likely to initiate tobacco-flavored ENDS and subsequently progress to regular use than with non-tobacco flavored ENDS. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first ENDS that they used was non-tobacco flavored. In another PATH Study, more youth, young adults, and adults who initiated ENDS use between Wave 1 and Wave 2 reported use of a non-tobacco flavored product than a tobacco-flavored product. Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older.[32] Additionally, existing literature on non-tobacco flavored product use suggests that non-tobacco flavors not only facilitate initiation, but also promote established regular ENDS use. For example, regional studies have found that the use of non-tobacco flavored ENDS was associated with a greater frequency of ENDS used per day among a sample of adolescents in Connecticut in 2014[33] and continuation of ENDS use in a sample of adolescents in California from 2014-2017.[34] Use of non-traditional flavors (vs. tobacco, mint/menthol, flavorless) was associated with increased likelihood of continued use and taking more puffs per episode.[34] Data from a regional survey in Philadelphia, PA found initial use of a non-tobacco flavored vs. tobacco flavored ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months. Finally, similar effects have been found in the PATH study among young adults (18-24 years), where “ever use” of non-tobacco flavored ENDS at Wave 1 was also

associated with increased odds of current regular ENDS use a year later at Wave 2. Collectively, these findings indicate that while all ENDS pose risks to youth, youth are less likely to initiate tobacco-flavored ENDS and subsequently progress to regular use, than with non-tobacco flavored ENDS.

- The applicant did not provide direct data on youth. In the applicant's "Likelihood of Use, Label Comprehension, and Risk Perceptions Testing for Vuse Solo E-Cigarette" study, adults 18 to 30 were oversampled to provide a sufficient sample of young adults ages 18 to 24 to serve as a proxy for youth. However, some subsamples of young adults were small and not all analyses were broken down by age to allow for young adults to serve as a proxy for youth. Further, data on most preferred flavor was not broken out by young adult and adult age categories which would have helped FDA in determining the appeal of the new products among youth in the absence of youth data.
- Generally, interest in tobacco flavors is low among youth. The available evidence (NYTS 2019) indicates that non-tobacco flavored ENDS are more likely to be used by youth than tobacco flavored ENDS.[35] The applicant's data demonstrate that adults had the highest purchase intent for original (28.6%), compared to menthol (23.2%) and mint/fruit flavors (between 6.4-14.7% depending on the flavor).
- According to National Youth Tobacco Survey (NYTS) 2020 data, prefilled pods or cartridges are the most common ENDS device types used among youth.[36] Sleek design, ability to use products discreetly, and user-friendly nature make pod mod (rechargeable cartridge-based ENDS) products appealing among youth.[33, 37, 38] Although the new products are not pod mods, they are sleek and small in design, user friendly cartridge-based, and easily rechargeable. Although there is some risk of youth uptake of these products, in general, tobacco-flavored ENDS are less appealing to youth compared to non-tobacco flavored ENDS, making the risk of youth initiation low for these products. Findings from a discrete choice experiment showed that non-tobacco flavors were associated with more curiosity, less perceived danger, and greater perceived ease-of-use among high school students, compared to tobacco flavor.[39] Additionally, the published literature indicates that youth report significantly higher preference for non-tobacco flavored ENDS compared to tobacco flavored ENDS.[33, 37, 38] Moreover, the evidence indicates that tobacco flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors. The findings from the 2020 Monitoring the Future (MTF) survey provide evidence that youth use of tobacco flavored ENDS is less common compared to other flavored ENDS including mint.[40] According to the 2020 MTF data, the prevalence of tobacco flavor was 2.9% among 10th and 12th graders while mint was the second most often used flavor (26.9%) after fruit (59.3%).[40]
- In addition, the digital marketing and TV and radio restrictions recommended by OHCE will help to mitigate the risk of youth initiation.

Per the epidemiology review:

- Observational evidence submitted by the applicant in both review cycles demonstrates that prevalence of use of the applicant's products among young adults declines with younger ages, and the majority of new product users (both experimental and established) are more likely to be older (>30 years of age).
- Some evidence in the peer-reviewed literature on youth device type preferences suggests youth report using closed systems (i.e., disposable devices or those that

use pre-filled pods or cartridges similar to the new products) most often.[41] The literature shows that non-tobacco flavor use is very common in both youth and adult ENDS users (irrespective of the device type). Furthermore, the proportion of reported youth use of the brand "Vuse" significantly increased from 2019 (1.2%) to 2020 (7.3%).[40] However, the study did not specify the type of Vuse-branded products or the flavor used by youth, so it is uncertain whether use of Vuse Solo products increased among youth. As previously discussed, the published literature shows that prevalence of youth use of tobacco-flavored ENDS is low and that tobacco flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors.

- Overall, the available evidence to date does not adequately address whether new product use in youth and young adults leads to regular smoking.

3.4.1.4. Vulnerable populations (other than youth)

- Per social science and epidemiology reviews, the applicant did not provide information on use of the new products among vulnerable populations—i.e., groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation. Evidence from the published literature indicates that all age groups with substance use or mental health issues are more likely to use ENDS compared to those without.[42-44] Additionally, the prevalence of ENDS use is higher among other vulnerable populations (e.g., pregnant persons, and lesbian, gay, and bisexual individuals).[45-49] While the evidence indicates that some vulnerable populations experience disproportionate ENDS use, there is a lack of currently available evidence to show whether the new products would help facilitate adult combusted cigarette smokers from vulnerable populations to switch or reduce CPD.
- Per the BCP review, no clinical studies were provided or reviewed by the applicant addressing use of the new products among vulnerable populations. Given the existing high rates of tobacco product use among vulnerable populations and the known difficulties that these populations have with cessation, ENDS use may serve as a harm reduction approach if users are able to completely switch or dramatically reduce other combusted tobacco use. Further, the applicant submitted two human abuse liability studies (CSD1303 and CSD170401) and four nicotine PK studies (CSD1502, CSD1503, CSD170303, and CSD170304) indicating lower abuse liability for the new products relative to combusted cigarettes, which suggests the new products will not pose greater initiation and addiction risks among vulnerable populations than combusted cigarettes. Nevertheless, due to insufficient information, from a BCP perspective, the impact of the new products on abuse liability and product use behavior in vulnerable populations other than youth is unknown.

3.4.1.5. Actions taken to mitigate risk of unintended use

Per the OHCE consult:

- The applicant submitted information on their proposed marketing restrictions in two letters dated November 9, 2018 and April 29, 2019.
- OHCE's review raised concerns about the potential broad reach of the applicant's plan for digital and broadcast marketing and concluded that, if the products are

authorized to be marketed, FDA should place restrictions on digital marketing and TV and radio marketing to protect youth.

- Additionally, OHCE noted concerns with the applicant's plans for print and point-of-sale advertising and recommended that any marketing granted order (MGO) letter encourage the applicant to take additional steps to limit youth exposure to print and point-of-sale advertising, including, for example, limiting advertising to print publications where 85% or more of the readership is 21 years of age or older and/or selecting publications that do not over-index for youth.
- The applicant describes the following measures it would take to help reduce the youth-appeal of its marketing materials: "No testimonials by sports figures or celebrities or any person with special appeal to persons under 21 years of age; No person appearing in any advertising materials shall be under age 25 or be styled to look under age 25; Content shall not include characters, images, or themes designed to target youth; Content shall not be related to youth or youth-oriented activities; Content shall not suggest that use of R.J. Reynolds Vapor Company's ("RJRV") products is essential to social prominence, distinction, success or sexual attraction, nor shall any content picture a person using any RJRV products in an exaggerated manner; and Content shall not depict persons participating in, or obviously just having participated in, a physical activity requiring stamina or athletic conditioning beyond that of normal recreation." OHCE noted support for the use of these measures because they are likely to further help mitigate risks to youth. OHCE recommended that any MGO letter for these products encourage the applicant to implement these measures.

3.4.1.6. Labeling and advertising

- The applicant provided labels that did not appear to contain anything potentially false or misleading.
- The applicant assessed label comprehension with a series of questions that measured knowledge about the products. The percentage of correct responses ranged from 74% to 94% across items and user groups.
- The applicant did not include information that indicates whether consumers will use the products as intended or designed. However, nothing in the applications suggest that potential issues would arise.

3.4.2. Synthesis

Per BCP, social science, and epidemiology reviews, the applicant states that use of the new products is likely to be higher among current tobacco users (in particular, current cigarette smokers) than among non-users of tobacco. Although the social science review indicates limitations with the applicant's algorithm study, self-reported measures from respondents were also provided. These data indicate that the mean projected product use rates are highest among current established cigarette smokers. Most non-tobacco users in the study were not interested in the new products (74.7% never established tobacco users, 84.3% former established tobacco users); whereas two-thirds of current established tobacco users (66.8%) and about half of current established non-combusted tobacco users were interested (52%). In addition, based on the applicant's analysis, switching from conventional cigarettes to ENDS does occur among a small proportion of users, typically through a period of dual use. The applicant reported that approximately 5% of dual users switched to exclusive ENDS

use at follow-up, which is consistent with published analyses of the PATH Study data looking at ENDS and cigarette transitions from Wave 1 to Wave 2.[27]

Per social science and epidemiology reviews, findings from the applicant's likelihood-of-use study suggest that current established cigarette smokers are more likely to prefer original (tobacco) flavor relative to other flavors (i.e., menthol, mint and fruit). In addition, respondents with a purchase intent of 2+ (on a 10-point scale) who selected original (26.4%) flavor were more likely to report intentions to use this flavor to stop smoking compared to 6 other flavors (12.7%, 20.0%, 23.7%, 22.3%, 16.1%, and 26.3% for mint, nectar, melon, tropical, fusion, and menthol, respectively). In Wave 2 of the PATH Study, tobacco flavor was used by 50.5% of adult ENDS users aged 25 years and older who used a single flavor while menthol/mint was used by 23.3%, fruit by 15.9%, and candy or sweets by 7.8%.[50] In addition, among adult dual users (18+) who used nonmenthol cigarettes, 32.3% reported exclusive tobacco flavor use.[51]

The evidence shows that original (tobacco) flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors. The findings from the 2020 MTF survey provide evidence that youth use of tobacco flavored ENDS is less common compared to other flavored ENDS including mint.[40] According to the 2020 MTF data, the prevalence of tobacco flavor was 2.9% among 10th and 12th graders while mint was the second most often used flavor (26.9%) after fruit (59.3%).[40] Although youth report using prefilled pods or cartridges most often, more data is needed to determine overall youth appeal of cig-a-like ENDS. The evidence from the peer-reviewed literature demonstrates that, while youth use of ENDS is common, the proportion of youth who report Vuse Solo as their usual brand is low. Although the overall youth use of ENDS has decreased from 2019 to 2020 among high school and middle school students,[36] the proportions of reported youth use of the brand "Vuse" significantly increased from 2019 to 2020 (1.2% to 7.3%) though the study did not specify by Vuse subbrands or by flavor, so specific findings for the new products are unknown.[40] Though youth use of ENDS is concerning, as previously discussed, the published literature shows that prevalence of youth use of tobacco-flavored ENDS is low and that tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors.

With respect to youth appeal and mitigation, I agree with OHCE's evaluation of the applicant's marketing plans and all recommendations in the OHCE consult. Accordingly, I recommend that the MGO letter include additional marketing requirements and recommendations.

The evidence summarized in this section describes relatively high interest among smokers in using the tobacco-flavored products. Although nicotine delivery is lower than for cigarette smoking, available evidence indicates that experienced ENDS users can increase nicotine uptake compared to inexperienced users, which increases the likelihood of switching. Use of these products would benefit smokers who switched completely or substantially reduced their cigarette smoking. The available information also shows that youth appeal/uptake of tobacco-flavored products is generally low among youth. Overall, I agree that the benefit of the new products to adult smokers is significant enough to overcome the risk to youth.

While the DPAL recommendation was for the marketing order for the new products to include an explicit reminder in the order that the applicant must comply with all applicable requirements, including the nicotine warning statements for covered tobacco products required under 21 CFR 1143.3, this is already covered. The main body of the order letter contains language reminding applicants of their responsibility to ensure the new products comply with all applicable statutory and regulatory requirements and notes that FDA monitors for compliance.

3.5. TOXICANT EXPOSURE

3.5.1. Discipline key findings

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

3.5.1.1. Toxicity

- Overall, there are significant reductions in HPHCs tested using the power unit (PM0000551) from the new products' aerosols compared to cigarette comparison data under both regimens. Elevations in glycerin and propylene glycol of the new products' aerosols were outweighed by decreases in other respiratory toxicants (i.e., acetaldehyde, acetyl propionyl, ammonia, anabasine, acrolein, crotonaldehyde, diacetyl, ethylene glycol, and formaldehyde) in the cigarette comparators. Observed glycerin and propylene glycol levels were comparable to levels seen in other ENDS market comparisons.

3.5.1.2. Biomarkers of exposure

Per the BCP review:

- Switching from cigarette smoking to ad libitum use of the new products in PM0000553 or PM0000554 (CSD1304), and PM0000560 (CSD170501) for five days resulted in significant reductions in the urinary and blood BOEs of similar magnitude to the reductions in the participants who abstained from smoking. While the long-term effects of switching were not assessed, these changes in systemic exposures are likely to provide the health benefit of reduced exposure to these HPHCs for current adult smokers should they completely switch to the products in the PMTAs.
- Changes in BOE and the associated health risks of dual use of cigarettes and the new products in the PMTAs have not been evaluated in longitudinal studies or under extended exposure conditions, thus conclusions on such long-term health risks cannot be made at this point.

3.5.2. Synthesis

Based on the toxicology review, the overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in HPHC yields in the new products' aerosol compared to cigarette comparators and results of nonclinical studies. Per the BCP review, significant reductions in blood and urinary BOE (e.g., VOCs, TSNAs, and PAHs) indicate that exposure to carcinogens and other toxicants present in cigarette smoke were greatly reduced with use of the new products. The magnitude of reductions in biomarker levels was similar to the reductions that occurred when smokers switched to nicotine gum. Although the impact on long-term disease risk has not been

evaluated, the applicant's results and existing evidence support that complete switching reduces exposure to tobacco-related toxicants and may result in less risk of tobacco-related diseases. A recent study examining Waves 1 and 2 of the PATH data reported that participants with moderate to high reductions in CPD had also lower levels of biomarkers.[52] The impact of dual use on BOE levels and the associated health risks were not assessed; however, based on the currently available evidence, reducing CPD likely leads to less exposure to harmful toxicants than continued smoking and may help for eventual quitting. Longitudinal data are needed to follow individuals over time to accurately determine use trajectories and potential impact of dual use on health risk.

I agree with the conclusion that available toxicological data, the demonstrated reductions in measured HPHC levels, and significant reductions in BOEs indicate the potential for a relative benefit compared to cigarette smoking for smokers who completely or partially switch to the new products.

3.6. HEALTH EFFECTS

3.6.1. Discipline key findings

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

3.6.1.1. Toxicology

- Results from the in vitro toxicology studies demonstrated that combusted cigarette smoke fractions (total particulate matter (TPM), gas vapor phase (GVP), or both) were mutagenic, cytotoxic, and genotoxic. By contrast, even at the maximum dose levels tested, neither the TPM nor GVP from any of the aerosols of all the new products or ENDS market comparisons was mutagenic, cytotoxic, or genotoxic under the test conditions.
- For the in vivo inhalation studies, the new products' aerosols consistently resulted in substantially lower nonclinical toxicity and histopathological changes compared to Newport Gold cigarette smoke. The Newport Gold cigarette was the only cigarette available with a market order at the time the in vitro and in vivo studies were started, and the cigarette measured many of similar HPHCs as the new products under both non-intense and intense puffing regimens. Therefore, the supportive findings relative to Newport Gold cigarette were considered sufficient for comparative determination.
- No in vivo studies were conducted comparing the new products' aerosols to the aerosols from ENDS market comparisons as none of the comparison products had received a positive marketing order at the time of PMTA submission. However, chemistry had determined that HPHC levels in the aerosol from the new products were comparable to similar closed ENDS market products. Based on these similar HPHC levels, as well as the accompanying in vitro studies, additional in vivo inhalation studies between the new products and marketed ENDS comparison product are not needed for a toxicological assessment.
- The BOE data from clinical studies indicated that exposure to carcinogens and other toxicants present in cigarette smoke were greatly reduced with use of the new products for five days in a controlled in-clinic setting.

3.6.1.2. BIMO inspection findings

- FDA has not conducted bioresearch monitoring (BIMO) inspections of clinical study sites used in these PMTAs, as studies were not pivotal and reported AEs did not raise clinically significant concerns.

3.6.1.3. Addiction as a health endpoint

Per the BCP review:

- The abuse liability of the new products is less than that of a cigarette in ENDS naïve exclusive smokers. Current cigarette smokers are likely to dual use the new products with cigarettes; however, daily use of the new products may be associated with reduced CPD. Exclusive daily users of the new products in the PMTAs are likely to have equivalent or lower overall nicotine dependence levels compared to exclusive cigarette smoking.

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

Per the medical review:

- In general, the published literature on the health effects of ENDS suggests that many ENDS aerosol constituents (e.g., TSNAs, VOCs, and PAHs) may be decreased compared with combusted cigarettes.[53-55] The National Academies of Sciences, Engineering, and Medicine (NASEM) states that ENDS aerosol contains lower levels of most toxicants than combusted cigarette smoke.[12] Some literature also reports that not all ENDS aerosol constituents are reduced (e.g., acrolein, acrylamide, acrylonitrile, and xylene)[54, 56], which may potentially off-set the potential health benefit of short and long-term reductions in exposure to other ENDS constituents. However, the ability to draw conclusions on the health effects of ENDS from the published literature is limited due to small sample sizes and short durations of exposure.
- Several study design issues limit the interpretation of health effect data from the applicant's short-term switching, abuse liability, and PK studies including small sample sizes, short-term exposure durations, and generally healthy participants. In addition, the applicant's switching studies did not assess dual use as it would be more likely to occur in real-world conditions.

Per the epidemiology review:

- Some published literature suggest 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.[57-59] As 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.
- Few observational studies have been published on the short- and long-term health effects of ENDS use. Biomarker data from observational studies generally show that ENDS users have higher exposure to nicotine, some VOCs, and TSNAs than do non-tobacco users.[53, 60] 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.[53, 61]
- A meta-analysis found that compared to heavy smokers, dual users who are able to reduce the number of cigarettes they smoke by at least 50% had a significant reduction in lung cancer risk.[62] However, 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.[62]

- Switching and smoking reduction likely reduce exposure to tobacco-related toxicants. In an observational study where smokers 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.[63] Another study, examining Waves 1 and 2 of PATH data, reported that participants with moderate reductions in cigarettes smoked per day had lower levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and 1-hydroxypyrene and participants with heavy reductions in cigarettes smoked per day had lower levels of NNAL, 2-fluorene, and MHB3 at Wave 2.[52]

3.6.1.5. Likelihood and effects of product misuse

- Per the medical review, the PMTAs did not specifically address human use factors or the potential for intentional product misuse (e.g., child resistant packaging). There is a potential risk of accidental exposure from misuse (using the product in ways other than intended such as product modifications, dripping, and stealth use), abuse, or unintended use resulting in exposure to nicotine and other toxicants. However, the new products have a closed system and are not intended to be opened. Therefore, the health risks are likely mitigated for accidental ingestion and exposure in children. Further, there have been no FDA reports of accidental exposure for these products. The authentication memory chip intended to minimize the potential for unintended use such as dry puffs (insufficient e-liquid) could also serve as a secondary safety feature preventing accidental ingestion and exposure in children.
- Per the BCP review, the low abuse liability of the new products among ENDS naïve users and added safety features help to contribute to a lower likelihood of the new product misuse.

3.6.1.6. Adverse experiences

Per the medical review:

- In short-term new product exposure switching, abuse liability, and PK studies, the numbers of AEs were generally low and characterized overall as mostly mild, transient, and expected. No deaths or serious AEs associated with use of the new products were reported.
- Two of the four consumer health-related AEs associated with the new products reported to the CTP Safety Reporting Portal were seizures. One was a “complex partial seizure” occurring 10 months after starting the new product and the other occurred after complete switching to the new product in one consumer without a prior medical history of seizures. Although additional follow-up information was not available, new product exposure may potentially be associated with seizures under real-world use conditions. However, it is premature to determine whether current seizure reports indicate an association with complete switching to the new products.
- The evidence is inconclusive for drawing health risk determinations based on the TPST AE data. The numbers of self-reported AEs were small (n=4 health-related AEs), and consumers did not specifically associate the AEs with the new products.
- FDA is aware of several health issues regarding the use of ENDS, specifically e-

cigarette or vaping use-associated lung injury (EVALI), seizures, and overheating/fire/explosion-related thermal burn injuries (OH/F/Exp):

- EVALI is a potential respiratory health effect that could occur in individuals who use vaping products. There were no reports of EVALI in the applicant's foundational clinical studies and there did not appear to be any subjects who experienced the constellation of symptoms indicative of EVALI as an AE that required hospitalization. However, since EVALI is associated with use of vaping products, CTP is interested in evaluating any additional information related to respiratory illness in association with ENDS and specifically the new products.
- There were no seizures reported as an AE in the applicant-submitted clinical studies. Two seizures were reported with new product use in the CTP Safety Reporting Portal. While this data is insufficient to fully evaluate the potential association of the new products with seizures, CTP is interested in monitoring an on-going evaluation of this potential health consequence of ENDS use.
- No OH/F/Exp were reported in the PMTAs. However, the risk is still an issue regarding ENDS use overall.

Therefore, to further monitor and evaluate potential ENDS health effects such as EVALI, seizures, and OH/F/Exp, medical recommends that post-market reporting include a specific plan to monitor respiratory-related illnesses, neurological symptoms, and AEs related to overheating and thermal burns associated with the products in the PMTAs.

- The Establishment Inspection Report (EIR) EX 33 reports only one verified case of a thermal burn which is described as a *"blister"* associated with use of Vuse Kit Original Solo 4.8% (RJRV-COMP-170669). No other cases of verified consumer-reported physical thermal burns or inhalational aerosol injuries were reported for the new products. Generally, consumer complaints of *"hot/excessive heat"* appeared to be a subjective sensation of increased temperature rather than actual corporeal burn injuries requiring medical treatment or hospitalization. Although consumer-reported data suggest that the risk is low, there is still a potential risk of burns associated with use of ENDS.

3.6.2. Synthesis

Per the toxicology review, the new products' aerosols are significantly less toxic than the combusted tobacco comparisons based on available nonclinical, HPHC, and BOE data. Per the BCP review, short-term (five days) switching from cigarette smoking to the new products resulted in significant reductions in the urinary and blood BOE. Per the medical review, the numbers of AEs were generally low and mostly mild and transient in short-term clinical studies. 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 is limited data about the long-term health effects of ENDS from large clinical studies or long-term epidemiological studies. In addition, the study design limitations (e.g., small sample size, generally healthy participants, 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 health effects and potential short and long-term health effects from dual use could not be evaluated. However, based on available information, I agree that adult smokers who switch to these products (either completely or with a significant reduction in cigarette consumption) would benefit from

reduced exposure to many HPHCs. While the effects of dual use were not assessed, significant reductions in systemic exposures after short-term switching and the available evidence suggest that daily use of the new products with concomitant reduction in CPD may provide health benefits from a harm reduction perspective in terms of reducing exposure to HPHCs relative to continued use of cigarette smoking alone.

Although available data show low risk for adverse effects, I agree with the medical review that, for the marketed new products, post-market reporting is needed to further monitor and evaluate potential health effects including EVALI, seizures, and OH/F/Exp.

I also agree with medical and BCP reviews that there are health risks for accidental exposure in children, but these risks are likely mitigated with the product design (i.e., closed system and authentication/memory chip).

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

The following discussion is based on the key findings provided in the epidemiology review:

3.7.1.1. Population health impact (PHI) model

- The applicant submitted a model that has been used previously to estimate the population health effects of the new products. The limitations of the model include an approach known to overestimate actual use of the product (i.e., using likelihood of use data without comparison to prevalence data observed under real-world conditions), overestimate product switching due to lack of consideration for periods of sustained dual use, and overestimate the net population health effect in the event of a marketing authorization given the optimistic risk reduction estimates used in the main analysis (i.e., the assumption of a 95% lower excess relative risk compared to cigarettes). Although the model description is clear, the model inputs do not rely on actual product use from surveys or real-world prevalence data (vs. likelihood of product use employed by the applicant) and do not account for periods of dual use. Therefore, it does not help evaluate mortality rates and survival estimates and the potential public health impact.

3.7.2. Synthesis

I agree with the epidemiology review conclusion that the model does not raise concerns in terms of model structure or tobacco use transitions. However, given the limitations associated with the model inputs described in the epidemiology review, the model is not particularly informative in the evaluation of whether the new products are appropriate for the protection of the public health.

3.8. STATUTORY REQUIREMENTS

3.8.1. Public health conclusion

Based on the findings and evaluations discussed in Sections 3.1-3.7, 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

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

3.8.3. Labeling

For all PMTAs, the applicant provided labels that did not contain any false or misleading information.

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.

4.2. ENVIRONMENTAL CONCLUSION

A finding of no significant impact (FONSI) was signed by Luis G. Valerio, Jr. on October 8, 2021. The FONSI was supported by an environmental assessment prepared by the applicant on October 20, 2020.

5. CONCLUSION AND RECOMMENDATION

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

FDA's evaluation of these PMTAs determined that there are adequate process controls and quality assurance procedures to help ensure both the device and e-liquids are manufactured consistently. Based on the information provided in the PMTAs, the abuse liability of the new products is lower than combusted cigarettes and is similar to, or lower than, that of other ENDS. The overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in aerosol HPHCs of the new products' compared to cigarettes and as evidenced by

results of nonclinical studies. Further, significant reductions in blood and urinary biomarkers of exposure (e.g., VOCs, TSNAs, and PAHs) indicate that exposure to carcinogens and other toxicants present in cigarette smoke was greatly reduced in smokers who switched completely to the use of the new products. In addition, current established cigarette users indicated the highest intentions to purchase among all groups, and the most preferred product among current established cigarette users was the tobacco (original) flavor. Therefore, the applicant has demonstrated the potential for these new products to benefit adult smokers.

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. Existing evidence consistently indicates that use of tobacco flavored ENDS is less common than non-tobacco flavored ENDS among youth. Nonetheless, given the strong evidence regarding the impact of youth marketing exposure to youth appeal and initiation of tobacco use, a marketing authorization should include postmarket requirements to help ensure that youth exposure to tobacco marketing is limited. In addition, the applicant's study findings demonstrated low intention to purchase the new products among adult never and former established tobacco users. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit smokers who switch completely or significantly reduce their cigarette use would outweigh the risk to youth, provided the applicant follows post-marketing requirements aimed at reducing youth exposure and access to the products.

Regarding product stability, the applicant stated that the shelf life of the new products is (b) (4) . The applicant provided chemistry data to support that the new products are chemically stable over (b) (4) . However, the applicant did not provide microbial data that would allow FDA to evaluate whether the products are microbially stable over (b) (4) . The applicant instead provided data that supports microbial stability of the products over (b) (4) . Because the microbial stability data for (b) (4) is acceptable and indicates that the products are low-risk for microbial growth over a (b) (4) h period and because there are no other stability concerns, the lack of microbial data for (b) (4) does not preclude an APPH finding for the products.

Based on my review of your PMTAs, 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 you have met the requirements of section 910(c) of the FD&C Act and authorizes marketing of your new products. Under the provisions of section 910, you 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 subject to this review, as identified on the cover page of this review.

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7. APPENDIX

Table 3. New tobacco products subject to Granted Orders

Common Attributes of PMTA	
Submission date	October 10, 2019
Receipt date	October 17, 2019
Applicant	R.J. Reynolds Vapor Company
Product manufacturer	R.J. Reynolds Vapor Company
Product category	ENDS (VAPES)
Attributes[6]	**New Tobacco Product**
STN	**PM0000551**
Product name	Vuse Solo Power Unit[7]
Product Sub-Category	ENDS Component
Package type	Paperboard Carton
Package quantity	1 Power Unit
Characterizing flavor[8]	None
Additional properties	Length: 87 mm Diameter: 9.6 mm Battery capacity: ≥ 270 milliAmpere hours (mAh) Wattage: 3.00 W Universal Serial Bus (USB) charger
STN	**PM0000553**
Product name	Vuse Replacement Cartridge Original 4.8% G1[7]
Product Sub-Category	Closed E-cigarettes
Package type	Paperboard Carton/Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Original
Nicotine Concentration	57.4 mg/mL
E-liquid Volume	0.5 mL/cartridge
PG/VG Ratio	21/79
Additional Properties	Length: 37.6 mm Diameter: 9.6 mm G1 Tube Material: Stainless Steel
STN	**PM0000560**
Product name	Vuse Replacement Cartridge Original 4.8% G2[7]
Product Sub-Category	Closed E-cigarettes
Package type	Paperboard Carton/Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Original
Nicotine Concentration	57.4 mg/mL

[6] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.
[7] Brand/sub-brand or other commercial name used in commercial distribution. The Vuse Solo "Original" e-liquid is a tobacco flavored e-liquid.
[8] Provided as part of product labeling

E-liquid Volume	0.5 mL/cartridge
PG/VG Ratio	21/79
Additional Properties	Length: 37.6 mm Diameter: 9.6 mm G2 Tube Material: (b) (4)

Table 4. Amendments received

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
December 23, 2019	December 23, 2019	PM0000582	All STNs	Yes	Response to December 12, 2019, Inspection Request Letter
November 10, 2020	November 10, 2020	PM0004236	All STNs	Yes	Response to May 19, 2020, Deficiency letter