FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review[i]	
Submission tracking numbers (STNs)	PM0000635, PM0000636, PM0000646, PM0000712, PM0004287, and PM0004293
Common Attributes	
Submission date	April 2, 2020 (PM0000635, PM0000636, PM0004287)
Receipt date	April 2, 2020 (PM0000635, PM0000636, PM0004287)
Submission date	April 15, 2020 (PM0000646, PM0000712, PM0004293)
Receipt date	April 15, 2020 (PM0000646, PM0000712, PM0004293)
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-Liquid
Cross-Referenced Submissions	
PM0000636, PM0000712	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	Remote Regulatory Assessment - Public Health Emergency (Pandemic), 3/25/2021
Recommendation	
Issue marketing granted order letter(s) for the new tobacco product(s) subject of this review.	

Technical Project Lead (TPL):

Digitally signed by Lynn C. Hull -S
Date: 2022.05.11 11:27:20 -04'00'

Lynn C. Hull, Ph.D.
Deputy Director
Division of Individual Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2022.05.12 06:34:21 -04'00'

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

[i] 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 (TPL) review, I find that permitting the marketing of the new products listed above ("new products") is appropriate for the protection of the public health (APPH) (*subject to certain marketing restrictions)* and that none of the other denial grounds specified in section 910(c)(2) apply. Accordingly, I recommend that marketing granted orders be issued for the new products, subject to the marketing restrictions and post-market 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 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)). FDA interprets the APPH standard to require evidence 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).

In making the APPH assessment for a noncombustible 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 adult cigarette smokers transitioning away from combustible cigarettes to the ENDS product. In order to show that an ENDS is APPH, an applicant must show that the benefits, including those to adult smokers, 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. For flavored ENDS[ii] (i.e., ENDS with e-liquid flavors other than tobacco or menthol, 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 adult smokers outweigh that risk. For tobacco-flavored ENDS the risk to youth is lower; accordingly, a lesser showing of benefit may suffice. Assessments for menthol-flavored ENDS will be addressed separately. When it comes to evaluating the risks and benefits of a marketing authorization, the assessment for menthol ENDS, as compared to other flavored ENDS, raises unique considerations.

In making the APPH assessment for a flavored ENDS, FDA has determined that it is appropriate to compare flavored ENDS with tobacco-flavored ENDS. Tobacco-flavored ENDS may offer the same type of public health benefit as flavored ENDS (i.e., increased switching and/or significant reduction

[ii] Throughout this document, we use the term "flavored ENDS" to refer to ENDS with flavors other than tobacco or menthol. We use the term "menthol-flavored ENDS" or "menthol ENDS" to refer to ENDS flavored to impart a menthol flavor and the term "tobacco-flavored ENDS" or "tobacco ENDS" to refer to ENDS flavored to impart a tobacco flavor.

in smoking) but do not pose the same degree of risk of youth uptake. Whether other products, such as tobacco-flavored ENDS, give adult smokers comparable options for switching or cigarette reduction bears on the extent of the public health benefit that the subject ENDS arguably provide to that population. Therefore, in making the APPH determination for a flavored ENDS, FDA considers whether the applicant has provided acceptably strong evidence of an added benefit relative to that of tobacco-flavored ENDS in helping smokers completely switch from or significantly reduce their smoking.

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.[iii] Rather, for flavored ENDS, only the most stringent mitigation measures – specifically device access restrictions – have such mitigation potential.[iv] 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 marketing grant orders (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.

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

[iii] *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").

[iv] Device access restrictions are novel and rare. To the extent flavored ENDS applicants purport 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.

1.2. SUBJECT APPLICATIONS

The new products are electronic nicotine delivery systems (ENDS) composed of disposable closed pre-filled e-liquid cartridges in Original[v] flavor (PM0000636, Vuse Vibe Tank 3%; PM0000712, Vuse Ciro Cartridge 1.5%) and reusable/rechargeable power units (PM0000635, PM0004287 Vuse Vibe Power Units; PM0000646, PM0004293 Vuse Ciro Power Units).

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.

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 that of combusted cigarettes and higher than that of 4mg nicotine gum in ENDS naïve exclusive smokers. The overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in aerosol harmful and potentially harmful constituents (HPHCs) of the new products compared to cigarettes, as evidenced by results of nonclinical studies. Comparative HPHC analyses between combusted tobacco comparison products and the new products demonstrated that corresponding HPHCs from the new product aerosols were either below the limit of detection or substantially reduced on a unit per mg nicotine basis under both a non-intense and an intense puffing regimen. The available toxicological data indicates that the new products' aerosols are significantly less toxic than the combusted cigarette comparison data based on available HPHC data comparisons and results of nonclinical studies. Furthermore, HPHC levels observed from new product aerosols in e-liquids (PM0000636 and PM0000712) were comparable to HPHC levels reported in twenty-two ENDS market comparison products.

Furthermore, significant reductions in blood and urinary non-nicotine biomarkers of exposure (BOE) after switching from combusted 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 use of the new products. No data was provided on the impact of long-term and dual use on BOE and the associated health risks. However, the currently available evidence indicates that smokers who switch completely to ENDS will have reduced toxic exposures and this likely leads to less risk of tobacco-related diseases. In the applicant's analysis, among all user groups (current established cigarette users, current established non-cigarette tobacco users, current tobacco experimenters, former tobacco users, and never tobacco users), current established cigarette users indicated among the highest intentions to purchase Vuse Vibe/Ciro products, and the most preferred flavor among these individuals was the tobacco (original) flavor compared to non-tobacco flavors (e.g., mint, tropical, nectar, melon, fusion, mango). Therefore, the applicant has demonstrated that current established adult cigarette users are particularly interested in the new tobacco-flavored 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

[v] "*Original*" refers to the applicant-provided characterizing flavor for PM0000636 and PM0000712. FDA determined that no additional information regarding characterizing flavor was necessary.

is less common compared to non-tobacco flavored ENDS among youth. The applicant's study findings indicate that the tobacco flavor of the new products is less appealing (relative to the other flavors) to youth. In addition, the applicant's study findings indicated that appeal of the tobacco-flavored new products is low in adult non-users. Generally, nonusers view the new products as a risk to developing poorer health, rate them as unappealing, and a lower proportion of this group indicated interest in purchasing the new products compared to current tobacco users. Also, the applicant's study findings demonstrated lower 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 post market 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 (PM0000636 and PM0000712) 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) (b) (4) Because the microbial stability data for (b) (4) acceptable and indicates that the products are low-risk for microbial growth over an (b) (4) eriod, 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.

Together, 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, would be APPH. The potential of the new products to benefit smokers who significantly reduce their combusted cigarette use (or who switch completely and experience combusted cigarette cessation) outweighs the risk to youth, provided that the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to marketing of the new products and youth access to the new products.

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

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the new products listed on the cover page (with more detail in the Appendix, Table 3), sold under the brand names Vuse Vibe and Vuse Ciro. The new products are electronic nicotine delivery systems (ENDS) comprised of disposable closed pre-filled e-liquid cartridges in Original[vi] (tobacco) flavor (PM0000636, Vuse Vibe Tank 3%;

[vi] The applicant describes the "Original" products as tobacco-flavored throughout its PMTAs. For example, in Section A. (General Information, Unique Identification Tables) and in Section C. (Descriptive Information, Unique Identification of the New Tobacco Products), the applicant describes the Vuse Vibe "Original" and the Vuse Ciro "Original" products as "a tobacco flavored e-liquid."

PM0000712, Vuse Ciro Cartridge 1.5%), a reusable/rechargeable power unit (PM0000635, PM0004287 Vuse Vibe Power Units; PM0000646, PM0004293 Vuse Ciro Power Units), and an accessory USB charger for the power unit.

2.2. REGULATORY ACTIVITY

On April 2, 2020 and April 15, 2020, FDA received 6 PMTAs from R.J. Reynolds Vapor Company. FDA issued Acceptance letters to the applicant on April 8, 2020, April 21, 2020, and December 11, 2020. FDA issued Filing letters to the applicant on April 17, 2020, May 4, 2020, and December 11, 2020. On November 9, 2020, FDA issued an Inspection Request Letter. A Deficiency letter was issued to the applicant on December 18, 2020. FDA issued a Correction Letter on February 17, 2021. FDA issued an Extension Denial Letter to the applicant on April 14, 2021.

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

2.3. SCOPE OF REVIEW

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

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Regulatory	Shireen Fotelargias	12/18/2020	Not Applicable (N/A)	N/A
Engineering	Robert Meyer	12/17/2020	Robert Meyer	5/4/2022
Chemistry	Stephanie Daniels	12/15/2020	Stephanie Daniels	5/5/2022
Microbiology	Matthew Holman	12/15/2020	Prashanthi Mulinti	5/4/2022
Toxicology	Chad Brocker	12/15/2020	N/A	N/A
Behavioral and Clinical Pharmacology	Rashmi Venkatesh	12/16/2020	Rashmi Venkatesh	5/5/2022
Medical	Omoye Imoisili	12/17/2020	Dara Lee	5/4/2022
Epidemiology	Gabriella Anic	12/16/2020	Bria Graham-Glover	5/9/2022
Social Science	Brittany Merson	12/21/2020	Brittany Merson	5/9/2022
Environmental Science	Bria Martin	12/14/2020	Bria Martin	5/5/2022
OCE – BIMO	Tara Singh	11/12/2020	Tara Singh	6/16/2021
OCE – Manufacturing/Lab	Jiali He	10/30/2020	N/A	N/A

Table 2. Consults

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
OCE – DPAL	Julie Nguyen	11/23/2020	Julie Nguyen	5/5/2022
OHCE	Emily Talbert	10/21/2020	Allison O'Donnell	2/24/2022
TPST	Susan Rudy	10/1/2020	Susan Rudy	2/2/2022

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.

3.1.1.1. Analytical evaluations and nonclinical studies

Per the chemistry review:

- The filtered cigarette, Newport Gold Non-Menthol KS Box (Newport Gold), was used as a comparison product to compare smoke yields of the cigarette to the aerosol yields of the new products. Newport Gold, which contains tobacco and uses burning coals as the heating source, is not in the same product category and subcategory as the new products. The applicant stated that the selection of Newport Gold as a comparison product was because it was the only R.J. Reynolds Tobacco Company (RJRT) cigarette with FDA marketing orders at the time the new products were tested. The chemistry review found Newport Gold to be an appropriate combusted tobacco comparison product as the applicant provided adequate data and rationale to support this choice.
- HPHC aerosol yields of six currently marketed ENDS brands (Blu PLUS+ 2.4%, Logic Pro 2.4%, Mistic 2.0, JUUL 5.0%, myblu 2.4%, and Vuse Solo G2 4.8%), with a range of flavors for each brand, for a total of 22 e-cigarettes were used as comparison products to the new products. A reasonable justification for the six ENDS brand comparison products was provided stating these brands and flavors were market leaders in the U.S. as of 2017.

Per the toxicology review:

- Newport Gold cigarettes were chosen as the combusted tobacco comparison product. A reasonable justification was provided indicating this was the only RJRT cigarette available with an FDA marketing order at the time the new product in vitro and in vivo studies were initiated. This combusted tobacco comparison product was used for the HPHC comparative analysis studies, in vitro toxicity studies, and in vivo inhalation studies.
- Twenty-two closed e-cigarette market comparison products were chosen as the comparator 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 among closed e-cigarette ENDS at the time studies were initiated. The justification for the ENDS market comparison products is reasonable. These 22 ENDS market comparison products were compared to the new products in comparative HPHC analysis studies. For in vitro toxicity studies, select new products (i.e., PM0000636, PM0000712) were compared against select closed e-cigarette ENDS market comparison products (i.e., Blu PLUS+ Classic Tobacco, Magnificent Menthol, Cherry Crush; Logic Pro Tobacco, Menthol, Cherry; Vuse Solo G2 Original, Menthol, Mint, Tropical, Fusion, Melon, Nectar).

3.1.1.2. Clinical and Observational Studies

Per the behavioral and clinical pharmacology (BCP) reviews:

- The applicant used usual brand (UB) cigarettes and 4 mg nicotine gum in one clinical study intended to evaluate abuse liability of the Vuse Vibe and Ciro Original flavor products (PM0000636 and PM0000712). In another clinical study, the applicant provided historical pharmacokinetic data from UB regular cigarettes and UB menthol cigarettes as comparison data for the EViGO Original products and Menthol flavored products. The EViGO products are a precursor product to the Vuse Vibe. Finally, the applicant used non-menthol UB cigarettes in a clinical study to evaluate change in BOE after switching to the Vuse Vibe or Vuse Ciro products.
- The rationale for choosing the comparison products in all studies was adequate. The applicant states that Vuse Vibe and Ciro products are intended as an alternative to combusted cigarettes; therefore, comparison to combusted cigarettes is appropriate. The comparison to nicotine gum was also appropriate since this product may be used by combusted cigarette smokers who are motivated to stop smoking and may use the Vuse Vibe and Ciro as an alternative to other nicotine replacement therapies such as nicotine gum.

Per the toxicology review:

- For clinical studies (such as BOE), select new products (i.e., PM0000635, PM0000636, PM0000646, PM0000712) were compared to the smokers' UB of combusted cigarette and the ENDS market comparison product Vuse Solo G2 (Original flavor).

Per the epidemiology review:

- The observational studies do not have an explicit comparison product. However, the information provided suggests that adult current cigarette smokers are a likely user population of these new products; therefore, an important comparison is the use of the new products among cigarette smokers versus non-smokers. The observational studies also evaluate whether the use of combusted cigarettes changes by different use patterns of the new products. Therefore, from an epidemiology perspective, the use of combusted cigarettes can be considered an important comparison product for these studies because current cigarette smokers are a likely user population.

Per the medical review:

- The rationale for choosing the comparison products, including other marketed ENDS as well as combusted cigarettes, was adequate from the medical perspective, across the eight submitted studies.

Per the social science review:

- The information provided by the applicant suggests that established combusted cigarette users are a likely user population of the new products. Therefore, from the social science perspective, comparisons between the new products and combusted cigarettes are appropriate.

3.1.2. Synthesis

The applicant's rationale for the selection of combusted cigarette, 4mg nicotine gum, and other ENDS as comparison products of the new products is appropriate. The applicant provided adequate data to support the comparison between the new products and their chosen comparison products in their analytical, nonclinical, clinical, and observational studies to aid in the determination of whether the new products are APPH.

As TPL, I agree with the chemistry, toxicology, and microbiology disciplines that the applicant provided adequate rationale for the selection of appropriate comparison products for their analytical and nonclinical studies. For these studies, including HPHC comparative analysis studies, in vitro toxicity studies, and in vivo inhalation studies, they used a filtered cigarette, Newport Gold Non-Menthol KS Box (Newport Gold) and currently marketed ENDS[vii] as their comparison products. The combusted cigarettes are not in the same product category and subcategory as the new products. 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 comparison products is appropriate. The rationale for selecting the ENDS comparison products is appropriate as they are in the same category and subcategory as the new products, were U.S. market leaders in 2017 for closed ENDS, and included a variety of flavors.

As TPL, I agree with the BCP, toxicology, epidemiology, medical, and social science disciplines that the applicant's rationale for the selection of comparison products for their clinical studies is adequate. For the clinical and observational studies, the applicant used combusted cigarettes (UB cigarettes), ENDS product Vuse Solo G2 (Original flavor), and nicotine gum as the comparison products. The applicant has stated that the Vuse Vibe and Ciro products are intended as an alternative to combusted cigarettes; therefore, their rationale for selecting combusted cigarettes as comparison products is appropriate. The rationale for selecting nicotine gum as a comparison product was also appropriate as the applicant states that the new products may be used by combusted cigarette smokers who are motivated to stop smoking and may use the new products as an alternative to other nicotine replacement therapies such as nicotine gum. The rationale for selecting other marketed ENDS as comparison products is also appropriate as the applicant states that the target user population of the new products is other ENDS users. For the observational studies, the applicant examined the comparative health risks of the new products relative to combusted cigarettes, which is appropriate given that the applicant's stated target population of the new products includes combusted cigarette smokers.

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:

- Vuse Vibe products utilize a PET (polyethylene terephthalate; polyester) fiber disk and a polypropylene tank compared to a ceramic fiber disk and a polyetherimide

[vii] Currently marketed ENDS as of 2017 when the studies were initiated.

tank in the EViGO (the predecessor product). Despite the material differences, the applicant justifies the use of chemical and toxicological study data for EViGO by adequately bridging it to Vuse Vibe products.

- All data submitted for Vuse Solo+ can be used to evaluate the new product, Vuse Ciro. The applicant stated that Vuse Solo+ and Vuse Ciro are identical in design and ingredients and that the products only differed in name. Vuse Ciro uses (b) (4) (copolyester) tank that acts as the e-liquid reservoir.
- PM0000635, PM0000646, PM0004287, and PM0004293 are power units.
- PM0000636 and PM0000712 are disposable closed pre-filled e-liquid cartridges in Original (tobacco) flavor.
    - Both new product e-liquids contain nicotine (3% for Vibe (PM0000636) and 1.5% for Ciro (PM0000712)). These two products' ingredients vary in other respects, namely various ratios of propylene glycol/glycerin (PG/VG), water, and flavor ingredients.
    - Both new product e-liquids contain (b) (4) (b) (4) free-base nicotine.
    - Both new product e-liquids contain lactic acid, which may form nicotine salts. The applicant provided total nicotine aerosol quantities and pH under non-intense and intense puffing regimens for both e-liquid new products. The amounts of nicotine salts in the e-liquids were calculated by the applicant from total nicotine and pH results. Although nicotine salts were present in the Original tobacco-flavored ENDS products (b) (4) mg/puff non-intense, (b) (4) mg/puff intense), the nicotine salt quantities in the Original tobacco-flavored ENDS products were comparable to the nicotine salt quantities reported in the ENDS market comparison products. Therefore, the presence of lactic acid in the Original tobacco-flavored ENDS products is not a concern from a chemistry perspective.

Per the engineering review:

- The applicant adequately describes the Vuse Vibe and Vuse Ciro power unit and e-liquid cartridge components and how they function together. The new products are operated by connecting a specific disposable cartridge to the appropriate rechargeable power unit. The system is activated by a user inhalation that is strong enough to trigger an internal sensor that is imbedded in the power unit. The new products are tamper-resistant and have no adjustable settings.
- The applicant provided the target specifications and upper and lower range limits for all of the design parameters for the new products.
- The design specifications, defined by the applicant as a parameter with established specifications that are measured and used to accept or reject products during manufacture, are as follows:
    - (b) (4)
    -
- The new products do not contain temperature controls and operate at coil temperatures ranging from 154-500°C for the Vuse Vibe and 115-264°C for the Vuse Ciro when puffed at an 80 mL puff volume, 15 second puff interval, 5 second puff

duration. BCP considers the applied intense smoke regime acceptable for evaluating the coil temperature.

- From an engineering perspective, the information provided regarding design and principles of operation adequately characterizes the new products and allows FDA to evaluate the potential risk or injury that may be caused from using the new products.

Per the microbiology review:

- The new products contain humectants (b) (4) (b) (4) and (b) (4), which may impact microbial activity during product shelf-life. However, the product stability data (see 3.2.1.3 below) indicates that the products are low risk for microbial growth.
- The applicant provided adequate information on the type and concentration of humectants that comprise the new products.

3.2.1.2. Manufacturing

Per the chemistry review:

- Target quantities for (b) (4), and (b) (4) used in the manufacturing of the e-liquid formulations were provided. Ranges (maximum and minimum values) for (b) (4) and (b) (4) used in the manufacturing of the e-liquid formulations were not provided. However, the applicant did provide the "rejected low," "rejected high," and target e-liquid fill weight for the cartridges (b) (4) of the target value). The information provided is acceptable for ensuring that the (b) (4) and (b) (4) quantities in the finished products are added in a consistent manner.
- The applicant provided sufficient details about the analytical testing methods used to generate HPHC aerosol yields in the new products. The applicant also provided sufficient information about the storage conditions and stability data to demonstrate that the storage conditions for the finished products are adequate.
- Therefore, the information on the quantities of (b) (4) and (b) (4) in the finished products, the HPHC aerosol data, the stability data, as well as the storage conditions is considered adequate from a chemistry perspective and provides evidence that the products are manufactured in a consistent manner that minimizes the variability in product quality.

Per the engineering review:

- The information on the manufacturing steps and the quality control measures in place assure FDA that the products meet manufacturing specifications for the Vuse Vibe and Vuse Ciro power units and cartridges. It is evident that the products are manufactured in a consistent manner that minimizes the variability in product quality.
    - The applicant outlined how the batteries' manufacturers were assessed prior to their agreement and outlined how the batteries are verified (b) (4)
    (b) (4)
    - The applicant provided standard operating procedures for all battery manufacturing and functional verifications. In addition, the applicant

described how it is are involved in continuous monitoring of their battery manufacturers.

- From review of the documents provided, the manufacturing information provided is acceptable and demonstrates that the processes in place will ensure products are manufactured properly and any non-conforming product will be identified and removed from distribution.

Per the microbiology review:

- A Remote Regulatory Assessment (RRA)[viii] of one of the manufacturing and packaging facilities (b) (4) was conducted on March 08, 15, 22 and 25, 2021. No objectionable conditions were found.

3.2.1.3. Product stability

Per the chemistry review:

- The analytical methods used in the chemical stability studies were fit for purpose and fully validated.
- The aerosol yields in PM0000636 and PM0000712 at t=0 months, t= (b) (4) and t= (b) (4) demonstrated no significant changes in the aerosol constituents over their established shelf-life (b) (4) for the new products.
- The aerosol extractable and leachable constituents' quantities from the e-liquid replacement cartridge components (including simulated leachable study in artificial saliva) and the aerosol leachables quantities from selected e-liquid replacement cartridges were minor. Chemistry concluded that it is unlikely that product characteristics negatively impact the aerosol extractable and leachable constituent levels.

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.[1,2] 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 data (water activity, N-nitrosonornicotine [NNN], and 4-(methylnitrosamino)-1-(3-pyridyl -1-butanone [NNK], endotoxin and (1→3)- β-D glucan) measured over (b) (4) of shelf-life was provided for PM0000636 and PM0000712 (original tobacco flavored ENDS products). The stability data indicates that the products are at low risk for microbial growth over (b) (4) However, the applicant's proposed shelf-life is (b) (4) Therefore, the data provided are sufficient to demonstrate microbial stability over (b) (4) but not sufficient to demonstrate microbial stability over the applicant-proposed shelf-life of (b) (4)

3.2.1.4. Product test data

Per the chemistry review:

- The e-liquid ingredients and quantities in Vuse Vibe and EVIGO (the predecessor product) for the original characterizing flavor are similar. The applicant reported the ingredients both in total mass (mg) per cartridge and in mass percent (mg

[viii] Due to the COVID-19 pandemic, an onsite inspection of the manufacturing facility was not possible.

ingredient/mg total mass*100). Although the total mass of the e-liquid in the Vuse Vibe (Original) is (b) (4) mg and the total mass of the e-liquid in Vuse Solo (Original) is (b) (4) mg, the percentages of common ingredients in the Vuse Solo compared to the Vuse Vibe are similar. The similarities in e-liquid formulation for Vuse Solo and Vuse Vibe support bridging the results of studies of Vuse Solo to Vuse Vibe. The Vuse Solo products the applicant is referring to are G1 and G2. Vuse Solo G2 was used to bridge Vuse Vibe in the toxicology study and Vuse Solo G1 was used to bridge to Vuse Vibe in the Environmental Emission study. Chemistry reviewed the list of ingredients in EViGO and concluded that its ingredients and their quantities are similar to those of Vuse Vibe. EViGO was used to bridge to Vuse Vibe in thermal profiling and clinical studies.

- The applicant stated that Vuse Solo+ and Vuse Ciro are identical in design and ingredients and that the products only differ in name. Data submitted for Vuse Solo+ can be used to evaluate the new product, Vuse Ciro.
- Compared to combusted filtered cigarettes, most of the aerosol yields under both non-intense and intense smoking regimens in PM0000636 and PM0000712 were lower, and chemistry did not have an issue with these values.
- The aerosol yields of constituents from the new products have higher mass quantities of nicotine, acetaldehyde, and formaldehyde compared to those found for the ENDS market comparison products. However, when reported in mass percent (mg ingredient/mg total mass*100), the yields are comparable. The aerosol yields of nicotine, acetaldehyde, and formaldehyde in the new products are significantly below the levels present in cigarette smoke.
- The analytical methods used to test the aerosol HPHC quantities were fit for purpose and fully validated.
- Aerosol HPHC yields reported for the new products under the intense puffing regimen may not be representative of the maximum exposure to a consumer if the maximum temperature of the heating element is reached. However, the applicant provided a consumer topography report to adequately justify why it is unlikely that a user will use a product to its functional limitations.

Per the engineering review:

- The applicant provided test data for the battery design parameters for all batteries, and it demonstrates the products are manufactured as intended. The batteries are manufactured properly and function to meet International Electrotechnical Commission (IEC) 62133, UN38.3, and UL 1642 battery standards.
- The PMTAs, PM0000635, PM0000636, and PM0004287 included thermal test reports in which the test facility noted changes in wick color, and it was uncertain whether the changes were due to dry puffing. FDA issued a deficiency to the applicant to clarify whether these thermal test report results were due to dry puffing. In response, the applicant submitted smoke testing data that applies an intense smoking regimen, which FDA considers adequate and demonstrated the e-liquid features associated with the new products adequately prevent a dry-puff hazard from occurring. The test data also demonstrates that thermal temperatures for PM0000635 and PM0004287 (the Vuse Vibe Power Units) are reasonably low and do not pose a burn hazard to users. These concerns were not present for the PM0000646 and PM0004293 Vuse Ciro power units.

- The test data demonstrates that the products will function as intended after foreseeable conditions are applied.
- The leak test data provided in Amendment PM0004600 demonstrates that the e-liquid cartridges are not likely to leak and that if a non-conforming product is manufactured, leaking would likely be identified prior to distribution.
- The missing test data for coil diameter and coil length is not a concern from an engineering perspective, because (b) (4)
(b) (4)
- Based on the information provided in the PMTAs for the devices and 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 the engineering, chemistry, and microbiology conclusions that these PMTAs contain sufficient information to characterize the product design and adequate processes and controls to help ensure that the products meet the manufacturer's specifications. The applicant only submitted microbial stability data for (b) (4) and not for the entire proposed shelf-life of (b) (4) However, because the stability data for (b) (4) months is acceptable and indicates that the products are low-risk for microbial growth over an (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.

3.2.2.1. Product Design and Composition

The Vuse Vibe and Vuse Ciro new products are ENDS composed of closed pre-filled e-liquid cartridges (i.e., Vuse Vibe PM0000636, Vuse Ciro PM0000712) and a power unit (i.e., PM0000635, PM0004287 Vuse Vibe power units; PM0000646, PM0004293 Vuse Ciro power units). PM0000636 and PM0000712 consist of e-liquid cartridges in Original flavor with 3.0% nicotine in PM0000636 and 1.5% nicotine in PM0000712. The battery in the power units (PM0000635, PM0000646, PM0004287, and PM0004293) conform to product standards UN38.3, IEC 62133, and UL 1642. All four power units use a Universal Serial Bus (USB) charger to charge the power units. Two batteries are used in the Vuse Vibe Power Units with design parameter specifications that are not identical. Since both batteries can be used in the same power system assembly, to differentiate the Vuse Vibe power units, PM0000635 is for the power unit that uses the battery manufactured by (b) (4) and PM0004287 is for the power unit that uses the battery manufactured by (b) (4) (b) (4) Two batteries were also used for the Vuse Ciro Power Units; separate STN numbers are used by CTP to differentiate the power units: PM0000646 is for the power unit that uses the battery manufactured by (b) (4) and PM0004293 is for the power unit that uses the battery manufactured by (b) (4)

The e-liquid formulations for the products in PM0000636 and PM0000712 are made up of PG, VG, nicotine, water, and flavor ingredients. Both e-liquids contain (b) (4) derived, (b) (4) free-base nicotine (3% for Vibe products and 1.5% for Ciro products).

Once the user has connected the power unit to a respective cartridge, the assembled unit is activated by inhaling air through the mouth-end of the cartridge. This puffing action and the resulting pressure differential activate the pressure sensor in the power unit. Activation of the pressure sensor signals the controller in the power unit to send power to the heater coil in the cartridge. The resistance of the cartridge is checked against a minimum threshold, and then the heater coil is powered for as long as the pressure sensor detects a pressure differential. PM0000635 and PM0004287 can be inhaled for a maximum of six seconds, and not be inhaled again for approximately three seconds. PM0000646 and PM0004293 can be inhaled for a maximum of (b) (4) and not be inhaled again for approximately three seconds. Users cannot alter the power source battery or the cartridge reservoir without damaging the enclosures. The power units and cartridges are not user-adjustable, and this mitigates the potential for a consumer to change product characteristics, adjust product performance, or modify product ingredients. The cartridges are not designed to be opened, refilled, or otherwise modified by the consumer. The user can control how often they inhale and how much suction force is applied during inhalation.

Summary

As TPL, I agree with the engineering, chemistry, and microbiology conclusions that these PMTAs contain sufficient information to characterize the product design and composition of the new products.

3.2.2.2. Manufacturing

The applicant stated that the manufacturing of the ENDS in PM0000635, PM0000636, PM0000646, PM0000712, PM0004287, and PM0004293 consists of four processes (i.e., e-liquid mixing, cartridge assembly and filling, power unit manufacturing, packaging). The e-liquids in PM0000636 and PM0000712 were manufactured by RJRT in Tobaccoville, NC. The power units used in PM0000635 and PM0004287 were manufactured by (b) (4) in (b) (4) for PM0000636, bulk e-liquids and finished power units were shipped to (b) (4) where cartridges (filled with e-liquid, sealed in the blister packs), final kits, and the USB charger were assembled. The power units in PM0000646 and PM0004293 were manufactured by (b) (4) For PM0000712, bulk e-liquids were shipped from Tobaccoville, NC to (b) (4) where cartridges (filled with e-liquid, sealed in the blister packs) and packaging were completed. The applicant does not state where the USB charger for PM0000646 and PM0004293 is manufactured. However, the USB charger's output is limited and controlled by the respective power units. In addition, the recharging function of the power unit and the associated charger were adequately demonstrated to function properly through testing. The finished ENDS are imported for distribution in the United States.

For all new products (PM0000635, PM0000636, PM0000646, PM0000712, PM0004287, and PM0004293), the applicant qualifies and monitors suppliers using processes governed by standard operating procedures. Processes are structured and implemented to prevent adverse material quality impact on finished products and to identify events that require corrective and preventive action. These processes include (b) (4)

(b) (4)

(b) (4)

(b) (4) processes that effectively anticipate or manage process or product issues.

FDA/CTP completed a Remote Regulatory Assessment (RRA) on December 15, 2020 of (b) (4) a second-party supplier that manufactures the e-liquid cartridges. The supplier does not manufacture the e-liquid, nor does it assemble power units. During the inspection, ORA did not find any significant findings.

Summary

As TPL, I agree with engineering, chemistry, and microbiology conclusions that the applicant demonstrates that the new products are manufactured in a consistent manner that minimizes variability in product quality.

3.2.2.3. Product Stability

The applicant provided the chemical stability data for representative e-liquid flavors, including PM0000636 and PM0000712, by monitoring the changes in the aerosol constituent levels and aerosol pH levels over the intended shelf-life (b) (4) of the e-liquid replacement cartridges. The aerosol yields in PM0000636 and PM0000712 at t=0 months, t= (b) (4) and t= (b) (4) demonstrated no significant changes in the aerosol constituents over the established shelf-life (b) (4) for the new products.

The e-liquid formulations of all new products consist of five "core ingredients" (b) (4) (b) (4) and (b) (4) that account for > 96% by weight, with (b) (4) representing the greatest proportion (> 89% by weight). The remaining ingredients in each e-liquid are all flavoring ingredients and collectively represent < 4% by weight of each formulation.

The applicant indicated that the expected shelf-life of all new products is (b) (4) However, the applicant submitted finished product microbial stability data (water activity, NNN, NNK, endotoxin and (1→3)-β-D-glucan data) measured over only (b) (4) of shelf-life for PM0000636 and PM0000712 (Original tobacco flavored ENDS products). All products were tested at three time points (beginning [time zero], middle (b) (4) and end (b) (4) (b) (4) over an (b) (4) time period. The stability data indicates that the products are low risk for microbial growth over (b) (4) As container-closure systems and product composition (i.e., humectants) could potentially affect tobacco product stability during complete shelf-life of the products, additional stability testing data beyond (b) (4) would be needed to determine the stability of these products for the entire shelf-life. However, because the stability data for (b) (4) is acceptable and indicates that the products are low-risk for microbial growth over an (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.

The applicant does not specify a lifetime or expiration date for the Vuse Vibe and Vuse Ciro power units. In Amendment PM0004600 the applicant explained why a lifetime is not applicable to either power unit. As TPL, I agree with the engineering discipline's determination that the applicant's justification is acceptable; lifetime is not applicable

because the products should stop powering e-liquid cartridges when their battery capacity reaches a lower limit, and this is not a safety hazard.

Summary
The submitted microbial stability data covers an (b) (4) period and was found to be sufficient in demonstrating the new products' microbial stability over (b) (4)

3.2.2.4. Product Test Data

Compared to mainstream smoke of the comparison combusted cigarette, aerosol quantities for acrylonitrile, 4-aminobiphenyl, 1-aminonaphthalene, 2-aminonaphthalene, ammonia, anabasine, benzene, B[a]P, 1,3-Butadiene, cadmium, chromium, crotonaldehyde, diacetyl, diethylene, isoprene, lead, menthol, nickel, NNK, NNN, and toluene were below the limit of detection and acetaldehyde, acrolein, and formaldehyde aerosol quantities were lower under both non-intense (74% - 100% lower) and intense (34%-100% lower) puffing/smoking regimens.

In some cases, PM0000636 and PM0000712 generated lower constituent quantities compared to the ENDS comparison products. However, the aerosol yields of constituents from the new products have higher absolute mass quantities of nicotine, acetaldehyde, and formaldehyde than those of the ENDS market comparison products (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. However, I agree with the chemistry conclusion that when these constituents are reported in mass-to-mass ratio the differences are minor. For PM0000636 and PM0000712, the aerosol quantities for the new products were lower compared to the cigarette mainstream smoke quantities.

The applicant provided test data for the battery design parameters for all batteries, and it demonstrates that the products are manufactured as intended. Most importantly, the batteries are manufactured properly and function to meet IEC 62133, UN38.3, and UL 1642 battery standards.

The applicant also provided test data for airflow rate, puff count, atomizer tank/cartridge volume, inhaled aerosol temperature, heating element diameter, heating element temperature range, power delivery unit (PDU) current operating range, PDU current cut-off, PDU temperature cut-off, and e-liquid volume. The applicant provided test data for each of these parameters except for the atomizer tank/cartridge volume, coil diameter, current operating range, current cut-off, and PDU temperature cut-off. For the parameters for which no test data is provided, the applicant provides adequate justification for why they are not provided (e.g., volume of cartridges is not tested because weight of e-liquid is measured, coil diameter is not tested because there is direct control of the resistance which indirectly controls the coil diameter).

In Amendment PM0004600 the applicant provided leak test data demonstrating that the e-liquid cartridges are not likely to leak and that if a non-conforming product is manufactured, leaking would likely be identified prior to distribution.

Summary

As TPL, I agree with the chemistry and engineering conclusions that the product test data indicated that adequate manufacturing processes and controls were used to ensure that the new products meet manufacturer's specifications.

3.3. ABUSE LIABILITY

The BCP review considered the seven applicant-sponsored clinical studies in adult smokers, six of which used the new products that are subject to the PMTAs, and one additional study using the EViGO, a predecessor of the Vuse Vibe products. Abuse liability-related outcomes from these studies included nicotine exposure, nicotine pharmacokinetics, product liking, and product use. The following discussion is based on key findings provided in the BCP discipline review.

3.3.1. Discipline key findings

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 product. 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 a product they are currently using with higher abuse liability. On the other hand, low abuse liability makes it less likely that new users will become addicted.
- In ENDS-naïve exclusive combusted cigarette smokers, the abuse liability of Vuse Vibe (3.0% nicotine) and Vuse Solo+ (Ciro, 1.5% nicotine) Original tobacco-flavored ENDS products (PM0000636 and PM0000712, respectively) is significantly lower than that of combusted cigarettes and slightly greater than that of 4mg nicotine replacement therapy (NRT) gum, evidenced by similar nicotine uptake and subjective effects after acute use. This may increase the likelihood of use of and adherence to the new products compared to NRT in smokers interested in quitting combusted cigarette smoking.
- Due to their puffing patterns, experienced ENDS users can obtain increased nicotine uptake from use of the Vuse Vibe products or Vuse Ciro products, which may promote switching, yet nicotine uptake remains lower than nicotine uptake from combusted cigarettes after acute use. With extended exclusive use of the Vuse Vibe or Vuse Ciro, the cumulative nicotine uptake could reach similar values as combusted cigarettes.
- 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 that experienced ENDS users achieve comparable nicotine uptake from ENDS relative to combusted cigarettes[3,4]; 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

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 that of combusted cigarettes and is greater than that of 4mg nicotine gum. However, with experience, users might reach higher nicotine levels to satisfy their withdrawal and craving symptoms. Data from the applicant's BOE study showed that urine total nicotine equivalent (TNE) levels for the Vuse Vibe Original flavor (PM0000636) and Vuse Solo+ (Ciro, 1.5% nicotine) Original flavor (PM0000712) approached UB cigarette levels after 5 days of ad libitum use (see section 3.5.1.2. for more information on BOE). 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 applicant did not include ENDS comparison products in the clinical studies, so the abuse liability of the new products in direct comparison to other ENDS is unknown. However, data from the applicant's clinical studies show that the maximum measured plasma nicotine concentration (Cmax) for Vuse Vibe and Vuse Ciro Original flavored products are within the range of other ENDS products' Cmax values as reported in the published literature."[5] Given the evidence from the literature, which indicates that the abuse liability of these new products is likely within the range of the abuse liability of other ENDS, as TPL I am satisfied with the information submitted by the applicant on abuse liability despite the lack of comparison to other ENDS. Collectively, the data suggest that the abuse liability of the Vuse Vibe and Vuse Ciro new products is lower than that of combusted cigarettes in current tobacco users. The nicotine levels that adult users of 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 non-tobacco users, as discussed in 3.4.2.3 below, appeal of the new products is low in non-tobacco users and therefore the risk of addiction for non-tobacco users does not outweigh the potential benefits to current tobacco-using adults.

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(s) (target population)

Per the BCP review:

- The applicant stated that the intended user population(s) for the Vuse Vibe products and Vuse Ciro products are current tobacco users, including current cigarette smokers and current ENDS users. The applicant submitted two clinical studies evaluating the PMTA products in exclusive cigarette smokers, and three clinical studies evaluating the PMTA products in ENDS and combusted cigarette dual users. These data provide adequate evidence to inform use behavior in those populations.

Per the epidemiology review:

- The applicant stated that the likely user population for Vuse Vibe and Vuse Ciro is current cigarette smokers. Data from observational studies characterizing users of these new products found that more than 90% of current established Vuse Vibe

users and more than 95% of current established Vuse Ciro users reported a history of cigarette smoking. The observational studies analyzed by the applicant provide sufficient information to evaluate the patterns of use of these new products in adult smokers.

Per the social science review:

- The applicant states that the intended user population is current tobacco users ages 21+. The applicant does not describe any other audience demographics or psychographic characteristics for its intended user population.
- The applicant provided "projected use" data indicating that current tobacco experimenters, established combustible cigarette users, and established non-cigarette tobacco users are projected to use the new products.

3.4.1.2. Current tobacco users

3.4.1.2.1. Precursors of product use

Per the social science review:

- The applicant used two studies with nearly identical research methods and analyses to provide "precursor to use" data for Vibe and Ciro. Participants were only exposed to a single product line (e.g., Vibe, Ciro) within a given study and provided responses to either Vibe or Ciro products, but not both. Findings were similar for Vibe and Ciro.
- The applicant asked participants to provide product appeal ratings for either Vibe or Ciro overall, not for each flavor within each product line. In other words, product appeal ratings were given for each product line as a whole (e.g., Vibe) but not for any specific flavor. The applicant study findings indicate that among all participants (adults ages 18-75) in all established tobacco user groups, the mean perceived product appeal for the new products was slightly above the midpoint of the 7-point appeal scale (Vibe 4.0-4.6; Ciro 4.2-4.4). Established cigarette users ages 18-75 reported that they found cigarettes about 1 point more appealing than the new products on a 7-point scale. The applicant study findings indicate that among all participants (adults ages 18-30) in current tobacco user groups, the mean perceived product appeal for the new products was also slightly above the midpoint of the 7-point appeal scale (Vibe 4.2-4.8; Ciro 4.5-4.8). Established cigarette users ages 18-30 found the cigarettes about equally appealing as the new products on a 7-point scale. This was an assessment of product appeal perceptions for Vibe or Ciro overall.
- The applicant asked participants to provide ratings of intention to buy the product for either Vibe or Ciro overall, not for each flavor within each product line. In other words, intention to buy ratings were given for the product line as a whole (e.g., Vibe) but not for any specific flavor. The applicant study findings indicate that for all participants (adults ages 18-75) among all current tobacco user groups, current tobacco experimenters (participants who have used one or more categories of tobacco products in the past 30 days but have not reached lifetime criteria of 100 uses of the product(s)) reported the highest mean intentions to buy the product (Vibe 5.9 (5.5-6.3); Ciro 6.0 (5.7-6.4)) on a 10-point scale) and have the highest mean projected product use rates (Vibe 18.2% (13.0-24.7); Ciro 17.9% (12.7-24.3)). The applicant study findings indicate that for young adult participants (adults ages 18-30) among all current tobacco user groups, current tobacco experimenters (participants who have used one or more categories of tobacco products in the past

30 days but have not reached lifetime criteria of 100 uses of the product(s)) reported the highest mean intentions to buy the product (Vibe 6.1 (5.6-6.6); Ciro 7.0 (6.5-7.5)) on a 10-point scale). This was an assessment of intention to buy the products for Vibe or Ciro overall.

- Current established cigarette users report various main reasons for their interest in using Vibe or Ciro. Among current cigarette users who selected Vibe Original flavor as their flavor of most interest, 47.4% selected "to reduce smoking"/"to stop smoking" as their main reasons for using Vibe. Among current cigarette users who selected Ciro Original flavor as their flavor of most interest, 46.8% selected "to reduce smoking"/"to stop smoking" as their main reasons for using Ciro.

3.4.1.2.2. Product Use

- Clinical or actual use studies
  Per the BCP review:
  - Dual/poly use
    - The abuse liability information provided suggests that Vuse Vibe products and Vuse Ciro products are less efficient at delivering nicotine than combusted cigarettes. Therefore, current combusted tobacco product users who initiate ENDS use with the new products are likely to dual-use the new products with cigarettes.

  - Complete switching
    - The abuse liability (i.e., nicotine exposure) of Vuse Vibe products and Vuse Ciro products is lower than that of combusted cigarettes; therefore, the likelihood that cigarette smokers who initiate use of the Vuse Vibe or Ciro will switch completely to the new products is low.

  - Cessation
    - Vuse Vibe 3.0% (Original) and Vuse Ciro 1.5% (Original) were associated with slightly greater abuse liability than 4mg NRT gum, which may increase the likelihood of use of the new products and adherence compared to NRT in cigarette smokers interested in quitting all tobacco products.

- Observational studies or surveys
  Per the epidemiology review:
  - Dual/poly use
    - Dual use is very common among users of these new products. Based on data from the National Tobacco Behavior Monitor (NTBM) and Total Tobacco Migration Tracker (TTM) population surveys, over 92% of current established Vuse Vibe users had a history of cigarette smoking and most were current established cigarette smokers (70.6% in NTBM, 77.7% in TTM). Vuse Vibe users who used the product daily reported slightly fewer cigarettes per day (CPD) than did non-daily users, although it was not reported whether these differences were statistically significant (NTBM: 9.7 CPD for daily users and 10.3 for non-

daily users; TTM: 9.7 CPD for daily users and 12.8 CPD for non-daily users).

- Almost all current established Vuse Ciro users had a history of smoking cigarettes in the NTBM (95.7%) and most were current established cigarette smokers (69.6%). Among current established smokers, the average number of CPD was 11.4 for daily Vuse Ciro users and 9.2 for non-daily users.

- Complete switching
  - In Cycle 1, data from the Population Assessment of Tobacco and Health (PATH) Study and the Colorado Longitudinal Study were used to evaluate transitions in tobacco use behavior (i.e., the transition to dual use or switching) in adult smokers. These analyses were not brand-specific. To increase sample size, analyses were conducted that evaluated some tobacco use behaviors among all ENDS users in the study and the results were bridged to Vuse Vibe and Vuse Ciro users with the justification that users of these products are not different than all ENDS users. To support this, the applicant provided data to show that Vuse Vibe and Vuse Ciro users have demographic characteristics and tobacco use histories that are not significantly different than all ENDS users in these studies regardless of brand used.
  - 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 switched to ENDS at the 6-month follow-up. Among those who were dual users at Month 6, 6.7% switched to ENDS by Month 12. While this study was able to show switching behavior, we are not able to determine whether that behavior was sustained based on the length of time covered; therefore, the long-term impact cannot be determined. All data on switching were bridged to all ENDS users and no data were provided on switching rates among Vuse Vibe or Vuse Ciro users. These findings are aligned with prior abuse liability findings (discussed in section 3.3) and indicate that current adult combusted cigarette users who initiate use of the new products have low likelihood of completely switching to the new products as they are more likely to dual-use with cigarettes.
  - In the cited studies, daily ENDS users were more likely to transition from dual use to exclusive ENDS use than were non-daily users. In the PATH Study, the odds of switching from dual use was 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 switching were nearly twice as high among daily ENDS users from baseline to Month 6 (7.3%) compared to non-daily users (4.1%).
  - Brand-specific longitudinal data were not provided, but the NTBM and TTM surveys were able to evaluate retrospective lifetime histories of

tobacco use among Vuse product users. In those studies, current Vuse Vibe users who were daily users were more likely than non-daily users to be former cigarette smokers (37.0% versus 13.3% in NTBM; 17.3% versus 7.6% in TTM). In the NTBM survey, daily Vuse Solo users (a proxy for Vuse Ciro) were almost three times more likely than non-daily Vuse Solo users to be former cigarette smokers (36.6% versus 12.7%). Additionally, based on retrospective smoking histories collected in the NTBM and TTM surveys, daily ENDS users reported significantly greater reductions in cigarette consumption over the previous one-year period than did non-daily ENDS users.

- The longitudinal data on switching submitted by the applicant are not brand-specific and show that a small percentage of smokers and dual users are able to switch to ENDS. Some cross-sectional brand-specific data were presented that found that daily users were more likely to report being a former smoker, suggesting that daily use may help with switching, but temporality between ENDS use patterns and quitting smoking cannot be established with these retrospective analyses.

3.4.1.3. Tobacco non-users (including youth)[ix]

3.4.1.3.1. Precursors of product use

Per the social science review:

- The applicant did not provide direct data on youth in its original submission or Amendment PM0004600. FDA determined in Cycle 1 that young adult data can be a proxy for youth data.
- The applicant study findings indicate that among non-users (ages 18-75) [x], the mean perceived risk of developing general poorer health from using each new product was high on the 7-point risk scale (range for both products: 5.9-6.0). Non-users rated the risk of developing generally poorer health from using cigarettes higher than that of the new products (.4-.8 points riskier than the new products on a 7-point scale).
- The applicant study findings indicate that among non-users ages 18-75, the new products were rated as unappealing (mean perceived product appeal on a 7-point scale; never users Vibe: 2.2/Ciro 2.3; former tobacco users Vibe 2.3/Ciro 2.5). Young adult non-users (ages 18-30) also found the new products unappealing (young adult never users: Vibe 2.7/Ciro 2.8; young adult former tobacco users: Vibe 3.0/Ciro 3.0); however, their ratings of the new products' appeal were higher than the ratings of the new products' appeal from the

[ix] 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 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 a benefit to adult smokers may not need to be as high.

[x] When reporting findings from its surveys, the applicant generally provided descriptive statistics for participants ages 18-75 in each tobacco user group; for some key measures, the applicant also provided descriptive statistics for only young adult (ages 18-30) participants in each tobacco user group.

sample with older participants. These appeal ratings were reported for the new devices overall, not broken down by flavor. Therefore, these appeal ratings cannot be used on their own to evaluate youth appeal of the tobacco ENDS (Original flavored products) that are the subject of this review. These data should be interpreted along with the applicant submitted data that young adult non-users did not select tobacco ENDS (Original flavored products) as flavor of most interest (compared to the non-tobacco flavored products). Additionally, these appeal ratings should be interpreted along with published National Youth Tobacco Survey (NYTS) data indicating that youth find cartridge-based products appealing but find tobacco ENDS less appealing than non-tobacco flavored products. More details about youth perceptions of cartridge-based and tobacco ENDS products are provided below.

- The applicant submitted one new analysis of overall product appeal for young adults under the age of tobacco sale (ages 18-20) to address concerns about the appeal of the new products for tobacco non-users, including youth. Due to statistical limitations of the linear regression analysis provided by the applicant (small sample sizes collected from only a subset of U.S. states; insufficient evidence that the applicant met the statistical assumptions for conducting this analysis; no reporting of key model specifications), the applicant's claim that "appeal for these products is unlikely to be higher among those under 18 years of age compared to those ages 18-30" is not supported. However, this data should be interpreted along with published NYTS data indicating that youth find cartridge-based products appealing but find tobacco ENDS less appealing than non-tobacco flavored products. More details about youth perceptions of cartridge-based and tobacco flavored ENDS products are provided below.
- The applicant study findings indicate that the proportion of participants interested in purchasing Vibe or Ciro was significantly higher in tobacco user groups (current cigarette users: Vibe 61%/Ciro 66%; current non-cigarette tobacco users: Vibe 56%/Ciro 54%; current tobacco experimenters: Vibe 76%/Ciro 73%), than in non-user groups (former users: Vibe 20%/Ciro 22%; never users: Vibe 8%/Ciro 9%). Compared to the sample of non-users ages 18-75, young adult non-users (ages 18-30) indicated more interest in purchasing Vibe or Ciro (young adult former users: Vibe 40%/Ciro 40%; young adult never users: Vibe 16%/Ciro 17%). These interest in purchasing data are not broken out by flavor and cannot be used to evaluate youth appeal of these tobacco-flavored products on their own; therefore, these data should be interpreted along with published data that youth find cartridge-based products appealing but find tobacco-flavored products unappealing. In summary, social science does not expect that the tobacco-flavored products will be especially youth-appealing. More details about youth perceptions of cartridge-based and tobacco ENDS products are provided below. According to National Youth Tobacco Survey (NYTS) 2021 data, 28.7% of middle and high school users reported prefilled or refillable pods or cartridges as the ENDS device types they used most often.[6] The ability to use products discreetly and the products' sleek design and user-friendly nature make pod mod (rechargeable cartridge-based ENDS) products appealing among youth. 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 flavored ENDS, making the risk of youth initiation low for these Original tobacco ENDS products. Generally, the interest in tobacco flavor is low among youth. The available evidence from NYTS 2019 and 2021 indicates that a higher percentage of middle and high school current tobacco users reported using non-tobacco ENDS (e.g., menthol, mint, clove or spice, alcoholic drinks, candy, fruit, chocolate) than tobacco ENDS.[6,7] 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.[8] Additionally, the published literature indicates that youth report significantly higher preference for non-tobacco flavored ENDS compared to tobacco-flavored ENDS.[9-11] 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 flavored ENDS. 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.[12] According to the 2020 MTF data, among ENDS users 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%).[12]
- In addition, FDA believes the digital marketing and TV and radio restrictions recommended by OHCE will help to mitigate the risk of youth initiation.

3.4.1.3.2. Product Use

- Clinical or actual use studies
  Per the BCP review:
  - Progression
    - The abuse liability of the Vuse Vibe products and Vuse Ciro products is lower than that of cigarettes in current adult cigarette smokers. No clinical studies of progression to regular use were conducted in non-tobacco users.
    - Due to the lower abuse liability of these products compared to cigarettes, former tobacco 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 as compared to cigarettes.
    - The applicant-provided analysis of the PATH youth survey data showed slightly lower dependence scores for ENDS than for combusted cigarettes in dual users, though this difference was not statistically significant. Among youth exclusive combusted cigarette smokers vs. exclusive ENDS users, dependence scores among the ENDS group were statistically significantly lower than those of combusted cigarette smokers.
    - This analysis was limited because it examined general ENDS use and incorporated data collected until 2016. Therefore, the results of this analysis do not reflect the ENDS currently

available on the market, nor does this analysis apply directly to the new products, limiting its generalizability.

- There were no clinical studies of initiation with the Vuse Vibe or Ciro conducted in non-tobacco users or adolescent tobacco users. 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 that 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).

- Observational studies or surveys
  Per the epidemiology review:
  - Initiation
    - Use of these products among adult never smokers is not common; 8% of established Vuse Vibe users and 4% of established Vuse Ciro users were never cigarette smokers. Brand-specific data provide strong evidence that use among adult never smokers is likely limited.
    - The applicant also assessed initiation of ENDS use among never tobacco users in Waves 1-3 of the PATH Study. Initiation of tobacco use with ENDS was uncommon. Only 0.2% of adult never tobacco users and 1.7% of youth never tobacco users initiated tobacco use with ENDS. However, it should be noted that these estimates were from data collected between 2013-2014 (Wave 1) and 2015-2016 (Wave 3), which was before ENDS use became more common in youth. No data were provided for the initiation of tobacco use with specific brands of ENDS.
  - Youth
    - In 2021, Vuse was one of the five most commonly reported usual brands among middle and high school current ENDS users.[6] Some evidence in the peer-reviewed literature on youth device type preferences suggests that 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.[13] However, 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 flavored ENDS.
    - The NTBM and TTM surveys that were analyzed by the applicant were composed 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 18-24 as a proxy for youth. Epidemiology considers this an

appropriate strategy in the absence of youth data. In these studies, increasing age was not associated with a change in the prevalence of young adults using Vuse Vibe (NTBM: OR=0.98, 95% CI: 0.93-1.04, p=50; TTM: OR=1.02, 95% CI: 0.90-1.41, p=0.79). However, increasing age was associated with increased likelihood of using Vuse Solo (a proxy for Vuse Ciro) (NTBM: OR=1.11, 95% CI: 1.03-1.19, p=0.005; TTM: OR=1.14, 95% CI: 1.01-1.29, p=0.0344), suggesting that younger people are less likely to use the product. Although the prevalence of Vuse Vibe use did not decrease with increasing age in young adults, most adult Vuse Vibe users are over age 30 (70.8% in NTBM, 73.8% in TTM).

- Former tobacco users
    - Data from PATH Wave 1 to Wave 3 were used to evaluate the likelihood of ENDS use among former tobacco users. However, no brand specific data were evaluated, and the applicant did not provide a justification for bridging the results from the PATH data to the new products to indicate the weight of this evidence. In PATH, 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.

- Progression
    - In an analysis conducted by the applicant using PATH youth survey data, 5.5% of never ENDS users at Waves 1-2, reported having ever used ENDS at Wave 3; however, 69.1% of those were not currently using ENDS at Wave 3, and the applicant states that the findings suggest that the use of ENDS in the youth population may be transient. Among youth who started using tobacco products as dual users, 25.6% stopped using any tobacco product a year later and another 9.5% stopped cigarette smoking but continued using ENDS. No brand-specific data were provided on the likelihood of progressing from ENDS use to cigarette smoking.
    - Some evidence in the peer-reviewed literature on youth device type preferences suggests that 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.[13] The literature shows that non-tobacco flavored ENDS use is very common in both youth and adult ENDS users (irrespective of the device type).
    - Overall, the available evidence to date does not adequately address whether ENDS use in youth and young adults leads to regular smoking. 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 flavored ENDS.

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

Per the BCP review:

- No clinical studies were provided or reviewed by the applicant addressing use of the new products among vulnerable populations. Vulnerable populations have increased difficulties with smoking cessation.[14-16] ENDS may serve as a harm reduction approach if users are able to completely switch or dramatically reduce combusted tobacco product use. However, 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.

Per the epidemiology review:

- Some published literature has found that the use and initiation of ENDS is higher among lesbian, gay, bisexual, and transgender (LGBT) youth and adults, people with a history of mental health problems, and American Indian/Alaskan Natives. The applicant did not provide information specific to vulnerable populations in its application; therefore, the impact of the new products on vulnerable user groups other than youth is unknown from an epidemiology perspective.

Per the social science review:

- The applicant presented data for the new products by tobacco user group; the applicant did not provide demographic information or a summary of the composition of these groups. No data was provided on vulnerable populations.
- Published research indicates that individuals with substance use or mental health issues are more likely to use ENDS compared to those without those health concerns.[17-21] Additionally, the prevalence of ENDS use by LGBT individuals is higher than in heterosexual individuals.[22-25] Younger women and women who use combusted cigarettes may use ENDS during pregnancy.[26-28]
- The applicant did not provide data to determine how participant characteristics, including membership in vulnerable populations, affect perceptions and intentions to use the new products. From a social science perspective, the impact of the new products on vulnerable populations is unknown.

3.4.1.5. Actions taken to mitigate risk to non-users, including youth

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

- The applicant submitted information on its proposed marketing in two letters dated November 9, 2018, and April 29, 2019.
- OHCE raised some concerns with certain aspects of the applicant's marketing information and indicated support for other aspects.

[xi] 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.

- For example, OHCE's review raised concerns about the potential broad reach of the applicant's plan for digital and television 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 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 that do not over-index for youth, requiring advertising to be placed inside the store, and placing product displays near other age-restricted products and away from toys and candy.
- Examples of measures OHCE expressed support for include the following: "Not use any social media platforms (e.g., Facebook, Instagram, Twitter) or social media influencers for marketing and promotional purposes; 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

Per the social science review:

- The applicant provided proposed labeling.
- The applicant made revisions to its "instruction insert" labeling in response to Deficiency 22. Revisions included changing the color of the labeling from colorful to predominately black and white, standardizing the text on the front panel, standardizing warning text font and content across products on the back panel, and changing the format and content of the use instructions for both products.
- Based on the information presented at this time, we have not concluded that the proposed labeling is false or misleading in any particular way. We note that the "instruction insert" includes instructions for consumers to visit the applicant-owned website "for important product information before use." Consumers who follow these instructions will be exposed to additional labeling/advertising materials when they search for product information. Additionally, the "Safety Information FAQs" that comprise the "important product information" include claims about product risk and appeal. This additional labeling/advertising includes information such as: "The ratio of vegetable glycerin (VG) and propylene glycol (PG) in Solo, Vibe, and Ciro liquids have been optimized to provide the optimal viscosity, flavor, and experience per device"; "We use food-grade flavorings designed for an adult palate"; and "Vuse products offer many advantages over traditional

cigarettes that adult tobacco consumers may find attractive- there's no ash and no burning odor." Although such statements could potentially convey modified risk, based on the information presented at this time there is insufficient information to conclude that they do. Accordingly, social science does not conclude that this labeling/advertising would cause the new tobacco products to be modified risk tobacco products (MRTPs).

3.4.2. Synthesis

The applicant states that the intended user population for the Vuse Vibe and Vuse Ciro new products is adult (ages 21+) current tobacco users, including current and former cigarette smokers and current and former ENDS users. The abuse liability of the new products, while sufficient for dual use or complete switching in those interested in quitting combusted cigarettes, is unlikely to support complete switching in a combusted cigarette user who is uninterested in quitting. The appeal of the tobacco-flavored new products is low in non-tobacco users. Generally, nonusers view the new products as a risk to developing poorer health, rate them as unappealing, and have a lower proportion of the group indicating interest in purchasing any flavor of the new products than tobacco users. There is also evidence that the tobacco flavor of the new products pose less risk to youth uptake given their lower appeal to underage youth compared to other flavors.

3.4.2.1. Intended User Population

As TPL, I agree with the BCP and social science disciplines that the stated applicant intended user population for Vuse Vibe and Vuse Ciro new products is adult (ages 21+) current tobacco users, including current cigarette smokers and current ENDS users. I also agree with the epidemiology discipline that the applicant stated that the likely user population for the new products is current and former adult cigarette smokers.

3.4.2.2. Current Tobacco Users

The evidence indicates that established tobacco users, and in particular established cigarette smokers, are interested in the new products, indicate that tobacco flavor is their flavor of interest more frequently than flavored tobacco products, and are interested in the new products as a way to reduce or stop smoking. This evidence supports that these products, if authorized, would be acceptable to cigarette smokers looking to either switch completely to the new products or become dual users and thereby potentially decreasing their cigarette consumption. As noted in the abuse liability and toxicant exposure/biomarkers of exposure sections (3.3., 3.5.1.2.), with increased user experience, these new products have the ability to deliver nicotine near combusted cigarette levels, and, as noted in the toxicant exposure/biomarkers of exposure section (3.5.1.2.), have reduced toxicant exposure. This supports the evidence in this section that these products could be an acceptable substitute for combusted cigarettes and thereby reduce HPHC exposures for dual users or complete switchers.

As TPL, I agree with the BCP and epidemiology disciplines that the abuse liability of the new products, while sufficient for dual use or in those interested in quitting combusted cigarettes, was unlikely to support complete switching in a combusted cigarette user who was uninterested in quitting. Given that the abuse liability of the new products in inexperienced users is lower than that of combusted cigarettes but higher than that of

nicotine replacement gum in ENDS-naïve exclusive smokers, it is likely that among the target population of combusted cigarette smokers, those not interested in quitting would dual-use them along with cigarettes rather than completely switch. They may reduce their CPD, which could potentially improve the impact of smoking on their health. Smokers interested in quitting may find these products to be a better substitute for smoking than nicotine replacement gum. There is also potential to increase nicotine exposure with experience. Therefore, in adult combusted cigarette users, experimenting with the new products could lead to dual use in those uninterested in quitting (or they may return to exclusive cigarette use). For those interested in quitting, the abuse liability may be enough to maintain dual or exclusive use of the ENDS better than NRT, and therefore could lead to better cigarette cessation outcomes.

3.4.2.3. Tobacco nonusers (including youth)

Precursors of Product Use

As TPL, I agree with the social science and epidemiology disciplines that the appeal of the new products is low in non-tobacco users. Generally, nonusers view the new products as a risk to developing poorer health, rate them as unappealing, and have a lower proportion of the group indicating interest in purchasing any flavor of the new products than tobacco users. Although youth and young adults generally find cartridge-based ENDS appealing, published research indicates that underage youth find tobacco-flavored ENDS less appealing than flavored ENDS. Therefore, the tobacco flavor of the new products likely poses less risk to youth uptake given their lower appeal to underage youth compared to other flavors.

Initiation and Progression to use

As TPL, I agree with the BCP and epidemiology disciplines that in inexperienced users the abuse liability of the new products is low relative to combusted cigarettes. For youth and non-users, the literature, combined with the abuse liability assessments of the new products in clinical studies of adult inexperienced ENDS users, suggests a low likelihood of initiation of Vuse Vibe or Vuse Ciro Original tobacco ENDS products; however, should non-users or youth initiate use of Vuse Vibe products or Vuse Ciro products, the likelihood of progression to regular use is low compared to combusted cigarettes. 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.

Vulnerable Populations[Error! Bookmark not defined.] *(other than youth)*

There is some evidence that indicates some vulnerable populations experience disproportionate ENDS use and have increased difficulties with smoking cessation. ENDS may serve as a harm reduction approach if users are able to completely switch or dramatically reduce combusted tobacco product use. However, as TPL, I agree that 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.

3.4.2.4. Summary of 3.4.2.1, 3.4.2.2, and 3.4.2.3

The evidence summarized in these sections describes relatively high interest among adult smokers in using the tobacco products and demonstrates that switching from combusted cigarettes to ENDS does occur among current adult smokers—typically through a period of dual use. Use of these products would benefit smokers who switch completely or

substantially reduce their cigarette smoking due to significant reductions in HPHCs of the new products compared to cigarettes (discussed in detail in Section 3.5). In addition, the abuse liability of the new products is lower than that of combusted cigarettes, mitigating concern of greater nicotine exposure than combusted cigarettes among youth. The available information also shows that, compared to flavored ENDS, appeal/uptake of tobacco products is generally lower among youth. Overall, I agree that the benefit of the new products to adult smokers is significant enough to overcome the risk to youth.

3.4.2.5. Actions taken to mitigate risks to non-users, including youth

With respect to marketing, OHCE reviewed the marketing information provided by the applicant, including information about advertising and promotion and sales access. OHCE expressed concerns with certain aspects of the information that was provided and was supportive of other aspects. As TPL, I agree with OHCE's evaluation. I also agree that the marketing restrictions recommended by OHCE are necessary to ensure that the new products sufficiently mitigate the risk to youth, especially with potential changes to the ENDS marketplace. Accordingly, I recommend that the MGO letter include the marketing requirements and recommendations specified in the OHCE consult.

3.4.2.6. Labeling and advertising

As TPL, I agree with the social science discipline conclusions. Based on the information presented at this time, I have not concluded that the proposed labeling is false or misleading in any particular. The applicant has provided evidence that users will be able to comprehend the product labeling accurately, thereby reducing the likelihood of misuse. The applicant revised the "instruction insert" labeling in Amendment PM0004600 in response to the Deficiency letter, and this addition of the required nicotine warning statement to the "instruction insert" is compliant with federal law.

Relatedly, the "instruction insert" includes instructions to visit the applicant-owned website "for important product information before use." Consumers who follow these instructions will be exposed to additional labeling materials when they search for product information. Additionally, the "Safety Information FAQs" that comprise the "important product information" include claims about product risk and appeal. These claims include "the ratio of vegetable glycerin (VG) and propylene glycol (PG) in Solo, Vibe, and Ciro liquids have been optimized to provide the optimal viscosity, flavor, and experience per device"; the products include "food-grade flavorings"; and that the products have an advantage over "traditional cigarettes" because there is "no ash and no burning odor." As TPL I also agree that, although such statements could potentially convey modified risk, based on the information presented at this time there is insufficient information to conclude that they do. Accordingly, I do not conclude that this labeling/advertising would cause the new tobacco products to be MRTPs.

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

Per the toxicology review:

- Two one-sided test (TOST) analyses indicated significant reductions in HPHCs from the new product aerosols compared to the combusted tobacco comparison products. Elevations in VG and PG in new product aerosols were outweighed by substantially lower yields of other respiratory toxicants (i.e., acetaldehyde, acetyl propionyl, ammonia, anabasine, acrolein, crotonaldehyde, diacetyl, ethylene glycol, formaldehyde) when compared to the combusted tobacco comparison products. Observed VG and PG levels were comparable to levels normally seen in other ENDS market comparison products.
- There is a decrease in HPHCs from the new product aerosols compared to the combusted cigarette comparison products. This decrease is likely to result in reduced toxic exposures for smokers who either completely switch to the new products or dual-use combusted cigarettes and the new products.

3.5.1.2. Biomarkers of exposure (BOE)

Per the BCP review:

- The applicant sponsored BOE study shows that non-nicotine BOE are significantly lower in combusted cigarette smokers who switch completely to the new products, and nicotine exposure is comparable to that of combusted cigarettes in smokers who switch to the new products for five days of ad libitum use. However, these data do not address smokers who dual use the new products with their combusted cigarettes. Therefore, the data the applicant provided for smokers are limited and may not reflect actual product use behaviors, such as dual use, for the new products.
- Complete switching from combusted cigarette smoking to ad libitum use of the Vuse Vibe product or Vuse Ciro product for five days resulted in significant reductions in the urinary and blood non-nicotine BOE of similar magnitude to the reductions in the participants who abstained from smoking. While the long-term effects of complete switching were not assessed, these changes in systemic exposures are likely to provide the health benefit of reduced exposure to these HPHCs for the current adult smokers who completely switch to the new products.

3.5.2. Synthesis

As TPL, I agree with the toxicology and BCP disciplines' conclusions that the applicant supplied sufficient information to characterize the products' toxicity, the data indicate that the new products have significantly lower toxicity compared to combusted cigarettes, and users who completely switch to the new products will have significantly reduced levels of BOE compared to combusted cigarettes.

3.5.2.1. Toxicity

3.5.2.1.1. Ingredients and HPHCs

Many of the new product e-liquid ingredients, especially those that are known to cause respiratory irritation and/or toxicity, are also found in commercially available cigarettes.[29,30] Similarly, many HPHCs are respiratory irritants/toxicants (e.g., acetaldehyde, formaldehyde). However, comparative HPHC analysis[xii] between combusted tobacco comparison products Newport Gold or FDA-50 cigarettes (composed of HPHC and product design data from the 50 top-selling cigarette brands from 2011) and the new products demonstrated that corresponding HPHCs from the new product aerosols were either below the limit of detection or substantially reduced on a unit per mg nicotine basis under both a non-intense and an intense puffing regimen. Taken together, in terms of carcinogenic and/or cardiovascular/respiratory/reproductive/developmental toxicant HPHCs, the new product aerosols consistently demonstrated reduced potential for overall toxicity compared to cigarette smoke from combusted tobacco comparison products. Furthermore, HPHC levels observed from new product aerosols in e-liquids PM0000636 and PM0000712 were comparable on a mass-to-mass basis with HPHC levels reported in 22 ENDS market comparison products. Given the magnitude and statistical significance of lower HPHC yields in the new product aerosols as compared to combusted cigarettes, I find that these new products are likely to result in reduced toxicity for smokers who switch to ENDS completely from combusted tobacco products. Furthermore, given the mass-to-mass comparability of HPHC levels with the ENDS market comparison products, any potential toxicities directly resulting from the specific ingredients found in these new products are unlikely to increase overall toxicological concern as compared to ENDS market comparison products.

3.5.2.1.2. Extractables and Leachables

The applicant also provided information regarding potential extractables and leachables from the components of the new products (PM0000636 and PM0000712). Leachable compounds in the aerosol were collected over a (b) (4) period under long-term storage conditions (b) (4) % relative humidity [RH] (b) (4) RH) and at a (b) (4) time point where test articles were stored under accelerated storage conditions (b) (4) (b) (4) Data from the (b) (4) accelerated timepoint are used for evaluations as they exhibited the highest leachable levels among timepoints measured. Over the (b) (4) testing period leachable compounds in aerosols reported above the limit of quantitation (LOQ) and above the International Council for Harmonization (ICH) and FDA CDER/CBER M7(R1) analytical exposure threshold (AET) for mutagenic impurities in drug products (1.5 µg/day) were assessed. Extractables and leachables were determined for PM0000636 and PM0000712. Mean leachable compound levels were converted to predicted exposures per day (µg/day) based on an estimated inhalation exposure equivalent of 80 puffs per day

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[xii] The applicant provided select HPHCs from the USFDA Draft and Final Guidance for Industry on PMTAs for ENDS.[31,32] These HPHCs included acetaldehyde; acetyl propionyl; acrolein; acrylonitrile; 4-aminobiphenyl; 1-aminonaphthalene; 2-aminonaphthalene; ammonia; anabasine; benzene; benzo[a]pyrene (B[a]P); 1,3-butadiene; cadmium; chromium; crotonaldehyde; diacetyl; diethylene glycol; ethylene glycol; formaldehyde; glycerin (also known as glycerol); (b) (4) soprene; lead; menthol; nickel; nicotine (free and total); 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK); N-nitrosonornicotine (NNN); propylene glycol; and toluene. While the above HPHCs were tested in the aerosol of the new products (PM0000636 and PM0000712), additional HPHCs including (b) (4) (b) (4) and (b) (4) were reported in separate analytical studies or from the e-liquid (if present).

(PM0000635, PM0004287, PM0000636) or 100 puffs per day (PM0000646, PM0004293 PM0000712). The estimated exposure equivalents were based on the reported mean user consumption of various ENDS platforms ranging from 78 to 250 puffs per day.[33-39] Nine organic and two elemental leachables were reported in the aerosols of PM0000636. Eight organic and one elemental leachable were reported in PM0000712. None of the compounds identified are listed as carcinogenic, genotoxic, or mutagenic by the European Chemicals Agency (ECHA) harmonized classification and labelling (CLH) database, the International Agency for Research on Cancer (IARC), or the US EPA's Integrated Risk Information System (IRIS).

The majority of elevated extractable and leachable compounds from the new product cartridges are known constituents of cigarette smoke from 3R4F research cigarettes and commercially available cigarettes.[29,40] This includes the leachable compounds that are known to cause respiratory irritation and/or toxicity.[29,30] The potential exposure to extractable and leachable compounds (including compounds that are also considered to be HPHCs) from the new product aerosols is substantially less than that observed from combusted cigarette smoke. Importantly, comparative HPHC analyses of combusted tobacco comparison products, Newport Gold or FDA-50 cigarette data, and the new products demonstrated that corresponding HPHCs from new product aerosols were either below the limit of detection or substantially reduced on a unit per mg nicotine basis under either a non-intense or intense puffing regimen. As discussed above, HPHC levels observed from the new products are also comparable on a mass-to-mass basis with the HPHC levels reported in the 22 ENDS market comparison products. In terms of carcinogenicity and/or cardiovascular/respiratory toxicant HPHCs, the new product aerosols consistently demonstrated reduced potential toxicity compared to cigarette smoke from combusted tobacco comparison products and exhibit similar toxicological risk as the ENDS market comparison products.

3.5.2.2. Biomarkers of exposure (BOE)

The applicant submitted one sponsored inpatient clinical study (CSD170501) that allowed for an evaluation of BOE following actual use of the Vuse Vibe (3.0% nicotine) Original flavor and Vuse Solo+ (previous name of Vuse Ciro, 1.5% nicotine) Original flavor products (PM0000636, PM0000712) in current adult exclusive cigarette smokers compared to a cigarette abstinent group ("abstinence cohort"). The BOE measured in the study and corresponding HPHCs are listed in Table 2 of the BCP review. BOE data examines biomarkers of nicotine exposure by measuring a variety of nicotine metabolites. After five days of switching from smoking combusted cigarettes to using the Vuse Vibe Original flavor (PM0000636) or Vuse Solo+ Original flavor products (PM0000712), there was a statistically significant reduction in all examined non-nicotine urinary BOE in both groups. The blood carboxyhemoglobin (COHb) percent saturation, a biomarker of exposure to carbon monoxide (CO), was statistically significantly reduced for all groups. The applicant concluded that these data demonstrate that complete switching from combusted cigarette smoking to the Vuse Vibe Original flavor (PM0000636) or Vuse Solo+ Original flavor (PM0000712) during five days of ad libitum use resulted in reductions in urinary and blood BOE of similar magnitude to the reductions in the abstinence cohort. While the applicant did not provide data on BOE in dual users of the new products and cigarettes, given the significant reduction in non-nicotine BOE in complete switchers similar in magnitude to the abstinence cohort, as

TPL I conclude that if dual users significantly reduce their CPD while using the new products, a reduction in non-nicotine BOE can be expected.

Urinary TNE values were statistically significantly reduced in the Vuse Solo+ Original flavor (PM0000712) cohort by 31% and in the abstinence cohort by 96% between baseline and Day 5. Although the urinary TNE values in the Vuse Vibe (PM0000636) cohort was reduced 9% compared to baseline, this change was not statistically significant from baseline. The difference in TNE reduction between the Vuse Vibe and Vuse Solo+ Original flavor products (PM0000636, PM0000712) could be due to the relative nicotine concentrations of the two products; while the Vuse Solo+'s accompanying e-liquid contains 1.5% nicotine, Vuse Vibe's accompanying e-liquid contains 3.0% nicotine, thereby delivering more total nicotine to users. Nicotine plasma concentrations measured in the evenings increased steadily in both the Vuse Vibe and Vuse Solo+ cohorts from Day 1 to Day 5, approaching UB cigarette baseline measurements by Day 5. Plasma cotinine levels also increased from Day -1 to Day 5 in both the Vuse Vibe and Vuse Solo+ cohorts, parallel to plasma nicotine levels. The applicant concluded that these data demonstrate the potential for nicotine exposure in the new products to reach levels of UB cigarettes. Therefore, with extended, exclusive use of either of these products, nicotine exposure can reach levels similar to those in users of combusted cigarettes, which may promote complete switching.

Summary

As TPL, I agree with the toxicology and BCP disciplines' conclusions that the toxicant exposure of the new products is lower than that of the combusted cigarette comparison product and similar to other marketed ENDS. There were many more HPHCs, at much higher levels, found in the combusted tobacco comparison products when compared to HPHCs from all the new product aerosols under both non-intense and intense puffing regimens. Additionally, the potential exposure to extractable and leachable compounds (including compounds that are also considered to be HPHCs) from the new product aerosols was substantially less than that observed from combusted cigarette smoke. The clinical data submitted by the applicant support that systemic exposure to several HPHCs is lower for users of the Vuse Vibe (PM0000636) Original flavor product and the Vuse Solo+ (PM0000712) Original flavor product compared to combusted cigarette smoking; switching from UB smoking to the new products significantly reduced the majority of BOE measured related to combustion. These findings support the conclusion that, if a combusted cigarette smoker either switches completely to the new products, or through dual use significantly reduces their CPD, they would have reduced toxicant exposure as a result.

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

Per the toxicology review:

3.6.1.1.1. Nonclinical studies

- Results from the in vitro toxicology studies demonstrated that combusted cigarette smoke fractions (total particulate matter (TPM) or gas vapor phase (GVP) fractions) were mutagenic, cytotoxic, and genotoxic. By contrast, neither the TPM nor GVP from any of the aerosols of the tested new products or ENDS market comparison products were mutagenic or genotoxic and exhibited no, or minimal, cytotoxicity except at the highest dose.
- The applicant attempted to bridge from the in vivo studies using Vuse Solo G2 comparison product aerosols. Vuse Solo G2 aerosols consistently resulted in substantially lower nonclinical toxicity and histopathological changes compared to Newport Gold cigarette smoke. Despite substantial overlap in ingredients, the new product aerosols were determined not to be equivalent to the Vuse Solo G2 aerosols from a toxicology perspective because several HPHC constituent yields were not analytically equivalent between corresponding products. Nonetheless, the observed reductions in HPHC yields in the new products and the Vuse Solo G2 ENDS comparison products when compared to the Newport Gold combusted cigarette comparison product does indicate that the new products are most likely also considerably less toxic in vivo.

3.6.1.1.2. Clinical data with toxicity endpoints

- From a toxicology standpoint, the comparison of select new products revealed that all urinary BOE, except for nicotine, are substantially lower when switching from combusted cigarettes to the new products. Moreover, BOE reductions in smokers who completely switched to the new products were similar to those measured in the abstinence cohort.

3.6.1.1.3. Toxicant and study integration

- The significantly lower aerosol HPHC yields in the new products compared to combusted cigarettes, and subsequent decrease in exposure to toxic and carcinogen constituents, are consistent with results from the corresponding nonclinical studies submitted by the applicant.
- The applicant's findings indicate that after five days of completely switching from smoking combusted cigarettes to using the Vuse Vibe Original flavor (PM0000636) or Vuse Solo+ Original flavor products (PM0000712), smokers who switched to the new products exhibited BOE similar to those of the abstinence cohort, providing further support that exposure to new product aerosols, and lower levels of HPHCs, would likely result in fewer toxic exposures than combusted cigarettes, assuming equal puff profiles and other exposure parameters.

- The toxicological evaluation of ingredients, leachables, HPHCs, nonclinical studies, and BOE studies shows that results are consistent and supports the conclusion that risks to users of the new products who completely switch or significantly reduce CPD are likely to be lower relative to continued use of combusted cigarettes.

3.6.1.2. BIMO inspection findings

No Bioresearch Monitoring (BIMO) inspections were recommended or conducted during either cycle of substantive review.

3.6.1.3. Addiction as a health endpoint

Per the BCP review:

- The abuse liability of the Vuse Vibe products and Vuse Ciro products is lower than that of combusted cigarettes, but higher than that of 4 mg nicotine replacement gum. Current combusted cigarette smokers (i.e., the applicant's stated intended user population for the new products) are likely to dual-use the new product with combusted cigarettes; however, combusted cigarette users who are motivated to quit smoking may use the Vuse Vibe products or Vuse Ciro products to reduce or quit smoking. Current cigarette smokers are likely to be able to maintain their nicotine addiction with the Vuse Vibe products or Vuse Ciro products, and smokers intending to use these products to aid in smoking cessation may find them more acceptable than nicotine replacement gum.
- Although the Vuse Vibe products and Vuse Ciro products have abuse liability profiles that are lower than that of combusted cigarettes, both products deliver enough nicotine to sustain addiction in nicotine-dependent populations and can have risks of initiation and developing addiction in nonusers to a similar degree as combusted cigarettes.
- The applicant's analysis of youth actual use behavior showed that youth who use ENDS exclusively may have lower nicotine dependence than those who use combusted cigarettes, though any level of youth nicotine dependence for ENDS use poses youth risk. This analysis was limited because it examined general ENDS use and incorporated data collected until 2016, before many of the ENDS currently used by youth, including the Vuse Vibe or Vuse Ciro products, were widely available, limiting its applicability to these new products. 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 flavored ENDS.

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

Per the epidemiology review:

- The applicant did not submit any observational health effects studies.
- 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.[41-43] However, many of these studies utilized cross-sectional surveys to examine these relationships;

therefore, 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.[44,45] Some biomarker data from observational studies have also found that dual users can have higher levels of certain BOE than exclusive cigarette smokers, including metabolites for nicotine, NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), 1-hydroxypyrene, acrolein, and 1,3-butadiene.[44,46] However, it has also been found that dual users have lower levels of some TSNAs and acrylonitrile.[47] The number of cigarettes smoked per day among dual users and exclusive smokers likely impacts whether certain biomarkers of tobacco exposure are higher or lower in dual users compared to exclusive smokers across studies.
- A meta-analysis found that, compared to heavy smokers, those who reduce their CPD by at least 50% had a significant reduction in lung cancer.[48] 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.[48] 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.
- Switching likely reduces 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.[49]

Per the medical review:

- No definitive health conclusions can be drawn about the new products' impact on human health based on review of the clinical data and health effects literature submitted by the applicant. 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.
- The likelihood of new product use leading to reduced incidence of chronic tobacco-related disease such as pulmonary disease, cardiovascular disease, or cancer in cigarette smokers who switch to these products has not been established. Long-term studies demonstrating such findings are not available, and the current bridging literature and results of biomarkers of potential harm (BOPH) measurements in the reduced exposure studies are not sufficiently robust to draw definitive conclusions about long-term health risks or disease from chronic product use and exposure.
- Overall, the applicant provided data to evaluate the short- and long-term health effects of new products and, based on the provided information, no significant safety concerns were identified. There are currently no published data for the health effects of the new products.
- Medical is not able to draw conclusions on the health effects of new products from the applicant's studies and published literature due to several study design limitations including:
  - Small sample sizes
  - Short study duration
  - Short-term exposure periods

- Enrollment of generally healthy subjects, which may under-estimate the incidence of real-world adverse experiences (AEs) in real-world ENDS consumers
- Switching studies that assessed complete switching but did not assess partial incomplete switching (or dual use)

- In general, the published literature on the health effects of ENDS suggests that many ENDS aerosol constituents (e.g., TSNAs, VOCs, PAHs) may be lower compared with combusted cigarettes.[44,50,51] The National Academies of Sciences, Engineering, and Medicine (NASEM) states that ENDS aerosol contains lower levels of most toxicants than combusted cigarette smoke.[52] Some literature also reports that not all ENDS aerosol constituents are reduced (e.g., acrolein, acrylamide, acrylonitrile, xylene),[50,53] 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.
- The literature is unclear regarding whether specific reductions in exposure to harmful constituents necessarily lead to a substantial or clinically significant reduction in tobacco-related health outcomes or disease 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. However, based on the currently available evidence, reducing CPD likely leads to less exposure to harmful toxicants than continued smoking and thus do not raise concerns from a medical perspective.[54]

3.6.1.5. Likelihood and effects of product misuse

Per the BCP review:

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

Per the medical review:

- Vuse Vibe and Vuse Ciro are closed systems consisting of a rechargeable power unit and disposable cartridge that is not intended to be opened. There is no child-resistant packaging report or General Certificate of Conformity included in the applications. However, the cartridges are blister packaged and provide a tamper evident seal, and the health risk is likely mitigated for accidental exposure in children.

3.6.1.6. Adverse experiences

Per the chemistry review:

- There were no chemistry-related AEs due to product design and composition of the new products reported to FDA at this time.

Per the engineering review:

- The applicant stated in a Failure Mode and Effects Analysis document that e-liquid leakage hazards were considered and mitigated through robust design and manufacturing techniques. The applicant also outlined all of the design verification and continuous manufacturing verification steps that are in place to ensure e-liquid cartridges will not leak.
- Engineering-related AEs from product design are adequately addressed. The applicant described 20 AEs in the original submission and in response to deficiencies, they explained that the AEs occurred only in the Vuse Vibe Power Units manufactured with the (b) (4) battery (PM0004287). The applicant adequately explains how it responded to the AEs: after determining that the AEs were a result of poor manufacturing practices, it instituted improved monitoring of battery production and increased the battery verification procedures. No AEs have been noted since the manufacturing oversight changes were applied.

Per the medical review:

- Short-term clinical studies submitted by the applicant demonstrate that the numbers of AEs were generally low and characterized overall as mostly mild, transient, and expected. No deaths or serious AEs were reported to be associated with use of the new products during the exposure studies.
- Based on Tobacco Product Surveillance Team (TPST) AE data, thermal events were associated with PM0004287. Of the 23 AEs reported for Vuse Vibe, 20 were reported to be associated with overheating/fire/explosions (OH/F/Ex). Of these, six were associated with burns. Reports of OH/F/Ex initiated a 2018 market voluntary withdrawal of Vuse Vibe. No OH/F/Ex were reported in the PMTAs for Vuse Vibe or Vuse Ciro.
- The potential for device malfunctions in the battery or coil temperature regulation could increase the potential health risk of thermal and aerosol-related burn injury from ENDS should temperatures rise above a 60°C threshold.[55] However, per the measurement values provided by the applicant and assessed by engineering, the temperatures are below 60°C.
- The package insert states that the device may overheat, and vusevapor.com mentions the risk of fire, but none of the submitted language includes the risk of explosion, despite the multiple reported AEs of explosion documented for PM0004287 as acknowledged by the applicant. The current PMTA submission states that there are now inspection criteria and increased testing of batteries at multiple process points, and improved and increased training of personnel is also reported; however, the applicant has not explicitly quantified the effectiveness of changes of that have been implemented. ENDS can explode and cause projectile injuries and burns to human users. However, the applicant provided sufficient information to demonstrate that the new products are not likely to explode or catch fire if they are used within the certified parameters tested (i.e., an 80 mL puff volume with a 5-second inhalation time and 15-second interval smoking regimen).
- E-cigarette, or vaping, product use-associated lung injury (EVALI) is still being fully characterized as a potential respiratory health effect that could occur in individuals who use vaping products. There were no reports of EVALI in this

PMTA, nor were there any subjects who experienced the full constellation of symptoms indicative of EVALI as an AE that required hospitalization. However, there were users who reported respiratory AEs to TPST, including one who required hospitalization after use of Vuse Vibe. EVALI is an emerging health issue associated with use of vaping products and could potentially occur with use of the new products.

- While there were no seizures reported as an AE in the applicant-submitted clinical studies, there were multiple neurological AEs reported. However, across all studies, these AEs were generally mild, transient (i.e., resolved by study end) and expected (e.g., headache, nausea). No deaths or serious AEs were reported to be associated with use of the PMTA products in the clinical studies. Several neurological AEs were reported to the Safety Reporting Portal (SRP) as associated with both Vuse Vibe and Vuse Ciro. However, the strength of evidence for determining causality of these AEs is inconclusive based on TPST data due to incomplete or potentially confounding information. CTP has received multiple reports of seizures in youth and young adults associated with ENDS use. However, current SRP data are insufficient to fully evaluate the potential association of the new products with seizures.
- Therefore, to further monitor and evaluate potential ENDS health effects such as EVALI and seizures, the medical discipline recommends that post-market reporting include a specific plan to monitor respiratory-related illnesses, neurological symptoms, and AEs related to thermal burns associated with the new products.
- The use of blister-packaged cartridges prevents accidental exposure to the nicotine-containing e-liquid. However, there are no data to demonstrate adequate mitigation of accidental exposure in children, such as any child-resistant packaging testing procedure reports or certifications. This limits the medical evaluation of the PMTA products in nonusers such as children. 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 can even be fatal.

3.6.2. Synthesis

Taken together the sum of the evidence for health effects of the new products is equivalent to the general health effects and risks of other ENDS and has the potential to improve health outcomes for a least a subset of smoking-related illnesses if combusted cigarette users completely switch or significantly reduce their cigarette consumption.

The abuse liability of the new products is lower than that of combusted cigarettes, but higher than that of nicotine replacement gum. This makes it likely that smokers not interested in quitting who use these products would dual use them along with their cigarettes rather than completely switch. They may reduce their CPD, which would potentially improve the impact of smoking on their health. Smokers interested in quitting may prefer these products as a substitute for smoking over nicotine replacement gum. Because these products do have abuse liability, there is the risk that nonusers who experiment with these products may become established nicotine users and develop addiction to a similar degree as combusted cigarettes.

Consumers are unlikely to be able to misuse these products (using the product in ways other than intended such as product modifications, dripping, and stealth use) due to their closed design and pre-filled e-liquid cartridges. The settings are non-adjustable and the e-liquid is enclosed in a cartridge, reducing the chance that users can manipulate the product settings or e-liquid constituents. The applicant has also reduced the likelihood of accidental exposure in children by using blister packaging for the e-liquid cartridges. Concerns about the potential for battery case fires and explosions have been reduced to the level of general concern for these types of AEs (which exist for all ENDS) due to the applicant's efforts to improve its battery manufacturing and testing procedures.

The new products show considerably less toxicity compared with combusted cigarettes. The nonclinical and clinical data indicate that there is less toxicity from the aerosols of the new products due to the reduction in HPHC yields and that the levels of BOE after smokers completely switched to the new products were similar to those measured in the abstinence cohort. Overall, it was concluded that the risks to users of the new products who completely switch or significantly reduce their CPD are likely to be lower relative to continued use of combusted cigarettes.

Of the data that the applicant was able to provide on the short- and long-term health effects of the new products, no significant safety concerns were identified, although both the applicant's studies and published literature had several study design limitations that preclude strong conclusions. While epidemiology stated that reducing cigarette smoking can lead to a significant reduction of certain smoking-related diseases, such as lung cancer, they agree with medical that it is unclear whether specific reductions in exposure to harmful constituents will lead to clinically significant reductions in tobacco-related health outcomes or disease risk as a whole. This significant knowledge gap counters the potential for a positive outcome from dual use, as these new products are most likely to be used, compared with completely switching and stopping use of combusted cigarettes. 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 even partial switching to the new products (assuming a significant reduction in cigarette consumption) may provide health benefits from a harm reduction perspective in terms of reducing exposure to HPHCs relative to continued use of cigarette smoking alone.

There were 23 AEs for Vuse Vibe, of which 20 were associated with overheating/fire/explosions (OH/F/Ex); six of these associated with burns. These reports of OH/F/Ex initiated a 2018 voluntary market withdrawal of Vuse Vibe. There were no instances of OH/F/Ex reported in the PMTAs for Vuse Vibe or Vuse Ciro. As TPL, I agree with the engineering discipline that the applicant has supplied adequate evidence that it was able to identify that the issue was with the Vuse Vibe Power Units manufactured with the (b) (4) battery (PM0004287) and that the applicant has taken appropriate actions to remedy the issue including improved monitoring of the battery production process and increased battery verification procedures. I also agree with the medical discipline that the applicant has provided sufficient information to demonstrate that the new products are not likely to explode or catch fire if they are used within the certified parameters tested.

Summary

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 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 assessed short-term complete switching but 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. Evidence from the published literature suggests that reducing CPD likely leads to lower exposure to harmful toxicants than continued smoking and exclusive ENDS users often have lower levels of nicotine, TSNAs, and VOCs compared to dual users of ENDS and combusted cigarettes. 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 of the new products 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 even partial switching to the new products (assuming a significant reduction in cigarette consumption) may provide health benefits from a harm reduction perspective in terms of reducing exposure to HPHCs relative to continued use of cigarette smoking alone.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

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

3.7.1.1. Toxicology

Per the toxicology review:

- From a toxicological perspective, given the magnitude and statistical significance of the decreases in HPHCs from the new product aerosols compared to combusted tobacco comparison products, the new products are likely to result in reduced toxicity due to reduced HPHC exposure among dual users (those who use combusted cigarettes and the new products) who significantly reduce CPD or who switch to ENDS completely.

3.7.1.2. Population health impact (PHI) model

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 Vibe and Vuse Ciro products are available in the

marketplace compared to a base case without Vuse Vibe and Vuse Ciro products' availability.

- Model inputs came from the 2018 National Survey on Drug Use and Health (NSDUH) data (smoking initiation) and 2015-2017 NSDUH data (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 using the Vuse Vibe or Vuse Ciro compared to cigarette smoking would result in tobacco-related mortality risk reductions of 90% and 95%. Probabilities for all primary transitions were based on the likelihood of use testing specific to Vuse Vibe and Vuse Ciro (Section H.5.2.3 of the PMTAs).
- The model suggests that the use of Vuse Vibe among tobacco users and nonusers would be projected to increase survival to age 72 for about 140,000 to 365,000 individuals in the U.S. population over a 60-year period. For Vuse Ciro, an additional 185,000 to 450,000 individuals would survive to age 72.
- There are some limitations to the inputs used in this model that may overestimate the population health benefit. However, without running the model again with different inputs, the amount of overestimation is unknown. First, the model used likelihood of use data rather than prevalence data observed in real-world surveys (i.e., TTM, NTBM). Second, 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, epidemiology generally agrees that the mortality rates due to combusted cigarette smoking will decrease and result in additional survivors in the population. However, as 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, it does not help evaluate mortality rates and survival estimates and the potential public health impact.

3.7.2. Synthesis

As TPL, I agree with the epidemiology discipline that the population health impact model submitted by the applicant does not raise concerns in terms of model structure or tobacco use transitions; however, as it may overestimate actual product use, the model does not help evaluate whether the new products are APPH.

As TPL, I also agree with the toxicology discipline's commentary on dual use of the new products with combusted cigarettes. They note that human dual use may be a highly heterogenous use scenario, with a wide range of use topographies. The applicant-submitted biomarker studies indicate a reduction in exposure to certain HPHCs among users who switch completely. If dual users significantly reduce the number of combusted cigarettes used per day, it can be expected that they will also reduce their exposure to certain HPHCs, although to a lesser degree than complete switchers. The risks to users of the new products who completely switch or significantly reduce their CPD are likely to be lower relative to continued use of combusted cigarettes.

As TPL, I agree with toxicology discipline's conclusions that switching completely from combusted cigarette smoking to the new products will result in large reduction in HPHC exposures. I also agree with the epidemiology review on the limitations of the applicant's

population health modeling methodology. The limitations include overestimating the actual switching rate from combusted cigarette smoking to exclusive ENDS use, as well as overlooking the scenarios of ENDS use among young people. Therefore, 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 APPH. The determination of APPH will be made based on overall information evaluated.

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

3.8.4. Product standards

There are no applicable product standards for 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 Bria Martin on May 2, 2022. The FONSI was supported by an environmental assessment prepared by FDA on May 5, 2022.

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 products, taking into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to considering information in a PMTA, and the agency may also consider any other

information before the agency, including the relevant existing scientific literature (see Section 910(c)(2)).

Based on its evaluation of these PMTAs, FDA determined that these PMTAs contain sufficient information to characterize the product design and that there are adequate process controls and quality assurance procedures to help ensure that 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 that of combusted cigarettes and higher than that of 4mg NRT gum. Evidence from the literature indicates that the new products likely have abuse liability that falls within the range of other ENDS based on nicotine pharmacokinetic data.[5] 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. Furthermore, significant reductions in blood and urinary biomarkers of exposure (e.g., VOCs, TSNAs, 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 products among current established cigarette users were the tobacco (Original) tobacco-flavored ENDS products. 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. Although ENDS products are the most widely used tobacco products among youth, existing evidence consistently indicates that use of tobacco-flavored ENDS is less common than non-tobacco flavored ENDS. Nonetheless, given the strong evidence regarding the impact of youth marketing exposure on youth appeal and initiation of tobacco use, any marketing authorization for the new products should include post-market requirements to help ensure that youth exposure to tobacco marketing is limited. In addition, the applicant's study findings demonstrated low intention to purchase the new products among adult never and former established tobacco users. 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 an (b) (4) eriod and because there are no other stability concerns, the lack of microbial data fo (b) (4) does not preclude an APPH finding for the new products.

Based on my review of the subject PMTAs, I find that permitting the marketing of the new products, as described in the applications, and specified in Appendix Table 3, is APPH. The issuance of 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 the 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[xiii, xiv]

Table 3. New tobacco products subject to Granted Orders

Common Attributes	
Applicant	R.J. Reynolds Vapor Company
Product manufacturer	R.J. Reynolds Vapor Company
Product category	ENDS (VAPES)
Attributes	**New Product**
STN	**PM0000635**
Submission date	April 2, 2020
Receipt date	April 2, 2020
Product name	Vuse Vibe Power Unit
Product subcategory[xv]	Closed E-Cigarette
Package type	Paperboard Carton
Package quantity	1 Power Unit
Characterizing flavor	Unflavored
Additional properties	Length: 82.5 mm Diameter: 13.0 mm Wattage:[xvi] 4.0-6.5 W Battery capacity>=550 milliAmpere hour (mAh) Universal Serial Bus (USB) Charger Battery Manufacturer: (b) (4)
STN	**PM0000636**
Submission date	April 2, 2020
Receipt date	April 2, 2020
Product name	Vuse Vibe Tank Original 3.0%
Product subcategory	Closed E-Liquid
Package type	Paperboard Carton/Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Tobacco[xvii]
E-liquid volume	1.9 mL per cartridge
Nicotine concentration	36.0 mg/mL
PG/VG ratio	20/80
Additional properties	Length: 59.0 mm Diameter: 13.0 mm Nicotine content: 3.0% w/w

[xiii] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.

[xiv] Brand/sub-brand or other commercial name used in commercial distribution.

[xv] FDA referred to these products as ENDS Components during the course of review to facilitate processing. However, at the close of review the accurate category and subcategory are reflected in the TPL review and supersede those listed in primary discipline reviews.

[xvi] The applicant states the wattage listed represents the nominal operating range; the upper and lower wattages have a variation of (b) (4)

[xvii] Labels may contain descriptive terms such as "Original".

STN	**PM0000646**
Submission date	April 15, 2020
Receipt date	April 15, 2020
Product name	Vuse Ciro Power Unit
Product subcategory	Closed E-Cigarette
Package type	Paperboard Carton
Package quantity	1 Power Unit
Characterizing flavor	Unflavored
Additional properties	Length: 83.5 mm Diameter: 9.2 mm Battery Capacity: ≥ 260 milliAmpere hour (mAh) Wattage:[xviii] Expected High: (b) (4) Expected Low: (b) (4) Universal Serial Bus (USB) Charger Battery Manufacturer: (b) (4)
STN	**PM0000712**
Submission date	April 15, 2020
Receipt date	April 15, 2020
Product name	Vuse Ciro Cartridge Original 1.5%
Product subcategory	Closed E-Liquid
Package type	Paperboard Carton/Blister Pack
Package quantity	3 Cartridges
Characterizing flavor	Tobacco[xvii]
Nicotine concentration	17.7 mg/mL
PG/VG ratio	29/71
E-liquid volume	0.9 ml per cartridge
Additional properties	Length: 50.0 mm Diameter: 9.2 mm Nicotine Content: 1.5% w/w
STN	**PM0004287**
Submission date	April 2, 2020
Receipt date	April 2, 2020
Product name	Vuse Vibe Power Unit
Product subcategory	Closed E-Cigarette
Package type	Paperboard Carton
Package quantity	1 Power Unit
Characterizing flavor	Unflavored
Additional property	Length: 82.5 mm Diameter: 13.0 mm Wattage:[xvi] 4.0-6.5 W Battery capacity:>=550 milliAmpere hour (mAh) Universal Serial Bus (USB) Charger Battery Manufacturer: (b) (4)

[xviii] The wattages listed represent the average of 15 samples ± 95% confidence interval.

STN	PM0004293
Submission date	April 15, 2020
Receipt date	April 15, 2020
Product name	Vuse Ciro Power Unit
Product subcategory	Closed E-Cigarette
Package type	Paperboard Carton
Package quantity	1 Power Unit
Characterizing flavor	Unflavored
Additional property	Length: 83.5 mm Diameter: 9.2 mm Wattage:[xviii] Expected High: (b) (4) Expected Low: (b) (4) Battery capacity:>=260 milliAmpere hour (mAh) Universal Serial Bus (USB) Charger Battery Manufacturer: (b) (4)

Table 4. Amendments

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Status	Brief Description
November 23, 2020	November 23, 2020	PM0004271	PM0000635, PM0000636, PM0000646, PM0000712	Yes	Active	Response to the Office of Compliance and Enforcement's Inspection Request Letter
February 18, 2021	February 18, 2021	PM0004566	All[xix]	Yes	Active	Request for Extension to Respond to FDA Deficiency Letter
March 18, 2021	March 18, 2021	PM0004600	All[xix]	Yes	Active	Response to Deficiency Letter

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