

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 ENDSⁱⁱ (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) 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 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."