FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review[1]	
STNs	PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1, see Appendix B
Common Attributes	
Submission date	July 29, 2020
Receipt date	July 29, 2020
Applicant	JUUL Labs Inc.
Product manufacturer	JUUL Labs Inc.
Application type	Standard
Product category	Electronic Nicotine Delivery Systems (ENDS) (VAPES)
Product subcategory	Closed E-Liquid[2], Closed E-Cigarette[3]
Cross-Referenced Submissions	
All STNs	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	• Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications (June 3, 2024) • Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications (June 3, 2024) • Summary of key points in the evolution of OS's approach to reviewing toxicological information, as applicable to PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1, PM0000879.PD9, and AP0000166 (June 4, 2024) • Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications Memorandum (July 8, 2025)
Recommendation	
Issue marketing granted orders for the new tobacco products subject to this review.	

[1] Product details, amendments, and dates provided in the Appendix. STN means submission tracking number including product static identification number (PD) if applicable. PMTA means premarket tobacco application.
[2] For PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, and PM0000876.PD1
[3] For PM0000878.PD1

Technical Project Lead (TPL):

Lynn C. Hull -S 2025.07.15 10:37:14 -04'00'

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

Signatory Decision: Concur with TPL recommendation and basis of recommendation

/S/

Benjamin Apelberg, Ph.D
Deputy Director
Office of Science

LIST OF TABLES

1. EXECUTIVE SUMMARY

This Technical Project Lead (TPL) review relates to premarket tobacco product applications (PMTAs) submitted under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), as amended by the Family Smoking Prevention and Tobacco Control Act (TCA). Based on the information provided in the applications and other scientific data, as described in this TPL review, I find that permitting the marketing of the new products listed above ("new products" or "subject ENDS"); [PM0000864.PD1 (JUULpods, Menthol 3.0%), PM0000872.PD1 (JUULpods, Menthol 5.0%), PM0000874.PD1 (JUULpods, Virginia Tobacco 3.0%), PM0000876.PD1 (JUULpods, Virginia Tobacco 5.0%), and PM0000878.PD1 (JUUL Device) - hereafter referred to as the JUUL System][4] is appropriate for the protection of the public health (APPH) (*subject to certain marketing restrictions*) and that none of the other denial grounds specified in section 910(c)(2) apply. Accordingly, I recommend that marketing granted orders (MGOs) be issued for the new products, subject to the marketing restrictions and post-market requirements.

1.1. APPH STANDARD

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

The statute further specifies that, in assessing whether permitting the marketing of the new products would be APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products. Section 910(c)(4). The APPH standard requires a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. As the statutory text makes clear, it is the applicant's burden to make a "showing"—with sufficient supporting information—that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole. In determining whether permitting the marketing of any new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit to adults who use combusted cigarettes (CC) and then completely switch to lower risk products).

In making the APPH assessment specifically for a noncombusted tobacco product such as an electronic nicotine delivery system (ENDS), FDA weighs, among other things, the negative public

[4] For the purposes of this document, the JUUL System is defined as the JUULpod and JUUL device together, the JUULpod is the pod containing an e-liquid unless otherwise noted, and the JUUL device is the device without a JUULpod.

health impact stemming from youth initiation and use of the product against the potential positive public health impact stemming from adults who use CC transitioning away (i.e., completely switching) from CC to the ENDS or significantly reducing CC smoking. In order to show that the marketing of an ENDS is APPH, an applicant must show that the benefits, including those to adults who smoke CC, outweigh the risks, including those to youth, resulting in a net benefit to the public health. As the known risks of the product increase or decrease, the burden of demonstrating a substantial enough benefit likewise increases or decreases.

Current scientific literature demonstrates that ENDS are generally likely to have different toxicological risk and be associated with lower health risks than CC. However, whether this is true for any particular new ENDS is considered on a case-by-case basis during the course of FDA's scientific review of a PMTA. FDA considers the potential that adults who smoke CCs may experience a reduction in toxicological risk and health risks if they switch completely to ENDS, or if they use both products but substantially reduce their CC smoking.

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

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 complete switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Whether other products, such as tobacco-flavored ENDS, give adults who smoke CC comparable options for complete switching or significant CC reduction bears on the extent of the public health benefit that the subject ENDS may provide to that population. Therefore, in making the APPH determination for a flavored ENDS, FDA considers whether the applicant has provided robust and reliable evidence of an added benefit from the flavored ENDS relative to that of tobacco-flavored ENDS in facilitating adults who smoke CC in completely switching from or significantly reducing their smoking.

Before determining that permitting the marketing of a new tobacco product would be APPH, FDA also considers the potential impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and use of tobacco products. Marketing restrictions include advertising and promotion restrictions intended to limit youth exposure to and appeal of tobacco product marketing (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, or even eliminating advertising in certain media channels altogether) and sales access restrictions intended to restrict youth access to tobacco products (e.g., measures such as selling products only in face-to-face interactions, in adult-only facilities, or via websites that require robust age and identity verification). In recent years, there have been efforts to develop novel and potentially more effective types of risk mitigation measures aimed at reducing youth initiation risks, such as 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. Thus far, FDA's experience shows that advertising and promotion restrictions and sales access restrictions cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH.[5] Rather, for flavored ENDS, only the most stringent mitigation measures have such potential; to date, the only such measures identified with the potential for that kind of impact have been device access restrictions. FDA is currently aware of no other restrictions with the potential to alter the overall net benefit assessment for flavored ENDS. In contrast to flavored ENDS, 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 Granted 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.

FDA also takes into account whether the applicant has provided sufficient information regarding product design, chemistry, stability, manufacturing controls including process controls and quality assurance procedures, toxicology, abuse liability, and other factors that can impact the product's risks and benefits to individual users, including relative to those of other tobacco products on the market. If an applicant does not include information that is needed for FDA to fully assess the risks and benefits of the product, the applicant has failed to carry its statutory burden of demonstrating that the product's benefits outweigh the risks.

1.2. SUBJECT APPLICATIONS

We have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate that marketing of the products would be APPH.

The new products are a closed-system pod-style, rechargeable, non-serviceable ENDS. The power settings for the new product device (PM0000878.PD1) are non-adjustable, and the e-liquids (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1) are enclosed in a pod. These product characteristics reduce the likelihood that users may manipulate ENDS settings and e-liquid constituents, including nicotine levels. These features also minimize the potential risk of poisoning during handling or use of the new products. 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 that the new products are manufactured consistently. The applicant submitted sufficient chemistry and microbiology data to support a (b) (4) shelf-life for the bulk e-liquid and a (b) (4) shelf-life for the finished new products, for a total shelf-life of (b) (4) (b) (4) from the date of manufacture. The applicant also submitted sufficient engineering data demonstrating the stability of the new products' components through the product life cycle and proposed shelf life. For purposes of scientific review, FDA compared the new products to CC and

[5] *See* FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry* 44 (Apr. 2020) ("The reality is that youth have continued access to ENDS products in the face of legal prohibitions and even after voluntary actions by some manufacturers."); *see also id.* at 45 (noting "data that many youth obtain their ENDS products from friends or sources in their social networks").

ENDS because the applicant identified that the new products are intended for adults who currently smoke CC and adults who currently use ENDS.

The new products include tobacco- and menthol-flavored ENDS. As discussed above, the literature demonstrates that flavored ENDS, including menthol-flavored ENDS, pose a risk with respect to youth appeal, initiation, and continued use. Data from the 2024 National Youth Tobacco Study (NYTS), a nationally representative survey, demonstrate that more than 8 out of 10 (87.6%) youth who used e-cigarettes in the past 30 days, used a flavored product (Park-Lee et al., 2024). Among youth who used flavored e-cigarettes in the past 30 days, the most common flavors were fruit (62.8%), candy/desserts/sweets (33.3%), mint (25.1%), and menthol (15.1%), with 8.5% reporting use of a tobacco-flavored e-liquid (Park-Lee et al., 2024). Furthermore, 12.6% of youth reported using JUUL-branded e-cigarette products within the past 30 days, with 3.2% reporting that JUUL was their usual brand (Park-Lee et al., 2024).

As noted above, 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. Rather, for flavored ENDS, only the most stringent mitigation measures – specifically device access restrictions – have such mitigation potential. These PMTAs do not propose device access restrictions.

Thus, the marketing of the new flavored products could be APPH only if the PMTAs present reliable and robust evidence of a potential benefit to adults who smoke CC and completely switch from, or significantly reduce, CC use that could outweigh that risk to youth. To effectively demonstrate this benefit in terms of product use behavior, the PMTAs generally need to provide product-specific evidence from a randomized controlled trial (RCT)[6] or longitudinal cohort study (LCS)[7], although FDA evaluates other types of evidence on a case-by-case basis to determine whether it is sufficiently reliable and robust to make the necessary showing. Moreover, tobacco-flavored ENDS may offer the same type of public health benefit claimed by flavored ENDS, i.e., increased complete switching and/or significant reduction in smoking, without posing the same degree of risk of youth uptake. Therefore, to evaluate the potential benefit to adults who currently smoke CC, FDA reviewed the PMTAs for any acceptably strong evidence that the flavored new products have a sufficient added benefit relative to that of a tobacco-flavored ENDS in facilitating complete switching away from or significantly reducing CC use among adults who smoke CC.

Data and analyses from an online RCT (PROT-01325) showed that adults who currently smoke who used the tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) reduced their CC per month (CPM) over time and approximately 18% switched completely. Additionally, the applicant submitted an observational cohort longitudinal study (the ADJUSST study; formerly the pooled analysis of Studies 10A and 10B) to evaluate switching rates from CC use to the use

[6] An RCT is a clinical investigation or a clinical study in which human subject(s) are prospectively, and randomly assigned to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on behavioral, biomedical, or health-related outcomes. Control or controlled means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (e.g., historical controls, including a human subject's own baseline data), as reflected in the pre-specified primary or secondary outcome measures.
[7] An LCS is an observational study in which human subjects from a defined population are examined prospectively over a period of time to assess an outcome or set of outcomes among study groups defined by a common characteristic (e.g., smoking cessation among those who use non-tobacco-flavored ENDS compared with those who use tobacco-flavored ENDS).

of the new product e-liquids containing 5.0% nicotine (PM0000872.PD1, PM0000876.PD1) with the new product device (PM0000878.PD1) over a two-year follow-up period. While PROT-01325 and the ADJUSST study only assessed the new products containing 5.0% nicotine, the data presented on the new products containing 5.0% nicotine (PM0000872.PD1, PM0000876.PD1) can be bridged to the new products containing 3.0% nicotine (PM0000864.PD1, PM0000874.PD1) when used with the new product device (PM0000878.PD1), because the abuse liability outcomes of the new products containing 3.0% nicotine are similar compared to the new products containing 5.0% nicotine, based on the findings from abuse liability studies (i.e., PROT-00030, PROT-00032, PROT-00033) reviewed by behavioral and clinical pharmacology (BCP). The nicotine pharmacokinetics (PK) outcomes (i.e., C_{max}, T_{max}, AUC) were not found to be different between the two nicotine concentrations for either the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) or the menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1). They also showed similar subjective effects from use of the new products containing 3.0% nicotine compared to the new products containing 5.0% nicotine with the new product device. The epidemiology review of the ADJUSST study data concluded the modeled switching rate from CC to the new products (i.e., PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) (38.4-51.9%) was substantially higher than smoking cessation rates reported in literature from unaided quitting (5-6%) as well as for those using nicotine replacement therapy (8-9%) (Lindson et al., 2023). Further information describing the evaluation of the new products' switching rates can be found in the corresponding epidemiology TPMF (b) (4) review. Thus, the ADJUSST study supports that the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) provide an adult benefit to smokers, and that the menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1) provide an added adult benefit over the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1), described in more detail below.

The ADJUSST Study assessed the role of flavors, including menthol, in adult user behavior. As noted above, the new products containing 5.0% nicotine (PM0000872.PD1, PM0000876.PD1) can be bridged to the new products containing 3.0% nicotine (PM0000864.PD1, PM0000874.PD1) when used with the new product device (PM0000878.PD1). Across a two-year follow-up, these study data show that the Menthol-flavored new product (PM0000872.PD1, PM0000878.PD1) is associated with a higher switching probability than the Virginia Tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) in adjusted analyses, regardless of the modeling method used (aRR = 1.11 to 1.15, depending on the methodology used: intent-to-treat, empirical imputation, and non-missing observations). Further information describing the evaluation of the new products' switching rates can be found in the corresponding epidemiology TPMF review. Epidemiology determined that the added benefit to adults from the Menthol-flavored new product (PM0000872.PD1, PM0000878.PD1) versus the Virginia Tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) can be characterized as moderately beneficial. This characterization can be bridged to the 3.0% nicotine new products as well (PM0000864.PD1, PM0000874.PD1, PM0000878.PD1). The analysis of these study data also found that those who used non-mentholated CC had higher rates of switching when using the Menthol-flavored new product (PM0000872.PD1, PM0000878.PD1) compared to the Virginia Tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) (aRR = 1.22 to 1.28, depending on the methodology used). The applicant-submitted clinical studies demonstrated that the new products' abuse liability is comparable to usual brand (UB) CC in adults who currently smoke. This suggests that the new products may be a suitable substitute for CC among

adults who smoke CC and who want to quit. Based on the data available from adults who smoke, adults who do not use tobacco who initiate use of the new products are likely to obtain nicotine exposures comparable to CC as they gain experience with the new products, thus leading to progression to regular use of the new products. Additionally, biomarker of exposure data from the applicant-sponsored study PROT-00030 found that switching from UB CC use to exclusive ad libitum use of the new products for six days resulted in significant reductions in the urinary and blood biomarkers of exposure (BOE) of similar magnitude to the reductions in the participants who abstained from CC smoking. Specifically, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 3-Hydroxypropylmercapturic acid (3-HPMA), Monohydroxybutenyl-mercapturic acid (MHBMA), S-Phenylmercapturic acid (S-PMA), carboxyhemoglobin (COHb), N-nitrosonornicotine (NNN), 3-Hydroxy-1-methylpropylmercapturic acid (HMPMA), 2-Cyanoethylmercapturic acid (CEMA), 1-Hydroxypyrene (1-OHP), ortho-toluidine (o-toluidine), 2-aminonaphthalene (2-NA), and 4-aminobiphenyl (4-ABP) significantly reduce following use of the new products. Chemical evaluation of the new products' aerosols suggests that the new products have fewer and lower levels of many harmful and potentially harmful constituents (HPHCs) compared to CC. A toxicology evaluation predicts that the new products' estimated excess lifetime cancer risk (ELCR)[8] is significantly lower than the ELCR in adults who smoke CC as all calculated cumulative ELCR ($ELCR_c$) values for the new products are less than 5% of the $ELCR_c$ for the University of Kentucky 1R6F reference CC. This suggests a significant benefit for adults who smoke CC and switch completely to using the new products relative to continuing to smoke CC. The applicant, therefore, has demonstrated the potential for these new products to benefit adults who smoke CC and switch to these products or significantly reduce CC compared to adults who continue to smoke CC exclusively.

FDA systematically reviewed adverse experience (AE) data for the new products by category and included AEs in applicant-sponsored studies, in the published literature, and reported by the public including FDA's Safety Reporting Portal (SRP) and the new products' customer service center. FDA also analyzed data pertaining to AEs of special interest (i.e., lung injury, seizures). In general, the frequency of AEs in applicant-sponsored studies was low and there were no unexpected AEs, deaths, or reports of either seizures or lung injury. Regarding AEs reported in the published literature, the majority of citations the applicant selected for review corroborated their conclusion that the new products are well tolerated and that the reported associated AEs are inconsequential. Between December 2018 and April 2025, the public reported 12 AEs associated with the new products through the FDA's SRP. However, these AEs were either not associated with significant health effects, were unable to be validated as bona fide medical events to directly link these reported AEs to the new products, or were already known and reported effects of ENDS and did not introduce new health effects. As such, the review of reported AEs does not raise concerns with issuing marketing orders for the new products.

Based on the information provided in the PMTAs and the available evidence, as TPL, I find that permitting the marketing of the new products, subject to certain marketing restrictions, is APPH. The PMTAs contain sufficient evidence to demonstrate the potential of the new products to benefit adults who smoke CC who significantly reduce their CC use (or who switch completely and achieve CC cessation) outweighs the risk to youth, provided that the applicant follows post-

[8] The main metric of risk characterization is an ELCR, which provides an extrapolated estimate of how many additional cases of cancer would be expected in a population exposed to a given toxicant concentration and intake level for an entire lifetime based on the toxicant's carcinogenic potency.

marketing requirements and implements marketing restrictions to reduce youth exposure to marketing of the new products and youth access to the new products.

The applicant proposed marketing plans that include restrictions beyond those required with PMTA authorization. The Office of Health Communication and Education (OHCE) has determined that these restrictions may help further limit youth exposure to the new products and the products' labeling, advertising, marketing, and/or promotion as well as the potential for youth initiation. For example, (b) (4)

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

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the new products listed in Appendix B, sold under the brand names JUULpods Menthol 3.0% (PM0000864.PD1), JUULpods Menthol 5.0% (PM0000872.PD1), JUULpods Virginia Tobacco 3.0% (PM0000874.PD1), JUULpods Virginia Tobacco 5.0% (PM0000876.PD1), and JUUL Device (PM0000878.PD1). Briefly, a complete JUUL ENDS is composed of a rechargeable power unit (device; PM0000878.PD1), a prefilled replacement cartridge containing the e-liquids, and an accessory USB charger for the power unit. The power unit and cartridge settings are not adjustable by the user. The cartridges contain e-liquids identified by the applicant as containing the following characterizing flavors in two nicotine concentrations each: tobacco-flavored (PM0000874.PD1 and PM0000876.PD1) and menthol-flavored (PM0000864.PD1 and PM0000872.PD1).

2.2. REGULATORY ACTIVITY

On July 29, 2020, FDA received the subject PMTAs from JUUL Labs Inc. (JLI). FDA completed an acceptance review and issued an Acceptance letter to the applicant on August 5, 2020. FDA issued a Filing letter to the applicant on August 17, 2020. FDA issued a Deficiency letter to the applicant on March 26, 2021. On June 22, 2021, FDA received the applicant's response to the Deficiency letter dated March 26, 2021 (PM0004760). On June 23, 2022, FDA issued Marketing Denial Orders (MDOs) for the products identified in Appendix B of this document. On July 5, 2022, FDA initiated an internal supervisory review pursuant to 21 C.F.R. § 10.75 and issued an administrative stay of the MDOs pursuant to 21 C.F.R. § 10.35(a), pending FDA's completion of that review. On July 29, 2022, JLI also filed a supervisory review of the MDOs pursuant to 21 C.F.R. § 10.75 (AP0000166). On June 6, 2024, FDA issued a Rescission letter to rescind the MDO letter dated June 23, 2022. On June 6, 2024, FDA also issued a Deficiency letter. On August 30, 2024, FDA received the applicant's response to the Deficiency letter dated June 6, 2024 (PM0008694).[9]

Refer to Appendix C 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 that are the subject of this review.

On August 30, 2024, the applicant submitted an amendment in response to the June 6, 2024, Deficiency letter, which was reviewed by the BCP, chemistry, engineering, environmental science, epidemiology, medical, microbiology, social science, and toxicology disciplines.

The Tobacco Product Master Files (TPMFs) (b) (4) were submitted by the TPMF owner. To evaluate these new products, the TPMFs and amendments were reviewed by the BCP, chemistry, engineering, epidemiology, medical, microbiology, social science, and toxicology disciplines.

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer	Review Date	Reviewer	Review Date
Regulatory	Donna Cheung	Not applicable (N/A)	Donna Cheung	N/A
Engineering	Nashaat Rasheed	3/24/2021	Anjali Verma	6/15/2022
Chemistry	Yuan-wei Nei	3/24/2021	Yuan-wei Nei	6/14/2022
Microbiology	Prashanthi Mulinti	3/24/2021	Jennifer Patro	6/15/2022

[9] In the August 30, 2024, amendment (PM0008694), the applicant noted "JLI submitted a request for supervisory review under 21 C.F.R. § 10.75 on July 29, 2022 (AP0000166). On November 6, 2023, JLI submitted an amendment to the appeal that OS did not consider in the re-review. JLI has included the information from the November 6, 2023, amendment in our Deficiency Response (TPMF (b) (4) 1-20-jli-1075-supplement-11-6-2023.pdf). However, for completeness and the avoidance of doubt, FDA should consider the November 6, 2023, amendment to be an amendment to the July 29, 2020, PMTAs." During the fourth cycle of review, FDA considered and reviewed all the information submitted in the November 6, 2023, amendment, thereby treating it as an amendment to the applicant's July 29, 2020, PMTAs. (b) (4)

Discipline	Cycle 1		Cycle 2	
	Reviewer	Review Date	Reviewer	Review Date
Toxicology	Matthew Hartog	3/24/2021	Matthew Hartog	6/16/2022
Behavioral and Clinical Pharmacology	Carolina Ramôa	3/26/2021	Kia Jackson	6/15/2022
Medical	Theresa Watkins-Bryant	3/25/2021	N/A	N/A
Epidemiology	Apostolos Alexandridis	3/23/2021	Apostolos Alexandridis	6/14/2022
Social science	Sabeeh Baig	3/24/2021	Sabeeh Baig	6/15/2022
Environmental science	William Brenner	3/26/2021	Thomas Creaven	6/15/2022
OCE – BIMO	Rachel Dailey	10/30/2020	Rachel Dailey	6/15/2022
OCE – manufacturing/lab	Abraham Agyapong	10/30/2020	Abraham Agyapong	1/5/2022

Discipline	Cycle 3		Cycle 4	
	Reviewer	Review Date	Reviewer	Review Date
Regulatory	Anab Kemal	5/9/2023	Rodney Hammond	N/A
Engineering	Pritesh Darji	6/5/2024	Pritesh Darji	TBD
Chemistry	Yuan-Wei Nei	6/5/2024	Yuan-Wei Nei	TBD
Microbiology	Jennifer Patro	6/5/2024	Terrence Gee	TBD
Toxicology	Hermes Reyes-Caballero	6/5/2024	Hermes Reyes-Caballero	TBD
Behavioral and Clinical Pharmacology	Kia Jackson	6/5/2024	In Heon Lee	TBD
Medical	Julie Clement	6/5/2024	Vy Nguyen	TBD
Epidemiology	Aaron Blakney	6/5/2024	Aaron Blakney	TBD
Social science	Marjorie A. Margolis	6/5/2024	Mehmet Ergun	TBD
Environmental science	N/A	N/A	William Brenner	TBD
OCE – BIMO	N/A	N/A	N/A	N/A
OCE – manufacturing/lab	N/A	N/A	Abraham Agyapong	12/12/2024

Table 2. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer	Review Date	Reviewer	Review Date
OCE – DPAL	Melissa View	11/23/2020	N/A	N/A
OHCE	Emily Talbert	10/30/2020	Allison O'Donnell	11/16/2021

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer	Review Date	Reviewer	Review Date
Tobacco Product Surveillance Team	Susan Rudy	9/16/2020	N/A	N/A

Discipline or Office	Cycle 3		Cycle 4	
	Reviewer	Review Date	Reviewer	Review Date
OCE – DPAL	N/A	N/A	Christopher Lee	5/22/2025
OHCE	N/A	N/A	Emily Talbert	2/12/2025
Tobacco Product Surveillance Team	Susan Rudy	8/31/2022	Vy Nguyen	4/10/2025
Statistics	Not Assigned	N/A	Jia Wang	May 14, 2025[10]

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

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

Per the engineering review:

- The applicant compared some of the key design and usability features of the JUUL Device and JUULpod with Vuse Alto, NJOY ACE, and blu PLUS+. These key design and usability features included: battery capacity, presence of closed loop temperature control, overall size and weight, materials, and LED function. Although the design parameters in sections G.1 and N.2.4 of the application represent only a few of the dozens of design parameters that are evaluated in this review for the JUUL Device and JUULpod, based on this limited information, the applicant's rationale for selection of these comparison products is acceptable from an engineering perspective.

Per the chemistry review:

- The applicant provided mainstream smoke HPHC yields for the University of Kentucky 3R4F reference CC. The 3R4F reference CC is not in the same product category and subcategory as the new products. However, the 3R4F reference CC was designed to be representative of the most popular CC in the U.S. CC market based on tobacco blend formulation. It is also well characterized in the literature and commonly used for research and standardization purposes. The applicant stated that comparing the new products to the 3R4F reference CC shows the potential benefit of switching from CCs to the JUUL System. Chemistry finds the

[10] Three statistics consultations were conducted on November 14, 2024, December 31, 2024, and March 31, 2025, by Jia Wang; all consults were finalized on May 14, 2025.

3R4F reference CC to be an appropriate comparison product to use to evaluate the new products' potential benefit for public health.

- The applicant provided aerosol HPHC yields for the IQOS Regular and Menthol Heatsticks. The IQOS heated tobacco system is not in the same product category and subcategory as the new products. However, chemistry considers IQOS Heatsticks to be an appropriate comparison product to use to evaluate the new products' potential benefit for public health because the IQOS system is an alternative non-combusted tobacco product. The data from the IQOS system are helpful in defining where the new products fit within the continuum of risk among nicotine-containing products and help evaluate potential public health benefits that may be achieved if current users switch to the new products. Both the 3R4F reference CC and IQOS Heatsticks are considered good reference standards for evaluating the health risk of the new products, in that they allow for a more complete assessment of potential health risks.
- The applicant measured whole pod aerosol HPHC yields of the comparison products Vuse Alto (Original 5% and Menthol 5%), blu PLUS+ (Classic Tobacco 2.4% and Menthol 2.4%), and NJOY Ace (Classic Tobacco 5% and Mint 5%). These tobacco products are in the same product category and subcategory and have similar e-liquid flavors as the new products. The applicant justified these comparison product selections based on their similarity to the new products (closed-system, pre-filled cartridge-based ENDS) as well as comparable total puff counts, nicotine content, and e-liquid ingredients. Chemistry determined the applicant's rationale for the selection of the ENDS comparison data is reasonable, and the products tested are appropriate comparison products.
- The applicant used an unvalidated mathematical model to extrapolate the whole pod aerosol HPHC yields for the new products. Some of the extrapolated whole pod aerosol HPHC yields for the new products are estimated values and are denoted with an "≤" sign. This is because some puff segments (beginning, middle, and end of pod) were measured below the level of detection (BLOD) or below the level of quantification (BLOQ). In addition, the standard deviation for these estimated values were not provided. This, however, is only a limitation because the whole pod aerosol HPHC yields are extrapolated with each analytical method's level of detection (LOD) or level of quantification (LOQ). Those denoted with a "≤" sign represent the most conservative estimates of HPHC yields. Whole pod aerosol HPHC yields that were extrapolated using three measured 50-puff segments (benzoic acid, formaldehyde, glycerol, nicotine, propylene glycol, and water) are close to measured whole pod aerosol HPHC yields. Therefore, the whole pod aerosol HPHC yields from the new products can still provide a semi-quantitative comparison to the comparison products and is adequate from a chemistry perspective.

Per the microbiology review:

- The applicant measured water activity (a_w), NNN, and NNK levels of the comparison products, NJOY Ace Classic Tobacco 5.0%, NJOY Ace Mint 5.0%, blu PLUS+ Classic Tobacco 2.4%, and blu PLUS+ Menthol 2.4%. These products are in the same product category and subcategory as the new products and are pre-filled with nicotine-containing e-liquids.
- a_w, NNN, and NNK levels are BLOD or BLOQ in the new and comparison

products.

Per the toxicology review:

- The applicant provided comparisons between the new product e-liquids used with the new product device (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1), a CC, and commercially available ENDS. The University of Kentucky 3R4F and 1R6F reference CC were used as a representative of the CC product category. The NJOY ACE Classic Tobacco 2.4%, NJOY Ace Classic Tobacco 5.0%, Vuse Alto Rich Tobacco 2.4%, NJOY Ace Menthol 2.4%, NJOY Ace Menthol 5.0%, NJOY Menthol 4.5%, NJOY Extra Menthol 6%, Vuse Alto Golden Tobacco 5%, Vuse Alto Golden Tobacco 2.4%, Vuse Alto Golden Tobacco 1.8%, Vuse Alto Rich Tobacco 5.0%, Vuse Alto Rich Tobacco 1.8%, Vuse Alto Menthol 5.0%, blu PLUS+ Classic Tobacco (2.4% nicotine) and blu PLUS+ Menthol (2.4% nicotine) were used as representatives of the closed system ENDS product category. The selection of ENDS comparison products is justified from the toxicology perspective because they belong to the same product category as the new products.
- In its response to the June 6, 2024, Deficiency letter, the applicant provided new data from in vitro mutagenicity and cytotoxicity assays (Ames and micronucleus assays) using aerosolized e-liquid from several ENDS products as comparators and the condensate of 1R6F and 3R4F CC smoke. The rationale for the comparison is to assert that results of the assays are the same regardless of the solvent or concentration of the test article in the comparator and new products. The choice of the comparison products is adequate for the purpose of this review. However, these assays are generally recognized as hazard identification assays and, as such, are not appropriately or routinely used for comparative risk assessment. Information about the limitations of these assays on the toxicological evaluation of the new products was communicated to the applicant in the June 6, 2024, Deficiency letter and reiterated in the FDA's response on July 18, 2024, to clarifying questions submitted by the applicant.
- The applicant attempted to calculate the ELCRs considering HPHCs alone, ingredients alone, or the $ELCR_c$ to compare the cancer risk of its new products and that of ENDS comparison products. These calculations were specifically compared to Vuse Alto tobacco and NJOY Ace Menthol products.
- For some of the comparison products, the applicant obtained HPHC and ingredient levels using semiquantitative chemical analysis. Although the choice of comparison products is adequate, the semiquantitative methodology is not because of the remaining uncertainty regarding the actual amounts of HPHCs and ingredients present that contribute to the ELCR. For example, the applicant provided semi-quantitative analysis of three ingredients from the NJOY Ace Tobacco comparator; however internal analysis shows that this does not sufficiently describe the risk of this comparator product. While this comparison was not adequate due to the methodology being inappropriate, the applicant's conclusion, with respect to the comparison of the new products to these ENDS is consistent with FDA's internal evaluations. The comparators and subsequent comparison are therefore considered sufficient from the toxicology perspective.
- The cancer risk evaluation of a new product requires a holistic consideration of all the contributors to the ELCR; therefore, from the toxicology perspective, the applicant's comparisons of ELCRs from HPHCs or ingredients alone are of limited

relevance as these individual ELCRs, for either ingredients alone or HPHCs alone, do not account for the total estimated lifetime cancer risk posed by the new products.

- The applicant also compared the ELCR values for the new products to ELCR values from comparison products, which were determined using information from publicly available TPL reports for other ENDS products, specifically for data such as percent of risk compared to reference CC smoke. The information from TPL reports was obtained from the following PMTAs: NJOY Ace Menthol 5.0% and NJOY Ace Menthol 2.4% (PM0000616.PD1 and PM0000617.PD1); NJOY Menthol 4.5% and NJOY Extra Menthol 6% (PM0000628.PD1 and PM0000629.PD1); NJOY Ace Classic Tobacco 5.0% (PM0000613.PD1, PM0000614.PD1,-PM0000615.PD1 and PM0000622.PD1); and Vuse Alto Rich Tobacco 5.0%, Vuse Alto Rich Tobacco 2.5%, Vuse Alto Rich Tobacco 1.8%, Vuse Alto Golden Tobacco 5%, Vuse Alto Golden Tobacco 2.4% and Vuse Alto Golden Tobacco 1.8% (PM0000973.PD1-PM0000973.PD3, PM0000973.PD6-PM0000973.PD7, PM0000973.PD10 and PM0000973.PD11). The rationale for the comparison to these products is to demonstrate that the risk descriptors of the new products are similar or better than those of the comparison products. The comparison to data obtained from previous reviews, such as percent of risk compared to reference CC, is adequate from the toxicology perspective. The new products have similar, or lower, qualitative risk management descriptors relative to other CTP-authorized ENDS products.
- The applicant also compared the estimated $ELCR_c$ to the CTP-authorized ENDS marketplace and 1R6F reference CC as a representative of the CC marketplace. The purpose of this comparison is to assign a risk management descriptor to the new products. Because of the adjustments made to the ELCR calculation in this toxicology review and subsequent memorandum addendum related to the ELCR calculation,[11] the $ELCR_c$ provided by the applicant differs from the one calculated in this review for all the new products. The adjustments were made to include all the ELCR contributors from HPHCs, leachables, and ingredients and to exclude Tier 5[12] constituents the applicant had included. Nevertheless, the risk management descriptor provided for the Virginia Tobacco 3.0% and 5.0% new products remains unchanged after the adjustments were made in this review. Thus, the applicant's conclusion with respect to the qualitative risk management descriptor is consistent with FDA's internal evaluations. The comparison is considered adequate from the toxicology perspective.
- In the third cycle toxicology review, using the median $ELCR_c$ of the CTP-authorized ENDS marketplace at that time,[13] the new menthol products had a qualitative risk management descriptor of moderate concern. However, adjustments made in this review (i.e., adjustments due to Memorandum: "Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications;" signed July 8, 2025) increased uncertainty in the cancer risk assessment for the Menthol-flavored 3.0% and 5.0% new products. Specifically,

[11] Per the memorandum "Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications Memorandum (July 8, 2025)"
[12] Per the memorandum "Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications," Tier 5 constituents are considered unlikely to contribute to the carcinogenic risk of ENDS; therefore, they are not included in the ELCRc calculations.
[13] Per the memorandum "Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications Memorandum (July 8, 2025)"

using the updated IURs and qualitative risk descriptors (Memorandum: "Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications;" signed July 8, 2025), the contributions of Tier 4D and 4E constituents in the Menthol-flavored new products change the qualitative risk management descriptor from lower to moderate concern. This added uncertainty precludes assignment of a discrete qualitative risk management descriptor for these products (i.e., lower or moderate concern). Instead, a range spanning from lower to moderate concern is assigned. Nevertheless, the applicant's conclusions regarding the comparative carcinogenic risk of these products, which assume a moderate concern, still hold because our internal evaluation extends the lower limit of the risk range, encompassing both the lower and moderate levels of concern. The comparison is considered adequate from this discipline's perspective.

Per the medical review:

- The applicant submitted 13 clinical studies that included a variety of comparison products.
  - In 755-00039, 755-00040, and PROT-00008 (PK studies), the tobacco flavored 5.0% nicotine concentration new product (PM0000876.PD1, PM0000878.PD1), or its precursor, were compared with either selected brand CCs (i.e., Pall Mall, Newport 100s) or with other flavored new products.
  - In PROT-00013 (PK study), the tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) was compared with a heated tobacco product (IQOS), other ENDS (i.e., VUSE, myBlu, Mark Ten, NJOY Daily, PHIX), and selected brand CCs (i.e., Marlboro Red).
  - In PROT-00032 (puff topography study), the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) were compared with other flavored JUUL ENDS products including the menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1).
  - In 755-00045 and PROT-00109 (environmental studies), CCs (e.g., Canadian, UB, Marlboro Gold King (tobacco flavor), Newport king-sized (menthol flavor)) and other flavored ENDS products, including other brand ENDS (755-0045) as well as other flavors of JUUL ENDS products not in this application (PROT-00109), were comparison products.
  - In the absence of applicant-sponsored clinical studies designed to assess health effects and appropriate published clinical studies from which to bridge, safety and AE data submitted by the applicant and from other sources (i.e., published literature, SRP reports) were used to assess the health effects of the new products.

Per the BCP review:

- The applicant compared the new products to UB CC or UB ENDS in all key clinical studies that provided data on abuse liability, use behaviors, and BOE. From a BCP perspective, CC and ENDS are appropriate for comparison to the new products, as the intended user population for the new products is current tobacco users, including people who smoke and people who use ENDS.

Per the epidemiology review:

- The applicant's menthol-specific analyses, submitted in the response to the deficiency and in previous cycles of review, included CC smokers. Based on the data provided and the peer-reviewed literature, current CC smokers are the intended and likely user population for these new products. Although some non-tobacco users will also likely use the products, comparisons between the new products and CCs are appropriate to include in FDA's determination of APPH because those who smoke CCs are a likely user population.

3.1.2. Synthesis

Chemistry found the mainstream smoke HPHC yields for the University of Kentucky 3R4F reference CC to be appropriate for comparison with the new products as it is representative of the most popular CC in the U.S. market, and these data allow for the evaluation of the potential benefit to a person who smokes CC switching to the new products. Chemistry found the submission of HPHC yields for IQOS Heatstick products to be appropriate as IQOS Heatstick products are an alternative non-combusted tobacco product. Chemistry also found the comparison to HPHC yields of other ENDS products to be appropriate based on these products' similarity to the new products. Finally, although chemistry found limitations to the unvalidated mathematical model used to extrapolate the whole pod aerosol HPHC yields for the new products, the values were close to measured fully quantitative whole pod aerosol HPHC yields. Therefore, the extrapolated whole pod aerosol HPHC yields are representative of the new products' actual HPHC yields and are considered adequate to provide a semi-quantitative comparison to the comparison products.

Microbiology did not raise any concerns with the comparison of the new products to other ENDS products as the a_w, NNN, and NNK levels are BLOD or BLOQ in both the new and comparison products. Toxicology found the comparison of the new products to the University of Kentucky 3R4F and 1R6F reference CC and other similar ENDS representative of the closed system ENDS product category to be appropriate. BCP found that the use of usual brand CC and UB ENDS in the key clinical studies was appropriate for comparisons to the new products since the intended user population for the new products are people who currently use tobacco, including people who smoke and people who use ENDS. Epidemiology also found that people who smoke CCs would be a likely target population for the new products, and therefore comparisons between new products and CCs was appropriate.

Engineering identified other ENDS as appropriate comparison products to the new products. The applicant-provided information on design parameters and operation as well as the applicant's rationale for selection of these comparison products is acceptable from an engineering perspective. Similarly, medical identified appropriate CCs and ENDS products as comparison products; however, while comparisons between the comparison products and the new products regarding health risks and health outcomes were not feasible based on the data provided by the applicant, this information was not necessary for the medical review because safety and AE data submitted by the applicant and from other sources (i.e., published literature, SRP reports) were used to assess the health effects of the new products. As TPL, I agree with engineering's assessment that the information and rationale provided by the applicant is sufficient for engineering's review of the application. I also agree with medical's assessment that the lack of information about the CC and ENDS comparison products is not necessary to draw conclusions

for medical's discipline review due to the AE data for the new products that was provided by the applicant and from other sources.

As TPL, I agree with the chemistry, microbiology, toxicology, BCP, and epidemiology reviews that the applicant's rationale for the selection of CCs, non-combusted cigarettes, and ENDS as comparison products is appropriate and that the applicant provided adequate data to support the comparison between the new products and their chosen comparison products. The rationale for selecting these comparison products is reasonable given their general product composition and design. This allows for a comparative evaluation of the JUUL System to a spectrum of tobacco products that are currently available on the U.S. market. Furthermore, as noted in the BCP and epidemiology reviews, the selection of comparison products also adequately reflects the intended user populations.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

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

3.2.1.1. Product design and composition

Per the engineering review:

- For the JUULpods (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, and PM0000876.PD1), the applicant provided the lower range limits for e-liquid viscosity (mPa*s) and the upper and lower range limits for coil length (millimeter (mm)). The information provided by the applicant is sufficient and no additional information is needed regarding e-liquid viscosity and coil length from an engineering perspective.
- For the JUUL Device (PM0000878.PD1), the applicant provided the target specification and upper and lower range limits for the current cut-off (mA) and the target specification and upper and lower range limits for charging temperature (°C). The information provided is sufficient and no additional information is needed regarding current cut-off and charging temperature limits, from an engineering perspective.
- For the JUUL System (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, and PM0000878.PD1), the applicant has provided the target specification and lower range limits for air flow rate (ml/s) and the target specification and upper and lower range limits for inhaled aerosol temperature (°C). The applicant did not provide the upper range limit for air flow rate; however, the applicant has provided a sufficient explanation and rationale and data that support its claim of consistent air flow rate of at least (b) (4) The information provided by the applicant is sufficient and no additional information is needed regarding air flow rate and inhaled aerosol temperature from an engineering perspective.
- The applicant provided target specification and range limits for all required design parameters. The provided information is sufficient and no additional information is needed regarding product design and composition, from an engineering perspective.

Per the chemistry review:

- The applicant provided quality agreements and certificates of analysis (COAs) from nicotine suppliers (b) (4) The applicant provided its testing specification for nicotine to verify manufacturers' COAs and the testing frequency.
- The applicant provided single chemical ingredients, function, Chemical Abstracts Services (CAS) Number, purity (grade), and concentration for all e-liquid formulations.
- The applicant provided partial information for the structural materials of the pod assembly in PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, and PM0000876.PD1. However, the lack of single chemical ingredients, with corresponding CAS Number and quantities, for all pod assembly components that are in direct contact with e-liquid and/or aerosol is only a limitation because the applicant provided extractable and leachable data that are sufficient to enable FDA to evaluate the potential health impacts of the components.

Per the microbiology review:

- The new products contain humectants (i.e., (b) (4) , which may impact microbial activity during the new products' proposed shelf life and raise concerns from a microbiology perspective. However, the applicant provided adequate information on the type and concentration of humectants that are used in the new products. Adequate stability data were provided for the finished product e-liquids (i.e., PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1) over the proposed shelf-life. The stability data demonstrated that the humectant levels did not impact microbial stability over the shelf life; therefore, the humectant levels of the new products do not raise concerns from a microbiology perspective.

3.2.1.2. Manufacturing

Per the engineering review:

- The applicant demonstrated that the JUUL System (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, and PM0000878.PD1) is designed and manufactured with appropriate controls for device components, e-liquid ingredients, methods, facilities, manufacturing, processing, and packaging, taking into account understanding of product stability, failure mode effects analysis, hazards assessment, and human factor performance. In addition, the applicant demonstrated that overall manufacturing processes and controls ensure the equipment, facilities, and controls used to manufacture, process, and package the JUUL System meet specifications in line with information submitted, which ensures consistency. For all PMTAs, the applicant demonstrates that the new products manufacturing is well-controlled. The information on the manufacturing steps and the quality control measures in place assure FDA that the products meet manufacturing specifications for the JUULpods and JUUL Device and that the products are manufactured in a consistent manner that minimizes product variability. The information provided by the applicant is sufficient and no additional information regarding manufacturing is needed from an engineering perspective.

Per the chemistry review:

- Bulk e-liquids used in the new products (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, and PM0000876.PD1) are manufactured by (b) (4) [redacted]
- The applicant provided manufacturing validation standards, manufacturing steps and controls, and bulk e-liquid storage specifications.
- The applicant provided representative ingredient COAs, raw ingredient quality control test specifications, batch verifications, liquid properties, and constituent measurements. All the provided data are within the acceptance criteria indicating batch consistency.

Per the microbiology review:

- The bulk e-liquid is manufactured and supplied by (b) (4) [redacted] All manufacturing processes are conducted in ISO 14644 Class 8 certified cleanrooms. Remote regulatory assessments (RRAs) were performed on the three pod-filling and packaging facilities. The manufacturing processes of the bulk e-liquid and finished new products do not raise concerns from a microbiology perspective.

3.2.1.3. Product life cycle

Per the engineering review:

- The applicant provided sufficient explanation and submitted data to support the stability and consistent delivery over the shelf life and use life of the new products. The applicant has demonstrated that the (b) (4) wick and (b) (4) 60 coil are inherently durable materials with minimal wear throughout the shelf life of the JUULpod and JUUL System. The applicant has demonstrated that the finished product stability studies support a minimum (b) (4) shelf life of the finished JUULpods, including the atomizer, wicking material, and coil, from the date of JUULpod filling. The applicant has demonstrated that the atomizer (wick and coil materials) is extremely durable and the materials' thermal stability (up to (b) (4), chemical stability, and chemical purity minimize potential degradation and ensure consistent performance over the entire lifetime of the JUULpods. During normal operation of the JUUL System, the coil typically reaches 261 °C to 289 °C, up to a maximum coil temperature of 334 °C. The applicant provided testing data to demonstrate that the wick is thermally stable up to at least (b) (4) In addition, the applicant explained that (b) (4) is highly resistant to dissolution. The nickel-chromium alloy used in JUULpods is thermally stable and suitable for use at temperatures up to 1150 °C, which far exceeds the temperature reached during normal operation of the JUUL System. Overall, the coil material is expected to be durable indefinitely under warehouse storage conditions and for the expected lifetime of the JUULpod under the conditions of use.
- The applicant provided information on product stability studies, shelf-life, and test data for the coil and has provided an explanation of how the atomizer, wicking

material, and coil wear throughout the shelf life of the JUULpods and JUUL Device. Based on the information provided, no additional information is needed regarding product stability; shelf life; test data for the coil; and atomizer, wicking material, and coil wear throughout the shelf life of the JUULpods and JUUL Device from an engineering perspective.

3.2.1.4. Product stability

Per the chemistry review:

- The applicant provided sufficient and adequate information for the analytical methods used in the extractable and leachable studies of all JUULpods.
- The applicant provided the full (b) (4) of bulk e-liquid stability data to support the shelf life claim for PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, and PM0000876.PD1.
- The applicant provided the full (b) (4) of finished product stability data for the new products.
- In response to Deficiency 2 in the FDA Deficiency letter dated June 6, 2024, the applicant provided information regarding the presence of two leachables (i.e., those previously identified as (b) (4) and (b) (4) in the new and comparison products. This information is reviewed in the corresponding chemistry TPMF review of (b) (4)

Per the microbiology review:

- (b) (4) and bioburden data provided to assess the bulk product stability of all new products were provided by the applicant. However, these data were not provided for the full length of the proposed shelf life (b) (4) for the bulk new products. The finished product stability data, along with low bioburden results, indicate little risk for microbial growth in the bulk product. In addition, final filling of the e-liquid into JUULpods uses automated systems, and stability data supplied for the final packaged product indicates no microbial contamination and low propensity for microbial growth over the shelf life. The proposed bulk shelf life is considered adequate from a microbiology perspective because the applicant-provided stability data were also acceptable for the finished products.
- pH, moisture, NNN, and NNK data over the proposed (b) (4) shelf life for the finished new products were provided for the new e-liquid products (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1). The increase in moisture content over time is not a concern from a microbiology perspective due to the low a_w levels in all new products over the proposed (b) (4) (b) (4) shelf life.
- a_w data provided by the applicant demonstrate a reduced risk of microbial growth in the finished new products over the proposed shelf life. Therefore, the proposed (b) (4) shelf life from the date of manufacture, which includes (b) (4) for the bulk e-liquid and (b) (4) for the finished products, is adequate from a microbiology perspective.
- (b) (4) and (b) (4) stability data provided by the applicant for time zero does not raise a concern from a microbiology perspective for the tobacco-flavored new products. High levels of (b) (4) in the menthol-flavored new

products are above reported values in the literature. The potential health risk to consumers from exposure (b) (4) present in the menthol-flavored new products is evaluated in section 3.5.

3.2.1.5. Product test data

Per the engineering review:

- The applicant submitted multiple quality control test methods with raw data for the JUULpods, JUUL e-liquids, and JUUL Device to ensure functional robustness, reliability, and durability. The JUUL e-liquids were evaluated separately from the JUULpods to ensure these e-liquids met applicant-specified quality control specifications for e-liquid viscosity and volume. The applicant designed and developed the JUUL System to meet target design parameters. Testing included the thermal shock test, high temperature and humidity test, charge/discharge cycle test, unpackaged vibration test, drop test, package handling and distribution test, and pod connector-mechanical cycle test. In addition to internal testing, the applicant demonstrates that the JUUL Device has been tested by external labs and complies with many international standards to meet the target design parameters.
- In addition, the applicant submitted design verification and validation tests for the JUUL System (JUUL Device and JUULpods) that demonstrated components and the USB charging dock accessories meet the JUUL product specifications. Based on the information provided in the PMTAs for the JUULpods and JUUL Device, adequate manufacturing processes and controls were used to demonstrate that the new products meet manufacturer's specifications, and that they will operate consistently throughout the lifetime of the products.
- For all PMTAs, the applicant has provided various target design parameters and testing results, design verification and validation test methods, and raw test data on the JUUL System. No additional information is needed regarding product test data from an engineering perspective.

Per the chemistry review:

- The HPHC analytical methods and validation are sufficient to support this review.
- The aerosol HPHC yields from the new products (e-liquids PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) are much lower than the mainstream smoke HPHC yields from the 3R4F reference CC, except for glycerol.
    - Glycerol yield in intense regimen
        - 795% (2.4 mg/puff) higher in PM0000864.PD1 compared to 3R4F
        - 625% (1.9 mg/puff) higher in PM0000872.PD1 compared to 3R4F
        - 602% (1.8 mg/puff) higher in PM0000874.PD1 compared to 3R4F
        - 553% (1.7 mg/puff) higher in PM0000876.PD1 compared to 3R4F
    - High level of glycerol aerosol yield in the new products is not a concern from a chemistry perspective since the level of formaldehyde and acrolein aerosol yields, common degradation products of glycerol upon heating, in the new products are lower than those in the mainstream smoke yields of the 3R4F reference CC.
- The aerosol HPHC yields from the new products (e-liquids PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) are lower

than the aerosol HPHC yields from the IQOS heated tobacco system, except for glycerol, nicotine, 1,3-butadiene, isoprene, and nickel.

- Glycerol yield in intense regimen
  - 718% (2.4 mg/puff) higher in PM0000864.PD1 compared to IQOS Menthol
  - 562% (1.9 mg/puff) higher in PM0000872.PD1 compared to IQOS Menthol
  - 445% (1.7 mg/puff) higher in PM0000874.PD1 compared to IQOS Regular
  - 408% (1.6 mg/puff) higher in PM0000876.PD1 compared to IQOS Regular
- Nicotine yield in intense regimen
  - 14% (14.2 µg/puff) higher in PM0000864.PD1 compared to IQOS Menthol
  - 66% (66.4 µg/puff) higher in PM0000872.PD1 compared to IQOS Menthol
  - 16% (17.7 µg/puff) lower in PM0000874.PD1 compared to IQOS Regular
  - 41% (44.7 µg/puff) higher in PM0000876.PD1 compared to IQOS Regular
- 1,3-Butadiene yield in intense regimen
  - ≤145% (≤32.1 ng/puff) higher in PM0000864.PD1 compared to IQOS Menthol
- Isoprene yield in intense regimen
  - ≤207% (≤364.7 ng/puff) higher in PM0000864.PD1 compared to IQOS Menthol
- Nickel yield in intense regimen
  - 45.83 pg/puff; below LOQ for IOQS Heatsticks,
  - ≤206.3 - ≤519.2 pg/puff in the new products
- The high level of glycerol aerosol yield in the new products is not a concern from a chemistry perspective since the levels of formaldehyde and acrolein aerosol yields in the new products are lower than those of IQOS Heatsticks.
- 1,3-Butadiene and isoprene aerosol yields are higher in PM0000864.PD1 compared to the IQOS Menthol Heatstick. These aerosol yields are reported as "≤" quantities because they are calculated using LOD or LOQ quantities in the applicant's whole pod aerosol calculations, and therefore can be thought of as a "most conservative estimate" with the actual quantities likely falling below these values. It is likely that PM0000864.PD1 contains higher 1,3-Butadiene and isoprene yields than the IQOS Menthol Heatstick. However, these differences are on the order of nanograms per puff (ng/puff). 1,3-Butadiene and isoprene aerosol yields in PM0000864.PD1 are included in toxicology's evaluation of the new products and $ELCR_c$ assessment, which is discussed in section 3.5.
- The low level of nickel in JUULpods aerosol yields may stem from the coil during aerosol production. However, absolute quantities of nickel in the new products' aerosols are low (in units of pg/puff) and are not of concern from a chemistry perspective.

- The applicant provided 40 HPHC and metabolite yields for the new and ENDS comparison products. The aerosol HPHC and metabolite yields from the new products (e-liquids PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) are mostly lower than those from the ENDS comparison products, except for those listed below:
  - JUUL Menthol 3% vs Vuse Alto Menthol 5%
    - ≤59% (≤42.8 ng/puff) higher for (b) (4) in PM00000864.PD1 compared to Vuse Alto Menthol 5%
  - JUUL Menthol 3% vs blu PLUS+ Menthol 2.4%
    - ≤59% (≤1.0 ng/puff) higher for acetyl propionyl in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤47% (≤14.4 ng/puff) higher for 1-butanol in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - 30% (356 µg/puff) higher for glycerol in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - 114% (11.5 µg/puff) higher for menthol in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - 5% (2.7 µg/puff) higher for nicotine in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤12% (≤0.8 ng/puff) higher for (b) (4) in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤36% (≤30.5 ng/puff) higher for (b) (4) in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - 4% (19.2 µg/puff) higher for propylene glycol in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤52% (≤819 pg/puff) higher for propylene oxide in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤14% (≤38.8 µg/puff) higher for water in PM00000864.PD1 compared to blu PLUS+ Menthol 2.4%
  - JUUL Menthol 3% vs NJOY Ace Mint 5%
    - 59% (8.1 µg/puff) higher for menthol in PM00000864.PD1 compared to NJOY Ace Mint 5%
  - JUUL Menthol 5% vs Vuse Alto Menthol 5%
    - ≤28% (≤20.4 ng/puff) higher for (b) (4) in PM0000872.PD1 compared to Vuse Alto Menthol 5%
  - JUUL Menthol 5% vs blu PLUS+ Menthol 2.4%
    - ≤64% (≤1.1 ng/puff) higher for acetyl propionyl in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤54% (≤16.5 ng/puff) higher for 1-butanol in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤59% (≤2.0 ng/puff) higher for cotinine in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - 21% (251 µg/puff) higher for glycerol in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - 102% (10.4 µg/puff) higher for menthol in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%

    - 72% (43.2 µg/puff) higher for nicotine in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤28% (≤1.9 ng/puff) higher for (b) (4) in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤10% (≤8.2 ng/puff) higher for (b) (4) in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - ≤55% (≤868 pg/puff) higher for propylene oxide in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
    - 18% (50.6 µg/puff) higher for water in PM0000872.PD1 compared to blu PLUS+ Menthol 2.4%
- JUUL Menthol 5% vs NJOY Ace Mint 5%
    - 51% (6.9 µg/puff) higher for menthol in PM0000872.PD1 compared to NJOY Ace Mint 5%
- JUUL Virginia Tobacco 3% vs Vuse Alto Original 5%
    - ≤37% (≤24.6 ng/puff) higher for (b) (4) in PM0000874.PD1 compared to Vuse Alto Original 5%
- JUUL Virginia Tobacco 3% vs blu PLUS+ Classic Tobacco 2.4%
    - ≤17% (≤0.7 ng/puff) higher for crotonaldehyde in PM0000874.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - 97% (736 µg/puff) higher for glycerol in PM0000874.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - 73% (27.9 µg/puff) higher for nicotine in PM0000874.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - ≤103% (≤46 ng/puff) higher for (b) (4) in PM0000874.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - 16% (75.7 µg/puff) higher for propylene glycol in PM0000874.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - 13% (38.2 µg/puff) higher for water in PM0000874.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
- JUUL Virginia Tobacco 3% vs NJOY Ace Classic Tobacco 5%
    - ≤37% (≤1.1 ng/puff) higher for cotinine in PM0000874.PD1 compared to NJOY Ace Classic Tobacco 5%
    - 326% (73.9 ng/puff) higher for formaldehyde in PM0000874.PD1 compared to NJOY Ace Classic Tobacco 5%
- JUUL Virginia Tobacco 5% vs blu PLUS+ Classic Tobacco 2.4%
    - ≤67% (≤2.8 ng/puff) higher for cotinine in PM0000876.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - ≤14% (≤0.5 ng/puff) higher for crotonaldehyde in PM0000876.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - 82% (624 µg/puff) higher for glycerol in PM0000876.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - 190% (72.7 µg/puff) higher for nicotine in PM0000876.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
    - 10% (49.4 µg/puff) higher for propylene glycol in PM0000876.PD1 compared to blu PLUS+ Classic Tobacco 2.4%
- JUUL Virginia Tobacco 5% vs NJOY Ace Classic Tobacco 5%

- ≤135% (≤4.0 ng/puff) higher for cotinine in PM0000876.PD1 compared to NJOY Ace Classic Tobacco 5%
- 293% (66.3 ng/puff) higher for formaldehyde in PM0000876.PD1 compared to NJOY Ace Classic Tobacco 5%
- ≤30% (≤2.0 ng/puff) higher for (b) (4) in PM0000876.PD1 compared to NJOY Ace Classic Tobacco 5%

- Acetyl propionyl, 1-butanol, cotinine, crotonaldehyde, formaldehyde, (b) (4) (b) (4), and (b) (4) aerosol yields are higher in the new products compared to the ENDS comparison products. These aerosol constituent yields in the new products are included in toxicology's evaluation of the new products and $ELCR_c$ assessment, which are discussed in section 3.5.

Per the microbiology review:

- Microbiological data of the comparison products provided by the applicant show that the a_w, NNN, and NNK levels are BLOD or BLOQ in the new and comparison products.

3.2.2. Synthesis

As TPL, I agree with the chemistry, engineering, and microbiology reviews that the product design, materials, and packaging contain sufficient information to characterize the product design, contain adequate manufacturing processing controls to help ensure that the new products meet the manufacturer's specifications, do not raise any concerns related to these disciplines, and also support our confidence in the use of the new products in the studies evaluated by other disciplines discussed in the sections below. The applicant provided single chemical ingredients, function, CAS number, purity (grade), and concentration for all e-liquid formulations as well as the quality agreement from the nicotine suppliers. While it is a limitation that the applicant did not provide complete information for the structural materials of the pod assembly for the four JUULpods, it did provide extractable and leachable data that were evaluated by toxicology (covered below in sections 3.5 and 3.6). This provided information is sufficient for a complete evaluation of the structural materials used to manufacture the new product e-liquid pods. The applicant also provided sufficient information about the humectants used in the new products as well as adequate stability data to conclude that the levels of humectants do not raise a concern related to microbiology. The applicant provided target specification, and range limits for all design parameters. The applicant supplied sufficient information about the e-liquid viscosity, coil length, current cut-offs, and charging temperature limits. The applicant also provided target specifications and lower range limits for air flow rate and upper and lower range limits for inhaled aerosol temperature. Despite not including the upper range limit for the air flow rate, the applicant provided a sufficient rationale and data supporting a consistent air flow rate of at least (b) (4) ml/s. These data on air flow rate and inhaled aerosol temperature are sufficient.

As TPL, I agree with the engineering, chemistry, and microbiology reviews that the manufacturing standards used by the applicant were appropriate. The applicant was able to demonstrate that the JUUL System is designed and manufactured with appropriate controls, device components, e-liquid ingredients, methods, facilities, manufacturing, processing, and packaging, taking into account an understanding of product stability, failure mode effects analysis, hazards assessment, and human factor performance. In addition, the applicant

demonstrated that overall manufacturing processes and controls ensure that the equipment, facilities, and controls used to manufacture, process, and package the JUUL System meet specifications in line with the information submitted. The applicant also provided sufficient manufacturing validation standards for the e-liquids, manufacturing steps and controls, bulk e-liquid storage specifications, raw ingredient quality control test specifications, batch verifications, liquid properties, and constituent measurements. This information was sufficient to indicate batch consistency. All the manufacturing processes are conducted in ISO 14644 Class 8 certified cleanrooms and RRAs were performed on the three pod-filling and packaging facilities. The manufacturing processes of the bulk e-liquid and finished new products do not raise concerns.

As TPL, I agree with the chemistry and microbiology reviews that the product stability data is sufficient for the (b) (4) proposed shelf life of the bulk new products as well as the (b) (4) shelf life for the finished new products. There were no concerns with the pH, moisture, nicotine stability, NNN, and NNK data and the increase in moisture content over time is not a concern from a microbiology perspective due to the low a_w levels in all new products over the proposed (b) (4) shelf life. The finished product stability data along with low bioburden results indicate little risk for microbial growth in the bulk product. In addition, final filling of the e-liquid into JUULpods uses automated systems, and stability data supplied for the final packaged product indicates no microbial contamination and low propensity for microbial growth over the shelf life. Therefore, the proposed (b) (4) shelf life from date of manufacture, including (b) (4) for the bulk e-liquid and (b) (4) for the finished products, is appropriate. The (b) (4) and (b) (4) (b) (4) stability data provided by the applicant for time zero do not raise a concern from a microbiology perspective for the tobacco-flavored new products.

I also agree with the engineering review that the product life cycle data are sufficient. The applicant provided information on product stability studies, shelf life, and test data for the coil and has provided an explanation on how the atomizer, wicking material, and coil wear through the shelf life of the JUULpod and JUUL System. The applicant provided sufficient explanation and data to support the stability and consistent delivery over the proposed shelf life and life cycle of the new products.

The microbiology review found that the microbiological data show that the a_w, NNN, and NNK levels are BLOD or BLOQ in the new and comparison products, and therefore are not a concern. As TPL, I agree with microbiology's assessment. The engineering review indicated that the applicant designed and developed the JUUL System to meet target design parameters and provided internal and external testing that indicated that the JUUL device complies with many international standards to meet the target design parameters. Additionally, the applicant submitted design verification and validation tests for the JUUL System that demonstrated the components and USB charging dock accessories meet the JUUL product requirements. I agree with engineering's conclusion that adequate manufacturing processes and controls were used to demonstrate that the new products meet manufacturer's specifications, and that they will operate consistently throughout the lifetime of the JUUL products.

As TPL, I agree with the chemistry review, which found that the HPHC analytical methods and validation are sufficient to support this review. Compared to the 3R4F CC, the JUUL System had lower aerosol HPHC yields for all constituents except glycerol. Chemistry did not find this to be a concern despite these higher glycerol yields because two common degradation products of

glycerol upon heating (formaldehyde and acrolein aerosol yields) were found to be much lower than those in the mainstream smoke yields of the 3R4F reference CC. Additionally, glycerol itself is classified by toxicology as a Tier 5 constituent per CTP-published supporting memoranda addressing genotoxicity hazard identification, meaning that glycerol is unlikely to contribute to the carcinogenic risk of ENDS.[14] Compared with the aerosol HPHC yields from the IQOS heated tobacco system, only glycerol, nicotine, 1,3-Butadiene, isoprene, and nickel yields were higher in the new products. The higher glycerol yield was not a concern because, similar to the results from the comparison to the 3R4F CC, the two common degradation products of glycerol upon heating, formaldehyde and acrolein aerosol yields, were lower than in the IQOS Heatsticks aerosol. 1,3-Butadiene and isoprene aerosol yields are higher in PM0000864.PD1 compared to IQOS Menthol Heatstick with the differences on the order of nanograms per puff (ng/puff). Toxicology evaluated these differences (covered below in sections 3.5 and 3.6). When compared to other ENDS, most of the aerosol HPHC yields were lower in the new products, but acetyl propionyl, 1-butanol, cotinine, crotonaldehyde, formaldehyde, (b) (4) and (b) (4) aerosol yields are higher in the new products. These aerosol constituent yields in the new products were evaluated by toxicology (covered below in sections 3.5 and 3.6).

3.3. ABUSE LIABILITY

3.3.1. Discipline key findings

The following discussion is based on key findings provided in the BCP review. The applicant submitted 11 clinical and behavioral studies and a literature review. Four of the studies and the applicant-provided literature review allowed for an assessment of abuse liability of all the new products. The applicant's studies provided information on the abuse liability of the new products based on nicotine PK, puff topography, and subjective effects following use of the new products compared to CC, ENDS, the IQOS heated tobacco product, and/or nicotine replacement therapy (NRT) gum. The applicant's literature review provided information on actual product use behaviors, BOE, and potential misuse of the new products by users.

The four studies allowing for an assessment of abuse liability are as follows:

- 755-00041 was a single-center, randomized, open-label, parallel study with JUUL 5.0% e-liquids in Virginia Tobacco (PM0000876.PD1 and PM0000878.PD1 JUUL Device), Cool Mint, Mango, and Crème Brûlée flavors and usual brand (UB) CC that looked at nicotine PK and puff count from prescribed (3s * 10 puffs, 30s interpuff) and 5-min ad libitum use after a 6 day use period; subjective effects, BOE, and pod weights from 5-day use in adults who smoke CC were reported.
- 755-00042 was a single-center, open-label study with JUUL 5.0% e-liquid in Virginia Tobacco flavor (PM0000876.PD1 and PM0000878.PD1 JUUL Device) that looked at puff topography, subjective effects, and pod weights from 60-min ad libitum use, daily product use, and cigarettes per day (CPD) during a 15-day use period in adults who smoke CC.
- PROT-00030 was a multi-center, randomized, open-label, parallel study with JUUL 3.0% and 5.0% e-liquids in Virginia Tobacco (3.0% nicotine PM0000874.PD1, 5.0% nicotine PM0000876.PD1, and PM0000878.PD1 JUUL Device), Menthol (3.0% nicotine PM0000864.PD1, 5.0% nicotine PM0000872.PD1, and PM0000878.PD1 JUUL Device),

[14] Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024

Mango, and Mint flavors and UB CC that looked at BOE, subjective effects, and pod weights from 6 days of ad libitum use in adults who smoke CC.

- PROT-00032 was a multi-center, randomized, open-label, within-subject (4-period crossover) study with JUUL 3.0% and 5.0% e-liquids in Virginia Tobacco (3.0% nicotine PM0000874.PD1, 5.0% nicotine PM0000876.PD1, and PM0000878.PD1 JUUL Device), Menthol (3.0% nicotine PM0000864.PD1, 5.0% nicotine PM0000872.PD1, and PM0000878.PD1 JUUL Device), Mint, and Mango flavors that looked at puff topography, subjective effects, and pod weights from 60-min ad libitum use in adults who use ENDS.

3.3.1.1. Abuse liability

- "Abuse liability" refers to the ability of a product to promote continued use and the development of addiction and dependence. This can be relevant to determining the likelihood that addicted users of one nicotine product would switch to another. For example, if a new tobacco product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted. Abuse liability evaluations include nicotine PK evaluations and consider the addictiveness and abuse potential of the tobacco products and the exposure to nicotine during product use.
- Findings support that the abuse liability of the new products is similar to that of UB CC in adults who gained experience with the new products. Nicotine PK and BOE data from 5- and 6-day nicotine BOE studies (i.e., 755-00041, PROT-00030) support that nicotine exposure from the new products is comparable to that from UB CC once users gain experience with the new products. These data are supported by the literature involving the new products, which finds that nicotine boost is lower than CC among JUUL-naïve users but comparable to CC among experienced users (Prochaska et al., 2022). Although data from abuse liability studies (i.e., PROT-00030, PROT-00033) support that nicotine PK parameters (i.e., nicotine C_{max}, T_{max}, $AUC_{0\text{-}120}$) and subjective effect measures (e.g., product liking) are initially lower after acute use of all the new products compared to UB CC in adults who smoke with limited or no prior ENDS experience, with extended exclusive use of the new products, the cumulative nicotine exposure and abuse liability will likely be comparable to CC.
- Puff topography data further support that adults who smoke alter their topography (e.g., take more puffs) in ways that can result in greater nicotine exposure after gaining experience with the new products. Data also support that puff count, volume, and duration are positively correlated with product liking. Adults who reported higher product liking scores took more frequent, larger, and longer puffs than individuals who reported lower product liking scores. While nicotine PK was not measured in the puff topography studies (i.e., 755-00042, PROT-00032), studies from the literature support that taking more frequent, longer, and larger puffs from ENDS can lead to greater nicotine exposure (Farsalinos et al., 2015; Hajek et al., 2015; Hiler et al., 2017).
- Published studies support that greater e-liquid nicotine concentration is associated with greater nicotine exposure (Baldassarri et al., 2018; Dawkins et al., 2016; Hiler et al., 2017; Lopez et al., 2016; Patev et al., 2024; Ramôa et al., 2016; Stiles et al., 2017; Stiles et al., 2018). Findings from the applicant-sponsored nicotine PK study (PROT-

00033) demonstrated similar or slightly higher nicotine C_{max} and AUC following use of the new products with 5.0% nicotine (i.e., PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) compared to the new products with 3.0% nicotine (i.e., PM0000864.PD1, PM0000874.PD1, PM0000878.PD1). FDA conducted a statistical analysis to compare the new products with different nicotine concentrations, and the nicotine PK outcomes (i.e., C_{max}, T_{max}, AUC) were not found to be different between the two nicotine concentrations for either the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) or the menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1). In addition, results from other applicant-sponsored studies (PROT-00030, PROT-00032) showed similar subjective effects from use of the new products with 5.0% nicotine and with 3.0% nicotine. Taken together, the data suggest that the abuse liability is similar between the new products with 3.0% and 5.0% nicotine.

- The applicant-submitted information suggests that, among adults who smoke, the new products, regardless of flavor, do not have an abuse liability that exceeds that of a CC.

3.3.2. Synthesis

As TPL, I agree with BCP's conclusions that the abuse liability of the new products is lower than that of CC in adults who smoke and have limited or no prior ENDS experience, and that it is similar to CC in adults who smoke once they gain experience using the new products. This suggests that the new products may be a suitable substitute for CC among adults who smoke CC and who want to quit. Based on the data available from adults who smoke, adults who do not use tobacco who initiate use of the new products are likely to obtain nicotine exposures comparable to CC as they gain experience with the new products, thus leading to progression to regular use of the new products. Importantly, BCP concluded that the abuse liability of all products, including the menthol-flavored ENDS, does not exceed that of a CC, and, as TPL, I agree with this conclusion.

In adults who were inexperienced with ENDS, the nicotine PK and subjective effects of the new products after acute use were lower than those of CC. However, when adults gained experience with the new products over five and six days (nicotine biomarker of exposure studies 755-00041, PROT-00030), the abuse liability was found to be similar to that of UB CC. These findings are supported by the literature, which shows that nicotine boost of ENDS is lower than that of CC among JUUL-naïve users (including the new products) but comparable to CC among experienced users (Prochaska et al., 2022). I agree with BCP's assessment that, with regular extended exclusive use of the new products, the cumulative nicotine exposure will likely reach similar values as that of CC.

The applicant also provided puff topography data that support that, with experience with the new products, people can alter their puff topography in ways that can result in more nicotine exposure. These studies provide evidence that adults who report higher product liking scores take more frequent, larger, and longer puffs than individuals who report lower product liking scores. The literature also supports this evidence and has shown that taking more frequent, longer, and larger puffs from ENDS can lead to greater nicotine exposure (Farsalinos et al., 2015; Hajek et al., 2015; Hiler et al., 2017).

Findings from the applicant-sponsored nicotine PK study found nicotine C_{max} and AUC following use of the new products with 5.0% nicotine (i.e., PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) to be higher than or similar to nicotine C_{max} and AUC following use of the new products with 3.0% nicotine (i.e., PM0000864.PD1, PM0000874.PD1, PM0000878.PD1). While the literature supports that greater e-liquid nicotine concentration is associated with greater nicotine exposure (Baldassarri et al., 2018; Dawkins et al., 2016; Hiler et al., 2017; Lopez et al., 2016; Patev et al., 2024; Ramôa et al., 2016; Stiles et al., 2017; Stiles et al., 2018), an FDA analysis determined that nicotine PK outcomes (i.e., C_{max}, T_{max}, AUC) were not different between the two nicotine concentrations for either the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) or the menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1). The applicant submitted data also showed similar subjective effects from use of the new products containing 3.0% nicotine compared to the new products containing 5.0% nicotine. Therefore, based on the findings from abuse liability studies reviewed by BCP (i.e., PROT-00030, PROT-00032, PROT-00033), the new products containing 5.0% nicotine (PM0000872.PD1, PM0000876.PD1) can be bridged to the new products containing 3.0% nicotine (PM0000864.PD1, PM0000874.PD1) when used with the new product device (PM0000878.PD1). Finally, although the literature demonstrates that flavors, including menthol, can influence abuse liability (Voos et al., 2020), the submitted data suggest that the new products, regardless of tobacco or menthol flavor, do not have an abuse liability that exceeds that of a CC.

3.4. USER POPULATIONS

3.4.1. Discipline key findings

The following discussion is based on key findings provided in discipline reviews. The BCP review considered two applicant-sponsored studies (PROT-01325, 755-00042):

- PROT-01325 was a 12-month longitudinal, online RCT with JUUL 5.0% e-liquids in Virginia Tobacco (PM0000876.PD1, PM0000878.PD1), Classic Tobacco, Mint, Menthol (PM0000872.PD1, PM0000878.PD1), Fruit, Mango, Creme, and Cucumber flavors that looked at self-reported past 30-day smoking and product use status in adults who smoke and have not used ENDS in the past 30 days. This RCT was conducted entirely online, meaning there were no in-person visits, and all outcome measure data were collected online. Participants were randomly assigned to one of three study arms: Virginia Tobacco, Flavor Variety (choice of eight flavors, including the flavors not subject to this review), or Printed Materials (no JUUL products provided, participants received only information from the CDC and Smokefree.gov about smoking abstinence services).
- 755-00042 was a single-center, open-label study with JUUL 5.0% e-liquid in Virginia Tobacco (PM0000876.PD1, PM0000878.PD1) that investigated puff topography, subjective effects, pod weights from 60-min ad libitum use, daily product use, and CPD during a 15-day use period in adults who smoke CC.

The epidemiology review considered one applicant-sponsored study, ADJUSST:

- The ADJUSST study was an observational longitudinal cohort study with JUUL 5.0% e-liquids in Virginia Tobacco (PM0000876.PD1, PM0000878.PD1), Classic Tobacco, Mint, Menthol (PM0000872.PD1, PM0000878.PD1), Fruit, Mango, Creme, and Cucumber flavors in adults who were new purchasers of JUUL products either in in-person retail

establishments or through e-commerce; this study investigated CC smoking status at baseline and then CC and JUUL product use at regular intervals for 24 months.

The social science review considered three applicant-sponsored studies (PROT-01331, PROT-01333, PROT-01343):

- PROT-01331 (Youth Patterns and Perceptions Study) was a repeated cross-sectional survey investigating curiosity to try, intentions to try, harm perceptions, addiction perceptions, interest in flavors, and reasons to use CC and JUUL devices in U.S. adolescents (ages 13-17).
- PROT-01333 (Adult Patterns and Perceptions of Use Study) was a cross-sectional survey looking at behavioral intentions, harm perceptions, addiction perceptions, interest in flavors, and reasons to use CC and JUUL devices in U.S. young adults (ages 18-24) and older adults (ages 25+).
- PROT-01343 (Perceptions and Behavioral Intentions Study) was a cross-sectional pre-post repeated-measures study investigating behavioral intentions, harm perceptions, addiction perceptions, reasons to use, and product appeal of JUUL ENDS, including the subject new products, after exposure to corresponding promotional materials in U.S. young adults (ages 21-24) and older adults (ages 25+).

3.4.1.1. Intended user population(s) (target population)

Per the BCP review:

- The applicant stated that the intended user population for the new products is current tobacco users, including people who smoke and people who use ENDS. The applicant submitted clinical studies and an RCT that were conducted with adults who smoke; these studies provided sufficient evidence to support conclusions about use behavior in adults who smoke.

Per the epidemiology review:

- The applicant stated that current CC smokers are among the intended user population for these new products.

3.4.1.2. Current tobacco users

- Precursors of product use

  Per the social science review:

  - Current smokers tended to perceive the new products as less harmful than, although similarly addictive as, CCs (PROT-01333)
  - Current smokers reported moderate to moderately high intentions to try and use the new products (PROT-01343). Some current smokers may use the new products to quit other tobacco products like CCs, or to cut down on the number of CCs smoked without quitting completely (PROT-01343).
  - Current smokers reported low interest in the Menthol and Virginia Tobacco flavors. Appeal of flavors appears to be an important reason for using JUUL ENDS among current users (PROT-01343).
  - The applicant did not present information on intentions to try among adults and adolescents that are comparable.

- Product use
  - Clinical or actual use studies

    Per the BCP review:

    - Results from the online RCT (PROT-01325) show that adults who smoke and used the new products (PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) reduced their CPM over time. These data from the 5.0% nicotine new products (PM0000872.PD1, PM0000876.PD1) can be bridged to the new products containing 3.0% nicotine (PM0000864.PD1, PM0000874.PD1) when used with the new product device PM0000878.PD1. The same study (PROT-01325) found that 17.9% of adults who used the tobacco-flavored new product PM0000876.PD1 with PM0000878.PD1 reported past 30-day abstinence from smoking, suggesting that use of PM0000876.PD1 is likely to promote substantial benefit to adults who smoke.
    - PROT-01325 included a post-hoc analysis to identify the impact of flavors used most often in the past 30 days on CPM. However, participants in the Flavor Variety group were not randomized to each individual flavor and were instead allowed to choose which flavor to use, including the flavors not subject to this review. Furthermore, this analysis was not prospective nor statistically powered, and the applicant did not provide justification to support their approach. Thus, these data were not used to estimate reductions in CPM for the Menthol-flavored new products.
    - Data showing decreases in exhaled carbon monoxide (eCO) levels in participants who used PM0000876.PD1 with PM0000878.PD1 more frequently in the puff topography study (755-00042) suggests an inverse relationship between more frequent use of PM0000876.PD1 with PM0000878.PD1 and decreased daily CC use.
    - The data support that individuals can achieve nicotine exposure comparable to UB CC as they gain experience using the new products; therefore, complete switching may occur over time, particularly among individuals with favorable subjective ratings of the new products (e.g., product liking, withdrawal alleviation). However, they are also likely to be addicted to the new products comparably to CC.
  - Observational studies or surveys

    Per the epidemiology review:

    - The new products have demonstrated wide uptake among ENDS product users and wide uptake among adult CC smokers. In the submitted Adult Prevalence Study (Wave 1: Apr-May 2019; Wave 2: Aug-Sep 2019), the applicant showed that there is uptake of the new products among adults who smoke CC, including 18-22% among younger adults and 4-6% among older adults (Table 9, N.6.2.2 – PROT-01329, p. 49).
    - In the response to the Deficiency letter dated June 6, 2024, the ADJUSST study found that the 30-day switching away from CC among those who used Virginia Tobacco (PM0000876.PD1) or Menthol (PM0000872.PD1) flavored new products with PM0000878.PD1 ranged from 48.0% to 55.1% (depending on methodology used) and the adjusted risk ratio (aRR = 1.11 to 1.15, depending on the methodology used) for relative switching comparing

menthol- to tobacco-flavored ENDS was incremental across two years of follow-up. These rates are substantially higher than seen in the literature from unaided quitting (5-6%) as well as nicotine replacement therapy (8-9%) (Lindson et al., 2023).

- Rates of switching away from CC to ENDS products vary widely in the observational epidemiology literature, with differences likely due to varying sampling design, heterogeneity in devices used, timeframe of data collection, and the study population. Longitudinal Population Assessment of Tobacco and Health (PATH) Study data (2015-2017) estimate that 6.2% of dual users quit CC but continued ENDS use (i.e., completely switched) and an additional 6.9% stopped both CC and ENDS, for a combined total of 13.1% (Abi Nehme et al., 2022). In a more recent study using PATH Study data, between Wave 5 (Dec 2018 - Nov 2019) and Wave 6 (Mar 2021 - Nov 2021), rates of CC discontinuation among adults who smoked CC was 30.9% for those who used ENDS compared to 20.0% of those who did not (Kasza et al., 2024).
- The applicant assessed the role of flavors, including menthol, in adult user behavior in the additional analyses based on ADJUSST study data. This study only evaluated the 5.0% nicotine Menthol-flavored (PM0000872.PD1) and Virginia Tobacco-flavored (PM0000876.PD1) new products used with the JUUL Device (PM0000878.PD1). However, the applicant-submitted data for the 5.0% nicotine new products (i.e., PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) can be bridged to the new products with 3.0% nicotine (i.e., PM0000864.PD1, PM0000874.PD1, PM0000878.PD1), per the BCP review. The applicant provided data on complete switching and significant CC reduction for its Menthol-flavored (PM0000872.PD1 with PM0000878.PD1) and Virginia Tobacco-flavored (PM0000876.PD1 with PM0000878.PD1) new products.
- Across a two-year follow-up, the data show that the (b) (4) [redacted] in adjusted analyses, regardless of the modeling method used (intent-to-treat, empirical imputation, and non-missing observations). Furthermore, epidemiology concludes the modeled switching rate (44.1-51.9% for the menthol-flavored new product and 38.4-46.6% for the tobacco-flavored new product) was substantial and the adjusted risk ratio (aRR = 1.11 to 1.15, depending on methodology used) for relative switching comparing menthol- to tobacco-flavored ENDS was incremental. Therefore, the added benefit to adults can be characterized as moderately beneficial.
- The applicant stratified switching probabilities by whether the participants used mentholated or nonmentholated CC at baseline. (b) (4) [redacted]

3.4.1.3. Tobacco non-users (including youth)

- Precursors of product use
  Per the social science review:
  - Adult former and never smokers as well as adolescents tended to perceive the new products as less harmful than, although similarly as addictive as, CCs (PROT-01333).
  - Adult former and never smokers reported low intentions to try the new products (PROT-01343). However, approximately half of adolescent never JUUL users reported curiosity about trying the new products while one-third reported some intentions to try (PROT-01331).
  - Adult former and never smokers as well as adolescents reported low interest in the new product flavors (PROT-01343). The only exceptions were adolescent current smokers and adolescent current JUUL ENDS users who reported moderately low to moderate interest in the new product flavors (PROT-01331).[15] Given the importance of flavor appeal in ENDS initiation among adolescents, adolescent tobacco product users may be somewhat more likely than adolescent non-users to initiate use of the new products. In contrast, adolescent non-users generally may not try the new products despite reporting some curiosity or intentions to do so due to the exclusive availability of flavors with low to moderate appeal (PROT-01331).
  - Adolescent current JUUL ENDS users commonly cited social reasons for use (PROT-01331). Thus, social reasons may be a more general driver of new product uptake among adolescents.
  - The applicant did not provide adolescent data on appeal of specific flavor or nicotine variants of the new products as it did for adults. These data may have been helpful in evaluating the likelihood of initiation among adolescents for each of the flavor and nicotine variants of the new products, in the context of the broader literature on the known risks to youth of marketing flavored ENDS, including menthol flavor.
- Product use
  - Clinical or actual use studies
    Per the BCP review:
    - The abuse liability of the new products is comparable to UB CC in adults who smoke. The applicant did not provide studies of progression to regular use of the new products in people who do not use tobacco products. BCP did not need this information to assess the abuse liability of the new products among people who do not use tobacco products because there is insufficient information available in the current scientific literature to conclude that the new product's impact would differ for these populations.
    - Based on the data in adults who smoke and adults who have experience with the new products, people who have not used tobacco products and initiate use of the new products are likely to obtain nicotine exposures comparable to CC as they gain experience with the new products, leading to progression to regular use of the new products.

[15] Participants were asked about flavors in general ("How interested would you be in using an e-cigarette flavored to taste like ...") rather than being asked specifically about the new products' flavors or nicotine concentrations.

- Observational studies or surveys
  Per the epidemiology review:
  - The 2024 NYTS data demonstrate that of youth who used ENDS in the past 30 days, more than 8 out of 10 (87.6%) used a flavored product (Park-Lee et al., 2024). Among past 30-day flavored ENDS users, the most commonly used flavors were fruit (62.8%), candy/desserts/sweets (33.3%), mint (25.1%), and menthol (15.1%) (Park-Lee et al., 2024).
  - There is substantial evidence that flavors in tobacco products, like menthol flavors in the new products, have significant appeal to youth and are associated with high likelihood of youth initiation and subsequent progression to regular use of such products when compared with tobacco-flavored ENDS. The literature demonstrates that the risk of menthol-flavored ENDS is higher than tobacco-flavored ENDS and indicates that youth are using menthol-flavored products more than tobacco-flavored products (Birdsey et al., 2023; Park-Lee et al., 2024).

3.4.1.4. Vulnerable populations (other than youth)[16]

Per the social science review:

- The applicant did not provide data on behavioral intentions, harm and addiction perceptions, or other outcomes relevant to vulnerable populations. Data on vulnerable populations are not required. Based upon the information submitted by the applicant (i.e., study reports that focus on vulnerable populations examining product use data), no additional information is needed concerning precursors of use by these populations from a social science perspective.

Per the BCP review:

- The applicant did not provide data on use of the new products among any specific vulnerable subpopulations to examine potential differences relative to a general sample of people who use tobacco. From BCP's perspective, there is insufficient information in the currently available scientific literature to conclude that the effects of the new products would differ for vulnerable populations other than youth. As such, BCP did not need this information to assess the abuse liability of the new products among vulnerable populations.

3.4.1.5. Actions taken to mitigate risk of unintended use

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

- OHCE concluded that the applicant generally describes a reasonable approach to marketing to its target audience and proposes measures to limit youth exposure to the new products' labeling, advertising, marketing, and promotion. However, OHCE noted that the applicant indicates it may explore the use of "excluded channels" (e.g., broadcast TV, radio) following authorization and could otherwise alter its marketing plans following authorization. OHCE states that if the new products are authorized, this concern should be addressed by incorporating the recommended marketing restrictions and reporting

[16] 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.

requirements, which are intended to limit youth exposure to the products' labeling, advertising, marketing, and promotion.

- The applicant describes an approach to market the new products to its target audience and proposes measures to limit youth exposure to the new products' labeling, advertising, marketing, and promotion.
- The applicant summarized several measures directed toward limiting youth exposure to the new products' marketing materials and activities which OHCE supports:
  - (b) (4)
  - (b) (4)
  - (b) (4)
  - (b) (4)
  - (b) (4)
  - (b) (4)
- OHCE recommends that any MGO letter for these new products note our evaluation that these measures are likely to help further limit youth exposure and the potential for youth initiation, as well as encourage the applicant to implement its proposed approaches to limit youth exposure to the new products' labeling, advertising, marketing, and/or promotion.

Per the social science review:

- The applicant's sales and distribution requirements and related initiatives to strengthen the efficacy of its existing point-of-sale restrictions are fundamentally sales access restrictions, which do not mitigate youth risk of

flavored ENDS sufficiently to reduce the magnitude of adult benefit required to establish APPH.

3.4.1.6. Labeling and advertising

- Instructions for use and likelihood of misuse, per the Office of Compliance and Enforcement's Division of Promotion, Advertising, and Labeling (OCE DPAL) memorandum:
    - The applicant provided specimens of proposed labeling and advertising of the new products. Based on the information presented at this time, there is no evidence to suggest that the labeling and advertisement are false or misleading in any particular.
    - OCE DPAL recommends the applicant be reminded of their responsibility to ensure the tobacco products subject to these marketing granted orders comply with the FD&C Act, FDA's implementing regulations, and all other applicable laws and regulations.

Per the social science review:

- No potential modified risk claims were identified in the labeling or advertising materials that were used as study stimuli for the new tobacco products.

3.4.2. Synthesis

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

The statute specifies that, in assessing whether permitting marketing of a new product would be APPH, FDA 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. My review of whether the marketing of the new products is APPH takes into account the information from the discipline reviews described above as well as other relevant information discussed below.

For the marketing of a new product to be found to be APPH, any risks posed to youth by a new product would need to be outweighed by a sufficient benefit to adult users, and as the known risks increase, so too does the burden of demonstrating a substantial enough benefit. For flavored ENDS, including menthol-flavored ENDS, there is a known and substantial risk to youth, as outlined below. Therefore, to show a net population health benefit, the evidence should demonstrate that the benefit of the new products is significant enough to overcome that high risk to youth. In particular, such evidence should permit FDA to assess whether there is any added or incremental benefit to a flavored ENDS over a tobacco-flavored variety in facilitating

the ability of people who use CC to completely switch or significantly reduce their smoking. Without evidence of such an incremental benefit, there would be insufficient justification to find the marketing of such products APPH, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. The availability of other products that provide similar opportunities for switching also informs the weight given to the asserted benefits of the subject products for adults who use CC. As the statutory text makes clear, it is the applicant's burden to make a "showing"—with sufficient supporting information—that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole.

Peer-reviewed Scientific Literature – Adults and Flavors

The scientific literature suggests that adults who use menthol CC show a preference for menthol-flavored ENDS, relative to non-menthol-flavored ENDS. Based on this literature, FDA explored whether that preference for menthol-flavored ENDS among adults who use menthol CC would be sufficient to demonstrate a benefit to adults who use CC that outweighs the increased youth risks relative to tobacco-flavored ENDS, such that FDA could authorize the marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS products. However, the existing literature and the applicant's own study, the ADJUSST study, do not demonstrate that menthol-flavored ENDS differentially facilitate complete switching or significant CC reduction for adults who use menthol CC (Goldenson et al., 2022); this is the behavioral outcome measurable with available methods that most directly and most robustly determines the potential benefit to users. In addition, the literature demonstrates that the youth risk of menthol-flavored ENDS is higher than tobacco-flavored ENDS. Ultimately, FDA has concluded that the existing scientific literature does not demonstrate a benefit to adults who use CC that outweighs the increased youth risks relative to tobacco-flavored ENDS, such that FDA could authorize the marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS. Thus, the approach to the APPH analysis for menthol-flavored ENDS is the same as for other non-tobacco-flavored ENDS, in that, to overcome the risk to youth, an applicant must provide evidence demonstrating its menthol-flavored ENDS products provide an added benefit for adults who use CC relative to tobacco-flavored ENDS.

The Risk to Youth of Flavored ENDS, Including the New Products

The APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood (U.S. Department of Health and Human Services, 2012) and thus youth are particularly susceptible to tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Almost 90% of adults who use CC daily started smoking by age 18 (U.S. Department of Health and Human Services, 2014). Adolescents who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood (Apelberg et al., 2014). On the other hand, youth and young adults who reach age 26 without ever starting to use CC will most likely never use CC daily (U.S. Department of Health and Human Services, 2014). Because of the

lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

The published literature demonstrates that flavored ENDS pose substantial risk in youth appeal and use. As of 2024, 7.8% of high school students and 3.5% of middle school students reported current ENDS use (Park-Lee et al., 2024). The majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time (Park-Lee et al., 2024). In the 2014 NYTS, 65.1% of high school and 55.1% of middle school current (past 30 day) e-cigarette[17] users reported using a flavored e-cigarette (Corey et al., 2015). By the 2024 NYTS, the percentage of youth who currently use e-cigarettes and reported using a flavored product[18] was up to 88.2% of high school users and 85.7% of middle school users (Park-Lee et al., 2024). In 2024, among youth who currently used flavored e-cigarettes, the most commonly used flavor type was fruit (62.8%), followed by candy, desserts, and other sweets (33.3%), mint (25.1%), and menthol (15.1%) (Park-Lee et al., 2024). Youth use of flavored ENDS (87.6%) is significantly higher than youth use of tobacco-flavored ENDS (8.5%), demonstrating that flavored ENDS—including menthol-flavored ENDS—pose a greater risk to youth. In addition, changes in the availability of products affect patterns of youth use, such that the reduced availability of certain flavored ENDS products may lead to increased use of available flavored ENDS products (Park-Lee et al., 2024).

The published literature shows that youth ENDS users are also more likely than adult ENDS users to use flavored ENDS. In the PATH Study Wave 5.5 (2020), 67.4% of youth ages 13-17 using ENDS reported using fruit, followed by 53.8% for mint/menthol, 23.4% for candy/dessert/other sweets, and 13.3% for tobacco flavor (internal FDA analysis[19]). In the 2020 PATH Adult Telephone Survey, 51.5% of adults ages 25+ using ENDS used fruit, 30.4% used mint/menthol, 24.1% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal FDA analysis[20]). Youth who currently use ENDS were also more likely than adults who currently use ENDS to use more than one flavor (Schneller et al., 2019).

Studies show that flavors influence youth initiation of ENDS use. In particular, data show that flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a flavored product. For instance, PATH Study Wave 1 (2013-2014), more than 81% of youth ages 12-17, 71% of young adults ages 18-24, and 53% of adults ages 25+ reported that the first e-cigarette they used was flavored (Villanti et al., 2019). In another PATH Study publication, more youth, young adults, and adults who initiated e-cigarette use between Wave 1 and Wave 2 reported use of a flavored product than a non-flavored product (Rose et al., 2020). Furthermore, in PATH Wave 4 (2016-2017), 93.2% of youth and 83.7% of young adults who ever used ENDS reported that their first ENDS product was flavored compared to 54.9% among adults ages 25+ who ever use ENDS (Rostron et al., 2020).

Existing literature on flavored tobacco product use suggests that flavors not only facilitate initiation, but also promote established regular ENDS use. In particular, the flavoring in tobacco

[17] We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.
[18] Flavored product use in these studies means use of flavors other than tobacco.
[19] The PATH Study Questionnaire from Wave 5.5 did not assess mint and menthol separately. However, subsequent data collections (ATS and Wave 6) have separated the two flavors.
[20] Data generated from PATH Wave 5.5 PATH-ATS Public Use Files (PUF) was released in October 2022, available at https://www.icpsr.umich.edu/web/NAHDAP/studies/37786/datadocumentation#.

products (including ENDS) makes them more palatable for novice youth and young adults, which can lead to initiation, more frequent and repeated use, and eventually established regular use. For example, regional studies have found that the use of flavored e-cigarettes was associated with a greater number of e-cigarettes used per day among a sample of adolescents in Connecticut in 2014 (Morean et al., 2018). Another study found use of non-traditional flavors (defined as flavors other than tobacco, mint/menthol, or flavorless) was associated with increased likelihood of continued use and taking more puffs per episode (Leventhal et al., 2019a). Data from a regional survey in Philadelphia, PA found initial use of a flavored (vs. unflavored or tobacco-flavored) ENDS was associated with progression to current ENDS use, as well as escalation in the number of days ENDS were used across 18 months (Audrain-McGovern et al., 2019). Also, similar effects have been found in the nationally representative PATH Study among young adults (ages 18-24), where "ever use" of flavored ENDS at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2 (Villanti et al., 2019). In sum, there is evidence that non-tobacco flavors, including menthol, may influence the rewarding and reinforcing effects of flavored ENDS in adults, including young adults, thereby facilitating ENDS use and increasing abuse liability, thus increasing concerns of addiction in youth.

ENDS use more than doubled among middle school and high school students from 2017 to 2019 (Miech et al., 2021); this substantial increase among youth coincided with the availability of flavored cartridge-based and pod-based ENDS in the marketplace. Following FDA's prioritized enforcement of premarket review requirements for certain ENDS[21] such as flavored cartridge-based or pod-based ENDS, use of these types of ENDS declined while a substantial increase in use of disposable flavored ENDS, which were not subject to the prioritized enforcement, was observed. Findings from the 2020 NYTS data showed that disposable ENDS were used by 26.5% of high school e-cigarette users (up from 2.4% in 2019) and 15.2% of middle school ENDS users (up from 3.0% in 2019) (Wang et al., 2020). Furthermore, more than 8 out of 10 youth ENDS users report use of flavored products, with fruit, mint, candy, and menthol among the most commonly used. Disposable use and flavor use among ENDS users continued to be high in 2021. In 2024, disposable ENDS continued to be the most widely used type of ENDS among middle and high school students with 58.7% of high school e-cigarette users and 47.0% of middle school e-cigarette users using disposable ENDS (Park-Lee et al., 2024). This illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that was available in the marketplace and offered the desired flavor options, underscoring the fundamental role of flavor in driving youth appeal and ENDS use.

Thus, menthol-flavored ENDS (like the new products) could be particularly appealing to youth, and use of the new products by youth ENDS users might change, depending on the availability of other products on the market. Indeed, the literature described above substantiates that menthol-flavored ENDS pose a known and substantial risk to youth.[22]

[21] Guidance for Industry: Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised). May 2019. https://www.fda.gov/media/133880/download

[22] The clear evidence of substantial use of menthol-flavored ENDS among youth also reflects evidence beyond what was available at the time that FDA issued a guidance that described a policy of prioritizing enforcement of non-tobacco/non-menthol flavored ENDS, "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market without Premarket Authorization." The 2019 NYTS survey instrument for the data cited in the guidance grouped mint-and menthol-flavored products together, so it was not possible to evaluate youth use of mint and menthol flavors

The latest NYTS data from 2024 show that about 15.6% of middle and high school e-cigarette users reported using prefilled or refillable pods or cartridges (17.1% among high school e-cigarette users and 15.1% among middle school e-cigarette users) (Park-Lee et al., 2024). Additionally, 12.6% of current youth e-cigarette users reported using a JUUL-branded product in the 30 days prior to survey administration, with 3.2% reporting using a JUUL product most often. The new menthol products could be particularly appealing to youth, and use of the new products by youth ENDS users might substantially change, depending on the availability of other products on the market.

Type of Evidence Needed to Outweigh the Risk to Youth[23]

Given the known and substantial risk to youth of the Menthol-flavored new products (PM0000864.PD1, PM0000872.PD1), sufficiently reliable and robust evidence that these flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating the ability of adults who use CC to completely switch or significantly reduce their CC use is needed to show a potential benefit to current adult users that would outweigh the new products' risk to youth.

Section 910(c)(5) of the FD&C Act provides that determining whether marketing of a new tobacco product is APPH shall, when appropriate, be based on "well-controlled investigations, which may include one or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product." FDA believes well-controlled investigations are "appropriate" for demonstrating whether permitting the marketing of flavored ENDS would be APPH in the face of the significant risks to youth. In order to adequately assess whether such an added benefit has been demonstrated, product-specific evidence should be submitted to demonstrate the extent to which the product is likely to promote switching and to enable a comparison between the applicant's flavored ENDS and an appropriate comparison tobacco-flavored ENDS in terms of their impact on tobacco use behavior among adults who use CC. Consistent with section 910(c)(5), the strongest types of evidence could be generated from (1) an RCT or (2) a longitudinal cohort study. Although RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity, cohort studies enable stronger generalizability because conditions are closer to real-world. FDA is aware of these trade-offs and generally does not favor one type over the other for addressing this question.

To be informative, a study using one of these two designs would measure the impact of use of the new and appropriate comparison product tobacco-flavored ENDS and flavored products on

separately (Cullen et al., 2019). Data from the Monitoring the Future Survey were available to separate out mint and menthol use at the time, but only for JUUL products specifically; these data showed greater youth use of mint compared to menthol-flavored JUUL products (Leventhal et al., 2019b). By contrast, the 2024 NYTS survey measured youth use of mint-and menthol-flavored ENDS separately and found the rates to be similar. As noted above, menthol-flavored ENDS were used by 15.1% of middle-and high-school users of flavored ENDS, which is similar to the use rates for mint (25.1%) and candy/desserts/sweets (33.3%) (Park-Lee et al., 2024).

[23] This framework applies to flavored ENDS PMTAs for which FDA has found that the applicant-proposed marketing restrictions and related measures cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH. See section 3.4.1.5 for details.

tobacco use behavior over time among adults who smoke CC,[24] as described above; include outcomes related to ENDS use and smoking behavior to assess switching and/or CC reduction; and enable comparisons of these outcomes based on flavor type. In some cases, evidence on each individual flavor option may not be feasible; bridging data from one of the applicant's flavors to other flavors of the same applicant in the same flavor category (e.g., "fruit") may be appropriate. Furthermore, consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging.[25] Likewise, if a flavor is tested with one nicotine concentration, it may be feasible for the applicant to bridge the study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging.

Data from one of these studies, or from another similarly robust type of study, could support a benefit to adults who use tobacco products if the findings showed that, compared to the new tobacco-flavored product, use of (each) new flavored product is associated with greater likelihood of either of these behavioral outcomes for adults who smoke CC: (1) complete switching from CC to exclusive use of the new product or (2) significant reduction in CPD.

It may be possible in some contexts for applicants who do not conduct their own behavioral studies to rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. However, that approach is insufficient here because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions regarding the risks of the category as a whole—the evidence regarding the role of flavored products in promoting switching among adults who use CC is far from conclusive. In fact, the findings are quite mixed and, as a result, the literature does not establish that flavored ENDS as a category differentially promote complete switching among ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due to the fact that the effectiveness of a product in promoting switching among people who smoke CC arises from a combination of its product features—including labeled characteristics like flavor and nicotine concentration—as well as the sensory and subjective experience of use (taste, throat hit, nicotine delivery), and can also be influenced by how the device itself looks and feels to the user. For these reasons, bridged data from the current literature on flavors generally cannot suffice to demonstrate a sufficient benefit of these products, and instead robust and direct product-specific evidence demonstrating potential benefit is needed. Given the state of the science on flavored ENDS and the known risks to youth, direct product-specific evidence is needed to support the statutorily required showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health. In the absence of strong direct evidence, FDA is unable to conclude that the benefit of the subject products outweighs the clear risks to youth.

[24] This could include studies that are long-term (i.e., six months or longer). In FDA's (2023) Guidance to Industry, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (Revised)," FDA has previously stated that it did not expect that applicants would need to conduct long-term studies to support an application for ENDS. Because the behavior change of interest (switching or CC reduction) occurs over a period of time, it is possible that to observe these outcomes, investigators designing these studies may decide to follow participants over a period of six months or longer.

[25] Bridging is discussed in FDA's (2023) Guidance to Industry, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (Revised)."

FDA will consider other types of evidence if it is sufficiently robust and direct to demonstrate the impact of the new ENDS on adult switching or CC reduction. Uptake and transition to ENDS use is a behavioral pattern that requires assessment at more than one time point. In addition, the transition from smoking to exclusive ENDS use typically involves a period of dual use. Therefore, evaluating the behavioral outcomes needed to show any benefit of the product requires observing the actual behavior of users over time. With both RCT and cohort study designs, enrolled participants are followed over a period of time, with periodic and repeated measurement of relevant outcomes.

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to recall and report on their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Consumer perception studies (surveys or experiments) typically assess outcomes believed to be precursors to behavior, such as preferences or intentions related to the new products, but are not designed to directly assess actual product use behavior.

In addition to reviewing the applicant-submitted information, and given that menthol-flavored CC currently remain on the market, FDA evaluated whether that literature established that menthol-flavored ENDS provide a sufficient benefit for adults who use CC relative to that of tobacco-flavored ENDS.

Although the current literature also includes some studies examining the impact of menthol ENDS use on smoking behavior over time, these studies do not substantiate that menthol-flavored ENDS provide a benefit to adults who use CC sufficient to outweigh the increased risks to youth relative to tobacco-flavored ENDS, i.e., that they are more effective in promoting complete switching or significant CC reduction among people who currently use CC (including people who use menthol CC) (Goldenson et al., 2022; Goldenson et al., 2021; Nollen et al., 2023). Moreover, an applicant cannot satisfy its burden by relying on current scientific literature that does not provide robust support for such a benefit but must instead conduct its own studies to determine whether the standard can be met with its product.[26]

Given the risk of youth use of flavored ENDS and given that the existing literature does not demonstrate a benefit to adults who use CC that outweighs that risk, FDA cannot authorize the marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS. Accordingly, for these menthol-flavored ENDS, the applicant must provide a similar level of reliable and robust evidence of benefit to adults who use CC as required for other types of flavored ENDS. As discussed below, the applicant provided reliable and robust evidence for its Menthol-flavored new products (i.e., PM0000864.PD1, PM0000872.PD1, PM0000878.PD1) to demonstrate an added benefit relative to a tobacco-flavored ENDS in facilitating the ability of adults who use CC to completely switch or significantly reduce their CC that outweighs the menthol-flavored new products' risk to youth.

[26] Moreover, given FDA's product application review knowledge and understanding of the variability in ENDS products in terms of adult switching behavior, even if direct behavioral data regarding switching or significant CC reduction were to become available for products other than those in an application, product-specific data would likely still be needed to demonstrate that the specific products under review provide a benefit to adults who use CCs in terms of completely switching or significantly reducing CC use beyond that of a tobacco-flavored ENDS.

Evidence Provided in the PMTAs

Youth Appeal and Prevalence

The social science review found that experience with tobacco products influenced the interest and likelihood of adolescents initiating use of the new products. Adolescents generally reported low interest in the new product flavors (PROT-01343, at both 3.0% and 5.0% nicotine) and adolescents who do not use tobacco products may not try the new products (PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) despite reporting some curiosity or intentions to do so, due to the exclusive availability of flavors with low to moderate appeal (PROT-01331). PROT-01331 evaluated the 5.0% nicotine new products PM0000872.PD1 and PM0000876.PD1 with the new product device PM0000878.PD1, among other flavored products not subject to this review; adolescents who currently smoke CC or use JUUL ENDS reported moderately low to moderate interest in the new product flavors at 5.0% nicotine (PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) (PROT-01331). Given the importance of flavor appeal in ENDS initiation among adolescents, adolescents who use tobacco products may be somewhat more likely to initiate use of the menthol-flavored new products than adolescents who do not. In addition, adolescents who currently use JUUL ENDS commonly cited social reasons for use (PROT-01331). Thus, social reasons may be a more general driver of new product uptake among adolescents.

The epidemiology review discussed data from the literature on adolescents and flavors. The 2024 NYTS data show that 87.6% of youth who used an e-cigarette in the past 30 days used a flavored product (Park-Lee et al., 2024). Among past 30-day flavored e-cigarette users, the most commonly used flavors were fruit (62.8%), candy/desserts/sweets (33.3%), mint (25.1%), and menthol (15.1%) (Park-Lee et al., 2024). There is substantial evidence that flavors in tobacco products, like menthol flavors in the new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1), have significant appeal to youth and are associated with high likelihood of youth initiation of and subsequent progression to regular use of such products when compared with tobacco-flavored ENDS.

There were some limitations to the adolescent data provided. The social science review found that the applicant did not provide data on appeal of specific flavors and nicotine variants of the new products in adolescents like they did for adults. The applicant also did not provide data on the effects of promotional materials for the new products on harm and addiction perceptions or behavioral intentions in adolescents like they did for adults. However, due to the other data supplied by the applicant (e.g., adolescents indicating generally low interest in the new product flavors), these data were not necessary for our decision-making purposes.

As TPL, I agree with the findings described in the social science and epidemiology reviews. Adolescents generally reported low interest in the new product flavors (PROT-01343) and adolescents who do not use tobacco products may not try the 5.0% nicotine new products (PM0000872.PD1, PM0000876.PD1, PM0000878.PD1), despite reporting some curiosity or intentions to do so, due to the exclusive availability of flavors with low to moderate appeal (PROT-01331). However, social factors may represent a broader driver of youth uptake of the new products. I, as TPL, also acknowledge that the 2024 NYTS data and other data discussed above suggest that the Menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1) pose a risk to youth. I also acknowledge that use of the new products by youth who use ENDS may change, depending on the availability of other products on the market. As discussed in section 3.4.1.5, the applicant's marketing plan, combined with FDA's marketing

order requirements, is expected to limit youth exposure to the new products and the products' labeling, advertising, marketing, and/or promotion.

Adult Use

The applicant submitted brand-specific data from an online RCT (PROT-01325) that contained evidence demonstrating significant reductions in CC per month and substantial rates of 30-day abstinence from smoking associated with use of the tobacco-flavored new product e-liquids (PM0000874.PD1, PM0000876.PD1) with the new product device (PM0000878.PD1). Additionally, the applicant submitted an observational longitudinal study (ADJUSST study) that assessed the role of flavors, including menthol, in adult user behavior. FDA considers this evidence in conjunction with the other aspects of user population data to determine whether the potential benefit to adults who use tobacco is adequate to make the required showing that permitting the marketing of the new products would have a net benefit to the public health based upon the risks and benefits to the population as a whole.

The PROT-01325 RCT demonstrated that dual use of the new products with CC will be a likely user behavior. These data also suggest that dual use of the new products may be marked by substantial reductions in CC consumption. However, adults who use the new products are also likely to be addicted to the new products comparably to CC. Importantly, the same data also demonstrated that users of PM0000876.PD1 with PM0000878.PD1 had a self-reported past 30-day smoking abstinence of 17.9% at 12-month follow-up.

Furthermore, the ADJUSST study determined that the 30-day switching away rates from CC among those who used the Virginia Tobacco- (PM0000876.PD1) or Menthol-flavored (PM0000872.PD1) new products with PM0000878.PD1 ranged from 38.4% to 51.9% (depending on the methodology used). These rates are substantially higher than those seen in the literature from unaided quitting (5-6%) or nicotine replacement therapy (8-9%) (Lindson et al., 2023) and are comparable to recent PATH Study data (between Wave 5 and Wave 6, 2018-2021), where the rate of CC discontinuation among adults who smoked CC was 30.9% of those who used ENDS, compared to 20.0% of those who did not (Kasza et al., 2024). The applicant also submitted Adult Prevalence Study results from 2019 showing that there is uptake of the new products among adults who smoke CC, including 18-22% among younger adults and 4-6% among older adults (Table 9, N.6.2.2 – PROT-01329, p. 49). Thus, the reductions in CPM and self-reported smoking abstinence with use of the new products demonstrate adult benefit.

Health benefits are expected upon complete switching from CC to ENDS (which is associated with substantial decrease in many BOE [see section 3.5.1.2.]) and complete tobacco cessation. The BCP review discusses additional applicant-provided clinical evidence (PROT-00030, evaluated all new products) and concludes that switching completely to the new products for six days resulted in significant reductions in the urinary and blood BOEs of similar magnitude to the reductions in participants who abstained from smoking; however, as reported by epidemiology, a study evaluating BOE and biomarkers of potential harm (BOPH) reported that nicotine BOE levels were found to be significantly higher in switchers who were heavy users of the new products (Shiffman et al., 2024). In this study, as discussed in the epidemiology review, the participants included in the "switchers" group consistently had higher usage of the JUUL products than what was reported in the ADJUSST study. This limits the generalizability of the reported nicotine BOE; however, the reduction of non-nicotine BOE and BOPH, even in this higher usage scenario, still supports the potential for health benefits following complete

switching from CC to the new products. Toxicological evaluation of the applicant-provided information and potential health benefits associated with switching from CC to the new products is discussed in the following sections 3.5 and 3.6.

The BCP review found that the abuse liability of the new products was comparable to usual brand CC in adults who smoke. In addition, based on the data in adults who smoke and adults who have experience with the new products, BCP concluded that people who have not used tobacco products and initiate use of the new products are likely to obtain nicotine exposures comparable to CC as they gain experience with the new products, leading to progression to regular use of the new products.

The social science review found that the new products were perceived as less harmful, although similarly addictive, as CCs in a study on adult patterns and perceptions of use (PROT-01333). In another study on perceptions and behavior intentions (PROT-01343), adults who smoke CC reported moderate to moderately high intentions to try and use the new products and that they may use the new products to quit other tobacco products or cut down on the number of CC used if they do not quit entirely. However, in PROT-01343, current smokers also reported low interest in the JUUL Menthol and Virginia Tobacco flavors. Nevertheless, flavors are an important reason for using JUUL ENDS among current ENDS users.

Flavors

The applicant assessed the role of flavors, including menthol, in adult user behavior in the additional analyses of ADJUSST study data collected through 24 months. The applicant provided data on complete switching and significant CC reduction for its 5.0% nicotine Menthol-flavored (PM0000872.PD1, PM0000878.PD1) and Virginia Tobacco-flavored (PM0000876.PD1, PM0000878.PD1) new products. The applicant appropriately bridged these study results to the corresponding 3.0% nicotine products (PM0000864.PD1, PM0000874.PD1, PM0000878.PD1) based on similar abuse liability profiles (Goldenson et al., 2020; Goldenson et al., 2021) per the BCP review.

Across the two-year follow-up, ADJUSST study data also show that the Menthol-flavored new product (PM0000872.PD1, PM0000878.PD1) is associated with a significantly higher switching probability than the Virginia Tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) in adjusted analyses, regardless of the modeling method used (aRR = 1.11 to 1.15, depending on the methodology used; intent-to-treat, empirical imputation, and non-missing observations). Further information describing the evaluation of the new products' switching rate can be found in the corresponding TPMF review. Epidemiology determined that the added benefit to adults from the Menthol-flavored new products (PM0000872.PD1, PM0000878.PD1) versus the Virginia Tobacco-flavored new products (PM0000876.PD1, PM0000878.PD1), can be characterized as moderately beneficial. Additionally, the applicant stratified switching probabilities by whether the participants used mentholated or nonmentholated CC at baseline. Those who smoked nonmentholated CC had higher rates of switching when the using Menthol-flavored new product compared to the Virginia Tobacco-flavored new product (aRR = 1.22 to 1.28, depending on the methodology used). As TPL, I agree with epidemiology that these results demonstrate a potential added benefit of the menthol-flavored new products compared to the tobacco-flavored new products among adult CC users.

Regarding the adult benefit associated with use of the tobacco-flavored new products, epidemiology's evaluation of the applicant-submitted ADJUSST study data found the observed (non-missing) results showed that 51.5% users of the Virginia Tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) had completely switched from CC use at 12-month follow-up. At 24-month follow-up, this proportion of complete switchers increased to 61.5% of individuals who reported using the tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1). These switching results were similar in other analyses used by epidemiology to evaluate the applicant-provided data (e.g., intent to treat, empirical imputation). As previously discussed, the results from the 5.0% nicotine tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) in the ADJUSST study can be bridged to the 3.0% nicotine product (PM0000874.PD1, PM0000878.PD1). As TPL, I agree with these findings described in epidemiology's review and conclude that these switching data demonstrate a benefit of the tobacco-flavored new products for adult users in complete switching away from regular CC use.

Vulnerable populations (other than youth):

The discipline reviews found that the applicant submitted limited or no data or information relevant to the new products on behavioral intentions, harm and addiction perceptions, or other outcomes relevant to vulnerable populations other than youth, and that the applicant-provided study reports focusing on vulnerable populations exclusively examine product use data. As TPL, I agree with the discipline findings that there is currently insufficient available information in the scientific literature to conclude that the effects of the new products would differ for vulnerable populations other than youth; however, as TPL, I agree with the overall discipline conclusions and find that the availability of ENDS products, which have been demonstrated to pose fewer and less severe health risks, may benefit populations with a higher prevalence of tobacco use.

Marketing Plans, Product Labeling, Packaging, and Advertising

To further evaluate the new products' potential risk to youth, FDA examined the applicant's marketing plans and restrictions. The OHCE consult reviewed the applicant-submitted marketing information and made recommendations that would encourage the applicant to take additional steps to limit youth exposure to its products' labeling, advertising, marketing, and/or promotion. OHCE concluded that the applicant generally describes a reasonable approach to marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion. However, OHCE noted concerns that the applicant indicates it may explore the use of "(b) (4)) following authorization and could otherwise alter its marketing plans following authorization. Thus, because I recommend issuing an MGO (see section 5), I also recommend that the MGO letter include the marketing requirements in section V of the OHCE consult and encourage the applicant to implement these items in its proposed marketing plans.

Regarding product labeling, packaging, and advertising, I agree with the social science and OCE DPAL reviews and conclude that the labels and statements do not contain misleading or false information. Based on the social science and OCE DPAL reviews, I recommend that the MGO letter include the standard language that the tobacco products subject to these MGOs comply with the FD&C Act, FDA's implementing regulations, and all other applicable laws and regulations.

Conclusions

Overall, as TPL, I conclude that while the menthol-flavored new products pose a risk to youth, the PMTAs provide reliable and robust evidence of adult behavioral benefit associated with the tobacco- and menthol-flavored new products, added adult behavioral benefit associated with the menthol-flavored new products, and the potential of the new products to promote CC cessation. This potential benefit is demonstrated, in part, by the applicant-provided data in the ADJUSST study using the 5.0% Virginia Tobacco- or Menthol-flavored new products (PM0000876.PD1, PM0000872.PD1) with PM0000878.PD1; the applicant bridged these results to the 3.0% Virginia Tobacco- and Menthol-flavored new products (PM0000874.PD1, PM0000864.PD1) with PM0000878.PD1. These data showed that the modeled switching rate away from CC among those who used the 5.0% nicotine Virginia Tobacco- or Menthol-flavored new products (PM0000876.PD1, PM0000872.PD1, PM0000878.PD1) ranged from 38.4% to 51.9% (depending on methodology used) across two years of follow-up. Overall, the evidence demonstrates switching rates for the new products that are significantly higher than smoking cessation rates reported in the literature for other methods of switching (i.e., unaided quitting (5-6%), nicotine replacement therapy (8-9%)) (Lindson et al., 2023). Furthermore, the data also demonstrated a statistically significant higher relative switching rate (aRR = 1.11 to 1.15, depending on the methodology used) associated with the Menthol-flavored new product (PM0000872.PD1, PM0000878.PD1) compared to the Virginia Tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1). Taken together, these data demonstrate an adult benefit associated with the tobacco- and menthol-flavored new products and a moderately beneficial added benefit of the menthol-flavored products compared to the tobacco-flavored products that outweighs the menthol-flavored products' risk to youth. This added benefit showing is required to outweigh the risks associated with flavored ENDS among youth. Thus, as TPL, I conclude that these PMTAs contain sufficient evidence demonstrating that the new products have the potential to benefit adults who smoke CC and who switch completely or significantly reduce their CC use that outweighs the risk to youth.

3.5. TOXICANT EXPOSURE

3.5.1. Discipline key findings

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

The toxicology review evaluated applicant-submitted whole smoke and whole aerosol nonclinical data (cytotoxicity, mutagenicity, and genotoxicity) for the new products, CC, and ENDS comparison products. In addition, toxicology quantitatively and qualitatively assessed the risks and hazards (cancer and noncancer) related to HPHCs, ingredients, and leachables that were observed in aerosol or used as constituents in the new products.

The BCP review considered one study, PROT-00030. This was a multi-center, randomized, open-label, parallel study with JUUL 3.0% and 5.0% e-liquids in Virginia Tobacco (3.0% nicotine PM0000874.PD1, 5.0% nicotine PM0000876.PD1, and PM0000878.PD1 JUUL Device), Menthol (3.0% nicotine PM0000864.PD1, 5.0% nicotine PM0000872.PD1, and PM0000878.PD1 JUUL Device), Mango, and Mint flavors and UB CC that looked at BOE, subjective effects, and pod weights across 6 days of ad libitum use in adults who smoke CC.

The epidemiology review considered the literature and one applicant-sponsored study, ADJUSST. The ADJUSST study was an observational longitudinal cohort study in adults who

were new purchasers of JUUL products either in in-person retail stores or through e-commerce; the study investigated CC smoking status at baseline and then CC and JUUL product use at regular intervals for 24 months.

3.5.1.1. Toxicity

Per the toxicology review:

- The applicant provided HPHC yields from the aerosolized e-liquids of the new products (i.e., PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1) used with the new product device (i.e., PM0000878.PD1) and of some comparison ENDS generated by intense and non-intense puffing regimens. The non-intense regimen produced the highest levels of exposure to HPHCs and was therefore used for cancer risk analysis. The applicant calculated the ELCR using thresholds of concern adjusted for inhalation (Inhalation Unit Risk; IURs), and if not available, the default threshold of toxicological concern (TTC), that conferred a risk of 1 in 100,000. For some IURs the applicant recommended, the IUR was not properly justified, and therefore the default TTC was used in the toxicology evaluation. The applicant compared the ELCR calculated using select HPHCs to the ELCR calculated using HPHCs from comparison products. Some HPHCs conferring risk were not included in this analysis. However, for the risk evaluation of the new products to be complete, the analysis of the ELCR should consider all the sources of risk, not only HPHCs; therefore, the applicant's comparative analysis is of limited use.
- The applicant initially provided a cancer risk assessment that focused solely on HPHCs in the aerosol produced from the new products. However, this risk evaluation was incomplete as genotoxic and/or carcinogenic constituents are present in the new product e-liquid mixture, and subsequently aerosolized by the new product device, and were not taken into account to provide a holistic risk evaluation of the new products. In response to the June 6, 2024, Deficiency letter, the applicant identified all sources of carcinogenic risk in the new products in its cancer risk evaluation.
- The applicant identified ingredients in the new product e-liquids with carcinogenic hazard based on studies published in the scientific literature or performed by the applicant. Other ingredients were identified to pose a carcinogenic risk during the review of the applicant's response to the June 6, 2024, Deficiency letter or during toxicology's review of the applicant's original submission and subsequent amendments. In addition, the applicant quantified ingredients from chemical analysis of e-liquids of some comparison products. The applicant's exposure analysis assumed heavy use of the product and transfer efficiency of the ingredients from the e-liquid to the aerosol of 100%. The ingredients were classified according to a tiering system of carcinogenic hazard and those with potential to contribute to the total carcinogenic risk were selected for calculation of the ELCR. Some ingredients were inappropriately identified as cancer hazards (i.e., the ingredients were actually Tier 5 hazards). The adjusted IUR (or default TTC) that corresponds to a level of risk of 1 in 100,000 was used in this calculation. The ingredients that contribute to the ELCR are as follows:
    - For Virginia Tobacco 3.0% and 5.0%: (b) (4)
      (b) (4)

- For Menthol 3.0% and 5.0%: (b) (4)

(b) (4)

- The applicant compared the ELCR of the new products to the ELCR of the comparison products based on ingredients only to assert that the new products have a lower risk. However, the cancer risk evaluation of a new product requires a holistic consideration of all the contributors to ELCR (i.e., not ingredients only or HPHCs only); therefore, from the toxicology perspective these ELCR comparisons using individual ingredient comparisons are of limited relevance for this review.
- While the applicant-calculated HPHCs-only and ingredient-only ELCR values are of limited relevance to toxicology's review of the new products, this did not preclude toxicology from conducting a complete toxicological review of the new products using applicant-provided information and, as needed, publicly available information. The cancer risk characterization process used by toxicology summarizes and integrates toxicity and exposure information to estimate and characterize overall cancer risk, both in quantitative expressions and qualitative statements.
    - The main metric of risk characterization for ENDS is an ELCR, which provides an extrapolated estimate for how many additional cases of cancer would be expected in a population exposed to a given toxicant concentration and intake level for an entire lifetime, based on the toxicant's carcinogenic potency.
    - The ELCR approach was used as an objective way to consistently estimate cancer risk resulting from individual constituents (e.g., ingredients, HPHCs, leachables) measured in the new products, and it allows for a robust comparative analysis to other ENDS products assessed in the same way.
    - Individual ELCRs for constituents produced by or within a given product were added together to obtain a $ELCR_c$, which was compared to the $ELCR_c$ for 1R6F Kentucky reference CC (which are representative of combusted tobacco products) and compared to the median $ELCR_c$ of the CTP-authorized ENDS marketplace.
- The new products contain ingredients, leachables, and HPHCs that have quantities at levels that exceed an individual cancer risk of 1 per 100,000, and, as such, add to the cumulative cancer risk of the new products.
    - Some of these constituents are Tier 1-3 hazards that have been evaluated by the International Agency for Research on Cancer (IARC) or the Environmental Protection Agency (EPA) for carcinogenicity, which increases toxicological certainty in the associated Tier 1-3 constituents contributing to cancer risk.
    - Other constituents are Tier 4A-C constituents, which are identified as concerns based primarily on genotoxicity assays that accurately and independently predict carcinogenicity (~70-90%), but in a weight of evidence analysis there is either a general lack of additional genotoxicity information or a mixture of conflicting results that reduce toxicological certainty in the associated Tier 4A-C constituents' contribution to cancer risk.

    - Additional constituents are Tier 4D and 4E constituents, which do not have sufficient data available, either in the application or in published literature, to allay or confirm genotoxicity and/or carcinogenicity concerns (i.e., there are not enough data to re-classify them into other tiers).
    - Future constituent-specific studies and methodologies could provide data that facilitate updated constituent tiering, depending on whether new information can be used to either rule out or confirm carcinogenic hazard. The applicant provided single ingredient, genotoxic and mutagenic testing (Ames and micronucleus assays). The results of those assays form part of the weight of evidence in the risk characterization of the test article constituents (b) (4)
- In response to the June 6, 2024, Deficiency letter, the applicant identified additional hazardous constituents that were not previously identified. Hazard identification analysis by toxicology indicated that some of these additional hazardous constituents were properly tiered and included in ELCR analysis, while others were incorrectly identified as cancer hazards (i.e., classified as Tier 4 but were actually Tier 5 constituents based on toxicology review), and therefore excluded by toxicology from ELCR analyses and related calculations.
- The applicant provided new information in response to the June 6, 2024, Deficiency letter to characterize the transfer efficiency of the leachable constituents into the aerosol, but the chemistry TPMF review (b) (4) section 2.2) finds limitations that invalidate those studies and results, therefore the assumption of 100% transfer for those constituents still holds.
- The contribution of identified Tier 4D and 4E constituents did not change the qualitative comparison between the new products Virginia Tobacco 3% and 5% (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) and 1R6F CC, nor did it change the comparison to the CTP-authorized ENDS MGO marketplace. As such, these ingredients were excluded from the final $ELCR_c$ value.
- However, for the menthol 3% and 5% new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1), the inclusion of Tier 4D and 4E constituents to the final $ELCR_c$ value does change their qualitative comparison with 1R6F CC. Including the Tier 4D and 4E constituents in this $ELCR_c$ assessment shifts the comparison of the menthol 3% and 5% new products and the 1R6F CCs from “lower concern” to “moderate concern.”. It also shifts the comparison to the CTP-authorized ENDS marketplace. Due to uncertainty in the hazard identification of Tier 4D and 4E constituents, and as specified in associated memoranda,[27,28] a final $ELCR_c$ is not calculated for these new products (i.e., PM0000864.PD1, PM0000872.PD1, PM0000878.PD1); instead, a range of qualitative (i.e., lower to moderate concern) and quantitative (i.e., ≤ 5% of the 1R6F CC) risk is provided.
- Specifically:
    - For PM0000864.PD1 used with PM0000878.PD1: The $ELCR_c$ ranges from 159-338 per 100,000 or 1 in 629 to 1 in 296, which corresponds to a lower to moderate concern qualitative risk descriptor. The contributors of this risk are Tier 1-4E constituents including (b) (4)

[27] Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024.
[28] Memorandum: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications; signed June 3, 2024.

(b) (4) [redacted] Tier 4D and 4E constituents were included in the analysis as they change the comparative evaluation of the cancer risk, adding some degree of uncertainty to the risk characterization. At this time, the cancer risk of PM0000864.PD1 used with PM0000878.PD1 is between 28% above and 40% below the CTP-authorized ENDS marketplace and 0.8-1.7% of 1R6F cancer risk indicating that the new product is in the lower to moderate concern categories.

- For PM0000872.PD1 used with PM0000878.PD1: The $ELCR_c$ ranges from 165-368 per 100,000 or 1 in 607 to 1 in 272. The contributors of this risk are Tier 1-4E constituents including (b) (4) [redacted] Tier 4D and 4E constituents were included in the analysis as they change the comparative evaluation of the cancer risk, adding some degree of uncertainty to the risk characterization. At this time, the cancer risk of PM0000872.PD1 used with PM0000878.PD1 is between 38% below and 39% above the CTP-authorized ENDS marketplace and 0.8-1.8% of 1R6F cancer risk indicating that the new product is in the lower to moderate concern categories.
- For PM0000874.PD1 used with PM0000878.PD1: The $ELCR_c$ is 411 per 100,000 or 1 in 243. The contributors of this risk are Tier 1-4C constituents including (b) (4) [redacted] hile Tier 4E constituents are present, these constituents were not included in the analysis as they do not change the comparative evaluation of the cancer risk of the new product. At this time, the cancer risk of PM0000874.PD1 used with PM0000878.PD1 is 55% above the CTP-authorized ENDS marketplace and 2.1% of 1R6F cancer risk indicating that the new product is in the moderate concern category.
- For PM0000876.PD1 used with PM0000878.PD1: The $ELCR_c$ is 373 per 100,000 or 1 in 269. The contributors of this risk are Tier 1-4C constituents including (b) (4) [redacted] While Tier 4E constituents are present, these constituents were not included in

the analysis as they do not change the comparative evaluation of the cancer risk of the new product. At this time, the cancer risk of PM0000876.PD1 used with PM0000878.PD1 is 41% above the CTP-authorized ENDS marketplace and 1.9% of 1R6F cancer risk indicating that the new product is in the moderate concern category.

- There are constituents within (b) (4) that contribute to the $ELCR_c$ and are Tier 4A-C constituents, that were identified in the applicant's response to the June 6, 2024, Deficiency letter. Assumptions were made in the calculation of risk (i.e., 100% aerosolization, the use of a TTC as a default potency factor) for these constituents. There are also Tier 4D and 4E constituents that do not impact the risk characterization of Virgina Tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) and are therefore excluded from this analysis. However, for the Menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1), inclusion of Tier 4D and 4E constituents does change the qualitative risk management descriptor and were considered in the calculation of the range of cancer risk. The applicant or TPMF owner did not provide additional data to address ingredient constituents of concern and assumptions, such as the 100% aerosolization transfer, that could impact the $ELCR_c$ and the associated risk characterization.
- Two leachables were identified in aged e-liquid and were not included in the calculation of the $ELCR_c$ by the applicant. These leachables were previously identified as (b) (4) However, new information described in the chemistry review of the TPMF re-identified one of the previously identified leachables (i.e., (b) (4) as a new constituent in (b) (4) These leachables are identified as Tier 4E cancer hazards (see the toxicology TPMF review), and these constituents are weighed in the $ELCR_c$ analysis performed by toxicology. Evaluation of the non-cancer risk of the new products indicates that the non-cancer risk is likely lower than that of CC. Specifically, the previous toxicology review (b) (4) toxicology reviews dated March 29, 2021 and June 15, 2022) indicated no non-cancer toxicity concerns regarding ingredients from the TPMF, as well as lower levels of measured HPHCs with non-cancer toxicity as compared to CC (toxicology reviews dated March 21, 2021 and June 16, 2022). While the non-cancer hazards presented by the leachables of concern are uncertain, based on the amount of the leachables present in the aged e-liquid, these leachables are unlikely to meaningfully change the overall non-cancer risk of the new products.
- In regard to non-cancer risk, there are two leachable constituents (i.e., (b) (4) and the leachable previously identified as (b) (4) that may contribute additional non-cancer risk to the new products. Both were identified as data-poor constituents whose exposure levels are above multiple thresholds of toxicological concern, suggestive of non-cancer toxicity. While the applicant asserts a <3% transfer efficacy of these leachable compounds, chemistry's TPMF review (b) (4) section 2.2) indicated that these studies are invalid and therefore the assumption of 100% transfer for those compounds should be made. Based on that assumption, the exposure to these leachable constituents is above multiple applicable TTC values, with margins of exposure that are <1. This indicates potential non-cancer risk. However, due to lack of information regarding hazard identification and dose

response of these constituents, there is uncertainty regarding how much, if any, non-cancer risk is conferred by these leachables. However, these leachables are unlikely to significantly change the total non-cancer risk of the new products, as discussed above. Also, because the yields of HPHCs and other toxicants having known and recognized non-cancer toxic effects are lower in the new products relative to their yields in CC, and as there is no available evidence indicative of specific non-cancer hazards associated with exposure to these specific leachables, toxicology concludes that the non-cancer risk to users of the new products is likely to be lower than that of CC.

- As described in the chemistry review of (b) (4) the TPMF owner provided data from chemical analyses to be used by toxicology in a comparison of the non-cancer risks of these specific leachables in the new products to comparison products. As noted in the chemistry TPMF review, the TPMF owner's methodology used in this study was invalid. Therefore, it is not possible to compare the non-cancer risks of these two leachables in the new products to comparison products using this limited data. However, these leachables are unlikely to meaningfully change the overall non-cancer risk of the new products, as discussed above. Also, because the yields of HPHCs and other toxicants having known and recognized non-cancer toxic effects are lower in the new products relative to their yields in CC, and as there is no available evidence indicative of specific non-cancer hazards associated with exposure to these specific leachables, I agree with the toxicology review that the overall non-cancer risk to users of the new products is likely to be lower than that of CC.
- The applicant-provided information on glucan content in the new products is sufficient and adequate for a toxicological evaluation of the new products. No toxicological issues were noted.

Limitations:

- All PMTAs for the new product e-liquids (i.e., PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1), which are intended to be used as a system with the new product device (PM0000878.PD1), identified the presence of two leachables, (b) (4) The data provided in support of a less than 3% transfer efficiency from the e-liquid to the aerosol is not sufficient to resolve the toxicity concerns due to technical limitations in the methodology of the experiments. Therefore, a transfer efficacy of 100% is assumed for those two leachables. The levels of these leachables in the e-liquid (b) (4) µg/pod for the newly reassigned leachable [previously (b) (4) and (b) (4) µg/pod (b) (4) result in margin of exposure values (calculated as the estimat exposure concentration divided by the reference toxicity level) of less than 1 when compared to TTC values from (Ball et al., 2007; Escher et al., 2010; Talhout et al., 2011). A literature search returned no information on known non-cancer hazards associated with these two leachables. Therefore, there is uncertainty with respect to the non-cancer toxicity of these two leachables in the new products. This represents a limitation of the toxicology review because, other than exposures exceeding multiple TTC values used for assessing data-poor potential hazards, the limited available scientific data do not allow for further analysis: no available studies suggest there is a toxicological concern associated with the presence of these leachables in the new products; however, there is also no

data available to confirm that these leachables are not a toxicological concern. Conclusions in future evaluations could change as additional information becomes available. Overall, the information submitted for the new products shows that the overall non-cancer hazard to users of the new products is likely to be lower relative to CC from a toxicological perspective, although there is uncertainty as to how much lower.

3.5.1.2. Biomarkers of exposure

Per the BCP review:

- Switching from UB CC smoking to exclusive ad libitum use of the new products (i.e., PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) for six days resulted in significant reductions in the urinary and blood BOE of similar magnitude to the reductions in the participants who abstained from smoking (PROT-00030). Specifically, NNAL, 3-HPMA, MHBMA, S-PMA, COHb, NNN, HMPMA, CEMA, 1-OHP, o-toluidine, 2-NA, and 4-ABP significantly reduced following use of the new products.

Per the epidemiology review:

- One study from the literature evaluating BOE and BOPH reported that nicotine BOE levels were significantly higher in switchers who were generally heavy users of unspecified JUUL products (Shiffman et al., 2024). The JUUL product usage in this study sample was consistently higher than that reported in the ADJUSST study. Other BOEs, including NNAL and HPMA3, were significantly lower in switchers than in smokers. BOPH were also significantly lower in switchers than in smokers. However, the inclusion criteria for this study were general to any JUUL product. Therefore, the results can only be considered as generally informative, not as product-specific information. Epidemiology's review of this biomarker data in the Shiffman study is largely consistent with other literature, except for the switchers who were heavy users of JUUL products having significantly higher nicotine concentrations than smokers (De Jesús et al., 2020; Hecht et al., 2014; Kaplan et al., 2023; Rubinstein et al., 2018; Shahab et al., 2017; Shiffman et al., 2024; Soriano Llobera et al., 2023; Xia et al., 2021).

3.5.2. Synthesis

As indicated by the chemistry review (see section 3.2.1.5), toxicology evaluated the applicant-provided yields of HPHCs in the aerosolized e-liquids of the new products and of some comparison ENDS generated by intense and non-intense puffing regimens. Toxicology found that the non-intense puffing regimen produced the highest levels of exposure to HPHCs and, therefore, used these HPHC levels for its subsequent cancer risk analysis. As TPL, I agree with the approach used by toxicology. In order to conduct a holistic review of the new products, the toxicology review also evaluated the applicant-provided data and information regarding user exposure to constituents other than HPHCs (e.g., ingredients, leachables) present in the new products.

The applicant calculated its own ELCR values for the constituents of the new products. The ELCR is a metric used to provide an extrapolated estimate for how many additional cases of cancer would be expected in a population exposed to a given toxicant concentration and intake level

for an entire lifetime based on the toxicant's carcinogenic potency. However, toxicology identified limitations in how the applicant calculated its ELCR values. The applicant provided information related to user exposure to the new product ingredients identified as being a carcinogenic hazard. The applicant also quantified ingredients in some comparison ENDS e-liquids. The applicant's exposure assessment assumed heavy use of the new product e-liquids with the new product device and a 100% transfer rate of the ingredients from the e-liquid into the aerosol. Only the ingredients identified as having potential to contribute to carcinogenic risk were selected for inclusion in the applicant's ELCR calculation. The applicant compared its ELCRs for the new products to the comparison products to assert that the new products have a lower risk. I, as TPL, agree with the toxicology conclusion that, for the risk evaluation of the new products to be complete, a holistic consideration of all contributors to the ELCR (e.g., ingredients, HPHCs, leachables) should be made; therefore the applicant-provided ELCRs for the new products that are based on exposure to HPHCs only or ingredients only are of limited relevance for review of the new products. Despite this, as discussed in detail below, toxicology was able to use the information in the applications to calculate the $ELCR_c$ for each of the new products.

The toxicology review notes that two leachables identified in the aged e-liquid were not included in the applicant-provided $ELCR_c$ calculation. Further information on the identification of one of these leachables is present in the corresponding chemistry TPMF review. These leachables were identified by toxicology as being Tier 4E cancer hazards (see corresponding toxicology TPMF review) and are included in toxicology's $ELCR_c$ evaluations for the Menthol-flavored products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1). However, the inclusion of these Tier 4E constituents did not change the qualitative comparison between the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) and 1R6F CCs or the direction of the comparison to the CTP-authorized ENDS marketplace for these new products. As such, these ingredients were excluded from the final $ELCR_c$ value for these products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1).

In order to perform a holistic review of the new products, toxicology calculated an $ELCR_c$ that includes exposure and risk assessment information for the complete constituents (e.g., ingredients, HPHCs, leachables) of the new products that users may be exposed to. Constituents present in the new products were identified for inclusion in the $ELCR_c$ calculation based on two CTP-published supporting memoranda addressing genotoxicity hazard identification and calculation of ELCR values.[29,30] The toxicology review indicates that, in terms of relating toxicant exposure from the new products to potential health effects, the $ELCR_c$ calculated by toxicology for all new products predicts that the new products' ELCR is significantly lower than the ELCR in adults who smoke CC, as all calculated $ELCR_c$ values for the new products are less than 5% of the $ELCR_c$ for the 1R6F CC. The toxicology review also compared the $ELCR_c$ of all new products to the ENDS products that comprise the CTP-authorized ENDS marketplace, as described in the CTP-published supporting memorandum addressing calculation of ELCR values.[31] The $ELCR_c$ of the Virginia Tobacco-flavored 3.0% and 5.0% new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) are higher than the median of the ENDS MGO marketplace by 55% and 41%,

[29] Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024.
[30] Memorandum: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications; signed June 3, 2024.
[31] Memorandum: Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications Memorandum (June 8, 2025).

respectively. The range of $ELCR_c$ values for the Menthol-flavored 3.0% and 5.0% new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1) span the median of the CTP-authorized ENDS marketplace from below by 40% to above by 28% and below by 38% to above by 39%, respectively. The low end includes only Tier 1-4C constituents, and the high end includes the additional Tier 4D and 4E constituents.

While the overall estimated $ELCR_C$ due to exclusive use of the new products is substantially lower than the estimated ELCR due to the use of CC (estimated to be less than 5% of the 1R6F $ELCR_c$), these estimates are based on chemical exposure, for which a reduction in exposure may not be proportionally associated with a reduction in cancer risk. Thus, there is uncertainty in how much less risk there is for a person who smokes CC and switches completely from CC to one of the new products. Importantly, due to the high cancer risk associated with CC use, even a substantial decrease in cancer risk relative to CC still results in a significant risk compared to adults who have never used or formerly used tobacco products. It is also important to consider the potential cancer risks associated with switching from a CTP-authorized ENDS to the new products given that adults who currently use ENDS are one of the applicant's intended populations. The conservative estimated $ELCR_c$ based on Tier 1-4 constituents for all the new products is higher than the median $ELCR_c$ of CTP-authorized ENDS, which indicates toxicology concerns regarding the cancer risk to users who completely switch to the new products from some other CTP-authorized ENDS; there may be a potentially higher risk associated with completely switching from some CTP-authorized ENDS to the new products. However, the benefit of adult smokers switching from CC to the new products is significant: the new products are estimated to present less than 5% of the lifetime cancer risk of CC, and exclusive use of the new products was shown to result in significantly reduced levels of non-nicotine BOEs. Therefore, as TPL, I find that the benefit of adult smokers switching to the new products outweighs the risk of using these new products relative to some alternative CTP-authorized ENDS. As TPL, I agree with toxicology's findings and conclusions regarding the cancer risk of the new products.

I acknowledge the limited information available in the toxicology review regarding the non-cancer risk of two leachable compounds (b) (4) [redacted] There is uncertainty with respect to the non-cancer toxicity of these two leachable constituents in the new products. Although the potential non-cancer hazard for the two leachable constituents is not well characterized and is considered a source of uncertainty, I agree with the toxicology review that, overall, the non-cancer hazard to users of the new products is likely to be lower than CC from a toxicological perspective. My conclusions below account for this potential, but uncertain, risk.

The BCP review found that switching from usual brand CC smoking to exclusive ad libitum use of the new products (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) for six days resulted in significant reductions in urinary and blood BOE (PROT-00030). These reductions in BOE were of similar magnitude to the BOE reductions in study participants who abstained from smoking. Specifically, NNAL, 3-HPMA, MHBMA, S-PMA, COHb, NNN, HMPMA, CEMA, 1-OHP, o-toluidine, 2-NA, and 4-ABP were significantly reduced following use of the new products.

The epidemiology literature review cited by the applicant found that in a study evaluating BOE and BOPH levels associated with use of the new products, reported nicotine BOE levels were

significantly higher in switchers (Shiffman et al., 2024). However, the study participants in the "switchers" group were recognized as generally heavy users of the new products, and their reported product usage was consistently higher than the usage reported by participants in the ADJUSST study. BOE, including NNAL and 3-HPMA, were significantly lower in switchers than in smokers. BOPH were also significantly lower in switchers than smokers.

Based on the toxicology, BCP, and epidemiology conclusions regarding toxicant exposure and the observed reductions in BOE and BOPH in users who completely switched to the new products from CC use, I find that there may be a potential health benefit for adults who smoke CC and switch completely to the new products. There may also be potential health benefits for dual use of the new products with a significant reduction in CC use, compared with exclusive CC use. These data are consistent with the literature on other ENDS and indicate a likely relative health benefit associated with exclusive use of the new products compared with exclusive use of CC (see section 3.6 – Health Effects). As discussed in section 3.4, the new products facilitate complete switching (i.e., CC cessation) at rates above those in the general ENDS literature, indicating that exclusive use of the new products is more likely than with other ENDS; thus, health benefits are expected with exclusive use of the new products.

3.6. HEALTH EFFECTS

3.6.1. Discipline key findings

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

3.6.1.1. Toxicology

Per the toxicology review
Nonclinical studies:

- While detection of hazards for individual ingredients or the e-liquid itself may be informative in absence of problems with the assays, hazard identification of full e-liquid mixtures and aerosols are generally inconclusive due to issues with adequate dosing of compounds being investigated, as discussed in a supporting memorandum.[32]
- The applicant measured mutagenicity of the new product e-liquid aerosols produced using the new product device, and the new product e-liquids themselves using the Ames assay. The mutagenicity results were inconclusive because the applicant used ethanol as the vehicle, which is capable of inactivating S9. Confirmation of S9 functioning activity is required to determine that the assay is capable of detecting mutagens that require metabolic activation. The provided positive control did not fully account for both fractions (cytosolic and microsomal) of the S9 mixture. In response to the June 6, 2024, Deficiency letter, the applicant repeated the Ames assays and the micronucleus assays using two other solvents, DMSO and acetone, using aerosol condensate and e-liquid as test articles, that had negative results and had positive controls that were valid. The assays evaluating the CC comparison product were valid as well.
- Previous in vitro testing on whole e-liquid demonstrated that PM0000872.PD1 and PM0000876.PD1 are genotoxic. Moreover, a third new product, PM0000874.PD1,

[32] Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024

used with PM0000878.PD1, also yielded a positive genotoxicity result in aerosol testing. While the known genotoxic pyrolysis products in the aerosol, produced using the new product device PM0000878.PD1, may be responsible for this result, it is also possible that ingredients in the e-liquid formulation are contributing to the positive result. Therefore, this result raises concerns about genotoxicity. Such concerns are addressed by using ELCR analyses with appropriate hazard identification of the new product e-liquid and aerosol.

- The in vivo assays tested a different test article (i.e., the aerosol) and are therefore of no utility in following up on the positive in vitro genotoxicity results identified in the e-liquids. The applicant's in vivo assays are also inconclusive because the dosing was likely inadequate due to dilution based on acute nicotine toxicity (see next bullet). The applicant did not provide pharmacokinetic information for constituents of concern, nor were there site-specific analyses that would allow an understanding as to whether the aerosol was taken up (e.g., exposure concentration and duration at the bone marrow or liver). Also, the applicant's statistical analyses of comet assays may have been confounded by non-normal distribution of results. New in vivo assays were not submitted in response to the June 6, 2024, Deficiency letter.
- Per the two DNCS Memoranda: "Summary of key points in the evolution of OS's approach to reviewing toxicological information, as applicable to PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1, PM0000879.PD9, and AP0000166"[33] (signed June 4, 2024) and "Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications,"[34] while ENDS devices expose users to aerosolized e-liquid, dosing in animal models is an issue because of the toxicity of nicotine. It is unclear whether the doses used in the applicant's in vivo assays were high enough to evaluate the genotoxicity of the aerosol. The fact that the aerosol contains known genotoxicants but the applicant's genotoxicity results were negative suggests that the dose was not high enough to be valid. The applicant did not address this sufficiently to support its assertion that the studies are relevant for genotoxicity evaluation of the new products.
- In response to the June 6, 2024, Deficiency letter, the results of new Ames and micronucleus assays using whole e-liquid and aerosol condensate, as well as single chemical ingredients, were submitted as an amendment to the TPMF. These assays are reviewed in the TPMF review (b) (4) However, hazard identification assays on the whole e-liquid or aerosol mixture generally do not contribute to the overall weight of evidence for the cancer risk assessment process as there are many limitations with these assays (as described in deficiency 3 in the Deficiency letter dated June 6, 2024, in response to clarifying questions to the applicant dated July 18, 2024, and in the Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications memorandum).[35]

[33] Memorandum: Summary of key points in the evolution of OS's approach to reviewing toxicological information, as applicable to PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1, PM0000879.PD9, and AP0000166; Signed June 4, 2024.

[34] Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024

[35] Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024

- As stated in deficiency 3 from the Deficiency letter signed June 6, 2024, clarifying questions to the applicant (July 18, 2024), and the Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications memorandum, [23] the usefulness of these assays to assess cancer risk of the new products is limited because the applicant tested the whole aerosol and e-liquid, which does not inform the risks posed by individual constituents in the new products. Therefore, these listed assay limitations for the in vitro and in vivo assays using whole e-liquid or aerosols were no longer a toxicology concern. The applicant and toxicology performed the hazard identification of individual constituents and cancer risk analyses as described above, and these are sufficient for our evaluation.

Toxicant and study integration:

- Clinical studies measuring BOE levels showed that after 6 days of exclusive use of the new products, study participants had BOE levels similar to those in the tobacco product cessation group (n-4-2-2-study-prot-00030-report.pdf). Dual use of either PM0000872.PD1 or PM0000874.PD1 with the new product device PM0000878.PD1 and CCs (CC consumption was limited to 50% of baseline amount) was associated with a significant reduction in levels of non-nicotine BOE, although levels were higher relative to the exclusive use of the new product and tobacco cessation groups.
- The BOE in the provided studies measure exposure to known HPHCs but not other potential ENDS constituents (i.e., ingredients, leachables). As discussed in the DNCS Memoranda "Summary of key points in the evolution of OS's approach to reviewing toxicological information, as applicable to PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1, PM0000879.PD9, and AP0000166"[36] and "Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications,"[37] CTP now recognizes that known HPHCs generated during use of the new products are not the only source of health risk from ENDS use. Specifically, both e-liquid ingredients and leachables may provide additional cancer risks (and non-cancer risks, discussed separately). As such, these constituents should be included in the risk analysis of the new products. The applicant, in its response to the June 6, 2024, Deficiency letter, confirmed these concerns regarding the need for additional constituents to be included in its ELCR analyses.
- The e-liquid ingredients of concern are distinct from and present additional cancer risk above and beyond the cancer risk presented by the known HPHCs generated by the new products. The BOE in the provided studies, in turn, are indicators of exposure only to specific compounds that are known HPHCs and are not indicators of relative or overall cancer risk more broadly. As such, the applicant's study demonstrating reduced exposure to known HPHCs, indicated by reduced urinary BOE, following use of the JUUL System is of limited utility because the initial

[36] Memorandum: Summary of key points in the evolution of OS's approach to reviewing toxicological information, as applicable to PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1, PM0000879.PD9, and AP0000166; Signed June 4, 2024

[37] Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024

mainstream aerosol concentrations of other genotoxic constituents (e.g., non-HPHC aerosol constituents) are unknown and are likely not captured in the BOE study.

3.6.1.2. Medical

Per the medical review:

- The applicant-sponsored clinical studies were not designed to evaluate differences in health outcomes and health risks between the new products and selected comparison products. Consequently, there are insufficient data to assess short-and long-term health effects associated with intended or unintended use and accidental exposure to the new products relative to the comparison products and other tobacco products. However, FDA used safety and AE data submitted by the applicant and from other sources (i.e., published literature, SRP reports) to assess the health effects of the new products.

3.6.1.3. BIMO inspection findings

FDA performed two clinical investigator inspections of George Konis, MD and Shari DeSilva, MD and one Remote Regulatory Assessment (RRA)[38]of Debra Kelish, MD for the following clinical studies to support CTP's review of these PMTAs:

- Protocol PROT-00009: A Randomized, Open-Label, Cross-Over Study to Estimate Nicotine Uptake and Assess Subjective Measures with Use of JUUL 5% Electronic Nicotine Delivery Systems (ENDS) Compared to Usual Brand CC, a Comparator E-Cigarette, and Nicotine Gum in Healthy Adult Smokers; Clinical Investigator: Debra Kelsh, M.D.[39]
- Protocol PROT-00033: A Randomized, Open-Label, Cross-Over Study to Characterize the Nicotine Uptake and Subjective Effects with Use of JUUL Electronic Nicotine Delivery Systems with Multiple Flavors and Nicotine Concentrations, Usual Brand of CC, a Comparator E-Cigarette and Nicotine Gum in Adult Smokers; Clinical Investigator: Debra Kelsh, M.D.
- Protocol PROT-00030: A Randomized, Open-Label, Parallel-Group Study in Adult Smokers to Evaluate Changes in Biomarkers of Cigarette Smoke Exposure After Switching Either Exclusively or Partly to Using JUUL Electronic Nicotine Delivery Systems with Two Different Nicotine Concentrations; Clinical Investigators: George Konis, M.D. and Shari DeSilva, M.D.

Protocols PROT-00009 and PROT-00033 were selected for inspection because the applicant identified both as pivotal studies. In addition, PROT-00009 included multiple products and a high number of protocol deviations. PROT-00033 was conducted at two sites; OCE and OS selected site #1005 for inspection because it reported the highest number of protocol deviations and AEs in the study. PROT-00030 was the largest clinical study submitted in the application, based on the number of subjects enrolled and the number of study sites (five total). OCE and OS selected Sites #1008 (Konis) and #1009

[38] Per the 2021 Investigations Operations Manual (IOM), FDA Centers will assign final classifications for inspections; however, per the Remote Regulatory Assessment Work Instruction (WI-000315), RRAs are considered alternatives to inspections and do not receive final classifications.

[39] Due to the COVID-19 pandemic, an onsite inspection of clinical investigator Debra Kelsh, M.D. (Site #1005 for PROT-00009 and PROT-00033) was not feasible. As a result, Office of Regulatory Affairs (ORA) and an Office of Compliance and Enforcement (OCE) Subject Matter Expert conducted a Remote Regulatory Assessment (RRA).

(DeSilva) for inspection because more than half of the total number of study subjects were enrolled at these two sites; these two sites had the highest number of protocol deviations and the majority of major protocol deviations.

For PROT-00030, which was conducted at two different sites (Konis and DeSilva), OCE and OS could not verify primary endpoint data (BOE) because testing data was not provided to the clinical site. Other key inspection findings for this study included:

- Inaccurate and/or inadequate investigational product control and accountability records.
- Inadequate recordkeeping, including inaccurate case histories and incomplete study records (supporting documentation and clinic notes).

The results of the Bioresearch Monitoring (BIMO) RRA and inspections did not reveal human subject protection issues. However, the findings from inspections of George Konis, M.D. and Shari DeSilva, M.D. revealed issues that may impact the reliability of the data submitted for protocol PROT-00030. BCP considered these inspection findings and their potential impact on data reliability in its evaluation of the study data and determined that they were not substantial enough to diminish conclusions from the totality of evidence. Ultimately, the BIMO inspection results for this study did not affect BCP's conclusions given the totality of all study data (published studies and literature) available.

3.6.1.4. Addiction as a health endpoint

Per the BCP review:

- Findings support that the abuse liability of the new products is comparable to that of UB CC among experienced users. Similar abuse liability of the new products and CC signifies that the new products can sustain and maintain addiction in nicotine-dependent populations and may have risks of initiation and developing addiction in non-users to a similar degree as CC. Thus, it is unlikely that switching completely to the new products will have a substantially lower risk of abuse liability and addiction relative to smoking CC. The limited data available on actual use in youth do not suggest that youth who smoke and use ENDS have greater levels of addiction compared to smoking CC.
- Among youth who initiate use of the new products, the presence of a non-tobacco flavor (i.e., menthol) in the new products PM0000864.PD1 and PM0000872.PD1 with PM0000878.PD1 may facilitate more frequent use of the new products compared to CC and other tobacco-flavored ENDS. Thus, the new products with non-tobacco flavors may lead to repeatedly exposing the developing adolescent brain to nicotine and increasing the likelihood of progression to regular use of the new products and subsequent nicotine dependence.
- In response to the March 26, 2021, Deficiency letter, the applicant submitted additional longitudinal, observational data from cohorts of retail and online JUUL consumers (PROT-01320, PROT-01321) showing that participants primarily using PM0000876.PD1 with the new product device PM0000878.PD1 report significantly decreased dependence scores compared to both their baseline (i.e., when they used UB CC) and when they were dually using PM0000876.PD1 (with the new product device PM0000878.PD1) and UB CC (but primarily using

PM0000876.PD1 with PM0000878.PD1). Results from product-specific dependence questions indicate that participants feel less dependent on the new product PM0000876.PD1 with PM0000878.PD1 than on their UB CC; however, without using a general nicotine dependence questionnaire, these findings do not support that participants are less dependent on nicotine in general following use of PM0000876.PD1 with PM0000878.PD1 compared to UB CC.

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

Per the medical review:

- As previously discussed, the 13 applicant-sponsored clinical studies were not designed to evaluate health effects and did not include substantive clinical endpoints or BOPH data. Although AEs were culled from these studies and from public repositories including the applicant's consumer complaint center and the FDA's SRP, overall, the AEs were mild in severity and relatively few in number. Collectively, these AE reports did not provide sufficient data to inform an assessment of short- and long-term health effects associated with the new products.
- The applicant did not address or provide individual health data for the following categories of health outcomes and health risks:
    - Health outcomes associated with switching completely from exclusive use of the comparison product(s) compared to exclusive use of each new product
    - Health outcomes associated with switching completely to another single tobacco product within the same product category (e.g., ENDS) or subcategory (e.g., closed system ENDS)
    - Health risks associated with the exclusive use of the new product(s) compared to use of an FDA-approved tobacco cessation medication and to quitting all tobacco products
    - Health risks to former tobacco product users who relapse into use of the new product(s)
    - Health risks to naïve tobacco users who initiate use of the new product(s) compared to never using any tobacco product
- The following additional limitations regarding health effects were noted:
    - Overall, the 13 clinical studies had very small sample sizes and were short in duration (ranging from 1-120 days). In addition, the study populations for these studies were not diverse and did not represent any vulnerable population groups (including youth).
    - Although the applicant concluded that the findings from the clinical studies demonstrate that the new products are associated with reduced health risk secondary to reduced exposure to nicotine and other toxicants, there were no individual health data linked to specific health effects or health outcomes. Questions regarding extrapolating short term health effects to inform the likelihood of long-term outcomes are therefore moot.
    - There was insufficient bridging from the published literature on ENDS associated health effects to the new products. Although the applicant conducted an extensive literature search on the ENDS category including the new products, the majority of the published clinical studies captured in

the literature search were never systematically reviewed. Furthermore, relatively few case reports, case reviews, and clinical studies on health effects associated with ENDS and/or the new products were identified in this literature search.

- Published scientific literature on nicotine PK, BOE, puffing topography and environmental exposure studies that used related study products and/or other ENDS not subject to this review was used to support the applicant-sponsored studies; however, these published studies did not address health effects.
- In some instances, inferences about reduced health risks with new products use were drawn from the clinical studies' results. For example, the applicant inferred from the environmental exposure studies' conclusions that health risks associated with secondhand exposure to new products' emissions are reduced.
    - Bridging from the scientific literature on ENDS-associated health effects to the new products would have been helpful in either corroborating or refuting the applicant's analysis of the findings from the 13 clinical studies.

- Questions remain regarding the potential impact of major protocol deviations on the integrity of the data in two of the clinical studies.
    - There were 340 major protocol deviations documented in PROT-00030 (a 6-day BOE study) primarily related to informed consent issues, failure to meet inclusion/exclusion criteria, randomization errors, product administration, collection of urine samples, missing questionnaires and questionnaire date discrepancies, and inappropriate termination of subjects.
    - Although selected subjects were excluded to preclude inaccurate assessment of BOE primary and secondary endpoints, the vast array of protocol deviations raises questions about potential errors associated with the atypical AE findings also reported in this study.
    - The applicant acknowledged that there was no explanation for the higher frequency of AEs reported for the new products PM0000864.PD1, PM0000874.PD1, and PM0000878.PD1 than for the new products PM0000872.PD1, PM0000876.PD1, and PM0000878.PD1 in PROT-00030 and in PROT-00032 (a puffing topography study). Furthermore, this phenomenon was only observed in these two studies exclusively with the new products, not with any of the other product flavors.
- Despite the limitations in assessing health effects in studies and in the published literature, the AE data submitted by the applicant and other sources reviewed by the FDA were mild in severity and reported at a frequency consistent with the product category. Therefore, from a medical perspective, the available information regarding short- and long-term health effects of the new products does not prevent a finding that the new products are APPH.

Per the epidemiology review:

- There is currently some epidemiologic evidence suggesting positive associations between ENDS use and some health outcomes such as cardiovascular disease, respiratory disease, and oral health. There is strong evidence that ENDS use is

linked with infrequent ENDS battery explosion-related burns and e-liquid nicotine poisoning. The biomarker literature shows that ENDS users generally have higher exposure to some constituents such as VOCs than non-users of tobacco.

- In general, data from the biomarker literature suggests that dual users may have higher levels of certain BOE including nicotine and its metabolites compared to CC smokers. Dual users have generally not been found to have reduced levels of constituents such as TSNAs and VOCs compared to smokers.
- A few studies specifically examine the effects of switching from CCs to ENDS. A published study found that levels of total nicotine and some polycyclic aromatic hydrocarbon (PAH) metabolites did not change after switching from CCs to e-cigarettes, but levels of all other biomarkers significantly decreased after one week of using e-cigarettes (Goniewicz et al., 2017). Researchers have generally found that ENDS users have lower levels of exposure to some constituents including TSNAs than do CC smokers. Nicotine levels among ENDS users have usually been found to be somewhat lower or comparable to levels among CC smokers.

3.6.1.6. Likelihood and effects of product misuse

Per the medical review:

- The applicant submitted warning labels for the device kit, pods containing 3.0% and 5.0% nicotine concentrations in the e-liquid packaged in refill kits, and a guidebook.
- From a medical perspective, the risk of product misuse is minimized among users and non-users (including children) as a result of the warning labels, packaging, and design of the pods, which collectively mitigate the risks of accidental exposure.
    - In general, the labels provide factual information that aligns with the risks associated with the use and/or misuse of the new products.
    - The proposed labeling contains warnings about: nicotine's addictive potential and harms, only using authentic pods, not refilling pods, avoiding dermal and/or dermal exposure, not ingesting the e-liquid, and keeping pods away from children and pets.
    - The packaging for both the device and refill kits is tamper evident and designed to make it difficult for children to access the e-liquid.
    - (b) (4)
- The following limitations were noted:
    - Although users are admonished to only use authentic company pods and to not refill pods, there is no explicit warning against mixing additional materials with the pre-packaged e-liquid.
    - Although inadvertent dermal and ocular exposure are referenced in the label warnings, the applicant does not discuss health effects associated with these AEs. Lethal health outcomes related to intentional injection or ingestion of e-liquids are also not addressed.
    - Finally, apart from a discussion on nicotine toxicity in the context of accidental exposure and seizures, the applicant did not bridge findings from

published case studies on nicotine toxicity associated with ENDS to the new products.

- Despite the limitations described above, the data submitted by the applicant and the other sources reviewed by FDA (i.e., published literature, SRP reports) do not identify concerning adverse health effects associated with short- or long-term use of the new products.

Per the BCP review:

- BCP defines product misuse as using the product in ways other than intended, such as product modifications, dripping, and stealth use, which may influence exposure to nicotine and other HPHCs in the aerosol.
- The new products are closed-system pod-style ENDS. The power settings for PM0000878.PD1 are non-adjustable, and the e-liquids (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1) are enclosed in a pod. These product characteristics reduce the likelihood that users may manipulate ENDS settings and e-liquid constituents, including nicotine levels.

3.6.1.7. Adverse experiences

No chemistry, engineering, or microbiology-related AEs due to product design and composition of the new products have been reported to FDA at this time.

Per the medical review:

- The FDA systematically reviewed AE data by category (i.e., AEs in applicant-sponsored studies, in the published literature, reported by the public to FDA's SRP and the applicant's customer service center). The FDA also analyzed data pertaining to AEs of special interest (i.e., lung injury, seizures).
- The applicant conducted a pooled analysis of AEs from the 13 clinical studies submitted in these PMTAs. In general, the frequency of AEs was low and there were no unexpected AEs, deaths, or reports of either seizures or lung injury. No reported AEs occurred at a frequency of ≥5%. Headache was the most frequently reported AE (1.9%) overall, followed by dizziness (1.4%) and presyncope (the sensation of feeling faint; 1.2%). Cough was the most frequently reported AE associated with the use of PM0000864.PD1 or PM0000872.PD1 (2.2%) with the new product device PM0000878.PD1.
- Although the applicant stated that there were no serious AEs reported in any of the clinical studies, a serious AE thought to be secondary to nicotine poisoning and attributed to use of the comparison product was reported in one of the pivotal PK studies (PROT-00033) and resulted in the participant's early termination from the study.
- The applicant also acknowledged that for the new products in PROT-00030 (a 6-day BOE study) and PROT-00032 (a puffing topography study), there were unexplained higher frequencies of AEs reported for the new products PM0000864.PD1, PM0000874.PD1, and PM0000878.PD1 than for the new products PM0000872.PD1, PM0000876.PD1, and PM0000878.PD1. These findings were limited to these two studies and were not observed for other flavors. Major protocol deviations were documented in both these studies, but a potential association between these protocol deviations and data errors remains unclear.

- The applicant culled self-reported health events and device malfunction data from four behavioral online studies (Studies 1C, 2A, 10A, and 10B with study data analyzed in reports PROT-01350, PROT-01374, and PROT-01349). However, the applicant concluded that these data were invalid and uninterpretable secondary to inherent flaws in the study design.
- AEs in the published literature:
  - The applicant identified five case reports/reviews of ENDS-associated AEs; two of which were specifically associated with the new products and aligned with National Academies of Sciences, Engineering, and Medicine conclusion statements 11-1 ("There is no available evidence whether or not e-cigarettes cause respiratory disease in humans") and 11-5 ("There is limited evidence of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies") (Eaton et al., 2018).
  - The applicant also provided an abbreviated overview on AEs of special interest (i.e. lung injury, seizures). However, articles pertaining specifically to the new products or comparison products in the same ENDS class were not reviewed. The applicant did not provide analyses for peer-reviewed articles or case reports on other categories of AEs known to be associated with ENDS and/or nicotine toxicity, including battery explosions and other injuries and poisonings secondary to intentional or accidental exposure to e-liquids.
  - In lieu of a comprehensive review of published studies and case reports on AEs associated with ENDS and/or the new products, the applicant referenced selected articles to support findings in the applicant-sponsored studies. Although the applicant asserted that referenced articles could be either congruent or incongruent with results from the 13 applicant-submitted clinical studies, it appeared that the majority of citations selected corroborated the applicant's conclusion that the new products are well tolerated and that associated AEs are inconsequential.
- AEs reported by the public:
  - Twelve reports on AEs associated with the new products were submitted to FDA's SRP between December 2018 and April 2025.
  - Four of these AE reports were related to leaky pods or contamination and apart from oral mucosal exposure were not associated with significant health effects. The remaining eight submissions reported cardiovascular complaints (new onset hypertension and tachycardia [rapid heartbeat] and severe dyspnea [shortness of breath] accompanied by chest pain and palpitations), neurological complaints (new onset seizure activity), and respiratory (severe dyspnea) complaints. The analysis of these reports was constrained, however, by the inability to validate these symptoms as bona fide medical events and/or to definitively link these AEs to the new products.
  - The applicant provided a synopsis of AEs retrieved from the applicant's customer service centers between November 4, 2017, through February 5, 2020. Of the 1,755,431 complaints received and processed by the company's complaint management system, 0.3% (n=6039) reports were identified as potentially associated with a health concern. These reports were associated with 11,154 individual AEs and included company products that are beyond the

scope of this PMTA (e.g., pods and devices distributed in foreign markets only, other flavors).

- Of note, the most frequently reported AEs were burning sensation (14.4%), laryngeal pain (9.1%), cough (8.7%), nausea (7.8%) and headache (4.4%). Together, these categories comprised close to 50% of all consumer-reported AEs.
- The applicant also identified 73 cases of potential battery-related AEs, which included events occurring outside of the U.S. and likely involved products not included in the scope of these PMTAs. Of these complaints, there were 10 instances where consumers received medical treatment for burns and blisters to the hand or face (n=9) or for shock by the device (n=1). Two case reports were submitted for serious injuries (i.e., the first case reported hospitalization secondary to facial burns and the loss of 2 digits; the second case reported burns sustained to the face, eyes and hands). The identification of each of these products remains in dispute since the applicant has been unable to retrieve either the products or product images or serial numbers from the alleged victims.
- There were no consumer-reported AEs or AEs from clinical studies associated with lung injury. There were 40 cases of alleged seizures (0.4% of all consumer-reported AEs). In most cases, further analysis did not support a causal relationship between these events and the new products.
- The applicant referenced a case where the consumer attributed an alleged seizure to multiple multicolored flashing lights triggered by the device's accelerometer de-bug function. A case report detailing this event was not submitted in the subject applications; however, the applicant plans to remove this feature from all devices.
- The applicant offered the following caveats for consideration when analyzing these AE data: there were no opportunities for validating self-reported health events; verifying that the complaint was linked to the new products and not to a surrogate; or confirming details of events as reported by consumers by assessing physical findings on examination and results of ancillary laboratory tests, electroencephalograms and imaging studies obtained to support a diagnosis of seizures. The likelihood of potential misidentification of other devices for the new products was also corroborated in an applicant-sponsored study that demonstrated the inability of most study participants to differentiate between the new products and look-alike devices.
- The applicant also provided an abbreviated overview on AEs of special interest (i.e., lung injury, seizures); however, published studies pertaining specifically to the new products were not cited.
- From a medical perspective, the review of reported AEs does not raise concerns with issuing MGOs for the new products; however, post-marketing surveillance reporting of neurological events (e.g., seizures), overheating, fire and explosion-related injuries, and respiratory symptoms characteristic of lung injury is recommended.

3.6.2. Synthesis

As TPL, I agree with the BCP review that the abuse liability of each new product is comparable to that of UB CC among experienced users. I agree with the BCP review that the similar abuse liability between the new products and CC signifies that the new products can sustain and maintain addiction in nicotine-dependent populations and may have similar risks of initiation and dependence in non-users as CC smokers. Regarding the youth population, I agree with the BCP finding that the limited data available on actual use in youth do not suggest that youth who smoke and use ENDS have greater levels of addiction compared to smoking CC. However, as noted in the BCP review, among youth who initiate use of the new products, the presence of a non-tobacco flavor (i.e., menthol) in the new products may facilitate more frequent use of the new products compared to CC and other tobacco-flavored ENDS. This more frequent usage of the non-tobacco-flavored new product may increase the likelihood of progression to regular use of the new products and subsequent nicotine dependence.

Regarding short- and long-term health effects, the epidemiology review indicates that there is some epidemiological evidence suggesting positive associations between ENDS use and some health outcomes, such as cardiovascular disease, respiratory disease, and oral health. However, the medical reviews state that the applicant-sponsored clinical studies were not designed to evaluate differences in health outcomes and health risks between the new products and selected comparison products, as these studies did not include substantive clinical endpoints or BOPH data. Similarly, the toxicology review states that the applicant did not provide or reference any clinical data with toxicity endpoints for the new products. However, clinical studies measuring BOE levels after six days of exclusive use of the new products showed that study participants had reductions of BOE levels that were similar to the tobacco product cessation group. Dual use of either PM0000872.PD1 or PM0000874.PD1 (with PM0000878.PD1) and CCs, with CC consumption limited to 50% of the baseline amount, was associated with significant reduction in levels of non-nicotine BOE, although these levels were higher relative to the exclusive use of the new products and tobacco cessation groups. As noted in the epidemiology review, in general, data from biomarker literature suggest that dual users have sometimes been found to have higher levels of certain BOE, including nicotine and its metabolites, compared to CC users, and dual users have generally not been found to have lower levels of constituents such as TSNAs and VOCs compared to CC users. As TPL, I agree with the findings and conclusions regarding the short- and long-term health effects of the new products that are reported in the epidemiology, medical, and toxicology reviews. The reported findings of significantly decreased BOE levels (specifically of NNAL, 3-HPMA, MHBMA, S-PMA, COHb, NNN, HMPMA, CEMA, 1-OHP, o-toluidine, 2-NA, and 4-ABP) following six days of exclusive use of the new products after switching from UB CC use, supports my conclusion that exclusive use of the new products may result in reduced short- and long-term health effects.

As noted in the toxicology review, the applicant provided toxicological data from nonclinical studies to address the genotoxic and mutagenic potential of the new products. See section 3.5.2 for a discussion on the carcinogenic risk of the new products. Regarding non-cancer risk, the toxicology review indicates that there are two leachable constituents that may contribute to additional non-cancer risk associated with use of the new products. Specifically, the applicant asserts a <3% transfer efficiency for these leachable constituents; however, chemistry's review states that these studies are invalid, and a 100% transfer rate should be assumed. Based on this assumption, user exposure to these leachable constituents is higher than multiple applicable

TTC values, with margins of exposure that are <1. This indicates the potential for non-cancer risk. However, the toxicology review notes that due to the lack of information regarding hazard identification and dose response, there is uncertainty regarding how much, if any, non-cancer risk is conferred by the presence of these leachables. Although the potential non-cancer hazard for the two leachable constituents are not well characterized, and are considered a source of uncertainty, I agree with the toxicology review that the non-cancer hazard risk to users of the new products is likely to be lower than CC. This is because the yields of HPHCs and other toxicants having known and recognized non-cancer toxic effects are meaningfully lower in the new products relative to their yields in CC, and as there is no available evidence indicative of specific non-cancer hazards associated with exposure to these specific leachables.

The medical and toxicology reviews note limitations in assessing health effects in studies and published literature relevant to the new products, as well as a lack of applicant provided clinical toxicity data for the new products. Taking into consideration the $ELCR_c$ calculations provided by toxicology, the reductions in BOE associated with exclusive use of the new products, and in light of the full APPH analysis along with the rest of the information discussed herein, as TPL I conclude that the available information regarding short- and long-term health effects of the new products does not prevent a finding that the new products are APPH. Furthermore, as TPL, I note the relatively small number of AEs reported regarding serious/significant adverse health outcomes. Considering the length of time that the products have been marketed, this is somewhat encouraging information with respect to the uncertain non-cancer risk presented by the products. In addition, the manufacturer's post-market reporting obligations will allow FDA to continue to monitor and assess reported AEs that may be related to the two leachable constituents.

Regarding product misuse and unintentional exposure to the new products, as TPL, I agree with the BCP review conclusion that the new products are closed-system pod-style ENDS, the new product device (PM0000878.PD1) has non-adjustable power settings, the new product e-liquids (PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, and PM0000876.PD1) are enclosed in a pod, and that these product characteristics reduce the likelihood that users may manipulate the ENDS settings and e-liquid constituents, including nicotine levels. I also agree with the medical review conclusions that the risk of product misuse is minimized among users and non-users (including children) as a result of the warning labels, packaging, and design of the pods, which collectively mitigate the risks of accidental exposure. An additional mitigating factor regarding product misuse is noted in the medical review and warrants mention. The applicant states that an Online Enforcement Team is used to monitor more than 1,000 e-commerce platforms and 20 international social media platforms for misinformation regarding the use of counterfeit and unauthorized products, removal of underage focused content, and the identification of manufacturers and distributors of "bogus" products.

Regarding AEs associated with the new products, the chemistry, engineering, and microbiology reviews report that no AEs due to product design and composition and relevant to these disciplines have been reported to FDA at this time. The medical review systematically reviewed AE data by category. These categories included AEs in applicant-sponsored studies, in the published literature, and reported by the public to FDA's SRP and/or the applicant's new products' customer service center. The medical review also analyzed data pertaining to AEs of special interest (i.e., lung injury, seizures). (b) (4) [redacted]

(b) (4)

(b) (4) FDA will continue to monitor and assess reported AEs for seizures associated with the device's multicolored flashing lights.[40] As TPL, I agree with the medical review conclusion that the review of reported AEs does not raise concerns with issuing marketing orders for the new products.

As part of the FDA BIMO program, FDA performed two clinical investigator inspections of George Konis, MD and Shari DeSilva, MD and one Remote Regulatory Assessment (RRA) of Debra Kelish, MD to support CTP's review of these PMTAs. The results of the BIMO RRA and inspections did not reveal human subject protection issues; however, the findings from inspections of George Konis, M.D. and Shari DeSilva, M.D. revealed issues that may impact the reliability of the data submitted for protocol PROT-00030. BCP considered these findings in its evaluation of the study data and determined that they were not substantial enough to diminish conclusions from the totality of evidence. Ultimately, the BIMO inspectional results for this study did not affect BCP's conclusions given the totality of all study data (published studies and literature) available. As TPL, I agree with BCP's findings and conclusions regarding the BIMO inspection results.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

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

3.7.1.1. Toxicology

Per the toxicology review:

- Applicant-provided risk assessment:
  - The applicant submitted carcinogenic risk analyses associated with the new products that identifies ingredients and HPHCs as contributors. The applicant asserted that using an adjusted IUR for furfural and glycidol was appropriate; however, the information provided was not sufficient to justify such use because the applicant did not identify how the adjusted IUR values were calculated or which values from the citations were pertinent; thus, the default TTC of 1.5 µg/day was used. Additionally, two leachable compounds were identified as Tier 4E constituents. In calculating the $ELCR_c$, toxicology included HPHCs, leachables, and ingredients in the analysis of cancer risk for users of the

[40] In its PMTA, the applicant indicated (b) (4)

(b) (4)

new product if their daily exposure was above the level to impart a risk of 1 in 100,000. As mentioned in the exposure analysis in section 3.5 above, this required an adjustment being made to the $ELCR_c$ calculation provided by the applicant. The adjustments made by toxicology do not change the qualitative risk descriptor provided and discussed in the application.

- The $ELCR_c$ values calculated by toxicology for the Virginia Tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1) correspond to a moderate concern when compared to CC. This assessment is based on their values falling within the range of 1-10% of the risk associated with 1R6F CC. The Menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1) have a range of cancer risk that spans from lower to moderate concern risk management descriptors, considering their values fall between <1 to 10% of the risk associated with 16RF CC. Additionally, the $ELCR_c$ values compare to the median of the CTP-authorized ENDS marketplace as follows: Virginia Tobacco 3.0% (PM0000874.PD1) is 55% above the median, while Virginia Tobacco 5.0% (PM0000876.PD1) is 41% above the median. For the Menthol 3.0% (PM0000864.PD1), the product ranges between 28% above and 40% below the median, while the Menthol 5.0% (PM0000872.PD1) ranges between 39% above and 38% below the median of the CTP-authorized ENDS marketplace.
- Inclusion of Tier 4D and Tier 4E constituents does not change the qualitative risk management descriptor nor the relative comparison to the CTP-authorized ENDS marketplace for PM0000874.PD1 and PM0000876.PD1 (Virginia Tobacco 3.0% and 5.0%), used with PM0000878.PD1. However, for the Menthol flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1), inclusion of Tier 4D and Tier 4E constituents does change both, the qualitative risk management descriptor and the relative comparison to the CTP-authorized ENDS marketplace.

Per the epidemiology review:

- Population health impact (PHI)
  - The applicant developed an agent-based population model to predict the total national impact of ENDS products on premature deaths averted in the 2000-2100 period. The model estimated that the introduction and sustained availability of ENDS products in the U.S. tobacco marketplace would result in 2.5 million premature deaths averted by 2100. The applicant then assumed a 35-50% ENDS market share and concluded that the new tobacco products could prevent between 875,000 and 1.25 million premature deaths.
  - Model inputs included both publicly available estimates and estimates derived from the submitted studies of the new tobacco products. The default values of some model input estimates were likely mis-specified in directions favorable for ENDS products. However, sufficient sensitivity analyses were provided to address concerns with these estimates. Other assumptions inherent to the model design were reasonable, such as the number of tobacco product use states, and a conservative approach treating all prevalent youth use as sustained.

- Model predictions were highly influenced by several ENDS-specific inputs including the ENDS cessation rate in complete switchers, the complete switching rates in smokers and dual users, and the excess relative risk of ENDS products relative to CC.
- Limitations: ENDS and CC were the only tobacco products modeled; the new tobacco products were not independently simulated. The applicants assumed 35-50% market share over 89 years cannot be plausibly applied to the products in this application alone. Recent publications have shown marked decrease of JUUL market share in the United States from 27.7% in 2022 to 17.8% in 2024 (Ganz et al., 2025). Default values for several behaviors, such as the complete switching rates in the default target case, were derived in part from the applicant's submitted longitudinal studies and were likely overestimated relative to other published findings (Coleman et al., 2019). The model findings, including estimates of deaths averted and key transitions identified, compare favorably with other published examples of agent-based, cohort-based, and decision-theoretic models, as well as studies using the SimSmoke model (Cherng et al., 2016; Levy et al., 2017; Levy et al., 2016; Warner et al., 2019). Despite these limitations, the data provided in the ADJUSST study suggest a population health benefit to the new products in facilitating complete switching from CCs even when utilizing conservative assumptions that all missing respondents were continued smokers.

3.7.2. Synthesis

While these toxicology cancer risk estimations assume that adults will exclusively use the new products, as TPL, I acknowledge that it is generally understood that a subpopulation of people who use the new products may continue to smoke CC. This dual use of the new products with CC may result in relative increased risks of cancer in this user population, compared to those who switch to the new products exclusively. However, as I described in section 3.6 – Toxic Effects, the dual use of either PM0000872.PD1 or PM0000874.PD1 (with the new product device PM0000878.PD1) and CC, with CC consumption limited to 50% of the baseline amount, was associated with significant reduction in levels of non-nicotine BOE, although these levels were higher relative to the exclusive use of the new products and tobacco cessation groups. Also, as noted in the epidemiology review, data from biomarker literature generally suggest that dual users have sometimes been found to have higher levels of certain BOE, including nicotine and its metabolites, compared to CC users, and dual users have generally not been found to have reduced levels of constituents such as TSNAs and VOCs compared to CC users.

The epidemiology review evaluated the applicant-developed agent-based population model that was used to predict the total national health impact of ENDS products on premature deaths averted in the 2000-2100 time period. Assuming a 35-50% ENDS market share for the new products, the applicant concluded that the new tobacco products could prevent between 875,000 and 1.25 million premature deaths. The epidemiology review found that the default values of some of the model input estimates were likely mis-specified in a direction favorable for ENDS products; however, there were sufficient sensitivity analyses provided to address epidemiological concerns with these estimates. Epidemiology found that other inherent assumptions within the model design were reasonable, such as the number of tobacco product use states and use of a conservative approach treating all prevalent youth use as sustained.

Epidemiology identified several limitations with the applicant-developed agent-based model; however, as TPL, I concur with epidemiology conclusions that the model design is reasonable. As TPL, I find that this model's findings of a long-term public health benefits associated with use of the new products, although likely overestimated, are informative.

3.8. STATUTORY REQUIREMENTS

3.8.1. Public health conclusion

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

3.8.2. Tobacco product manufacturing practices[41]

The PMTAs contain sufficient information to characterize the tobacco product design and adequate processes and controls to help ensure that the new products meet the manufacturer's specifications. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of the new products 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 concluded that the proposed labeling is not 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 Hans Rosenfeldt on July 10, 2025. The FONSI was supported by a Programmatic Environmental Assessment prepared by FDA on July 10, 2025.

5. CONCLUSION AND RECOMMENDATION

Section 910 of the FD&C Act requires that, for a product to receive a PMTA marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute specifies that, in assessing whether the marketing of the new products would be APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products.

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

Section 910(c)(4). FDA interprets the APPH standard to require a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. In determining whether permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adults who completely switch to less harmful tobacco products).

Current scientific literature demonstrates that ENDS are generally likely to have different toxicological risk and be associated with lower health risks than CC. However, whether this is true for any particular new ENDS is considered on a case-by-case basis during the course of FDA's scientific review of a PMTA. FDA considers the potential that adults who smoke CCs may experience a reduction in toxicological risk and health risks if they switch completely to ENDS, or if they use both products but substantially reduce their CC smoking.

As part of an APPH determination, tobacco products must undergo an evaluation of their potential carcinogenic and non-cancer health effects before a marketing order can be granted. While risk comparisons between CC and ENDS based upon HPHCs are a useful initial assessment, this approach does not consider other toxic constituents present in ENDS that are not on the established HPHC list in the overall risk evaluation. ENDS users are potentially exposed to toxic constituents present in the inhaled aerosol from ENDS products arising from three distinct sources:

- Thermal degradation or reaction products of e-liquid constituents (e.g., ingredients, leachables), or chemical adducts of e-liquid constituents, that transfer to the aerosol
- E-liquid ingredients that transfer directly to the aerosol
- Leachables that migrate from ENDS container closure systems and components into the e-liquid and transfer to the aerosol

Of these three sources, many toxic thermal degradation products associated with ENDS are found on FDA's HPHC list established in 2012. This preliminary list of 93 HPHCs and the proposed list of 19 additional HPHCs collectively identify chemicals linked to the five most serious health effects of tobacco product use (i.e., cancer, cardiovascular disease, respiratory, reproductive toxicities, addiction). Our experience from review of PMTAs indicates that other constituents, along with those on the established HPHC list, have the potential to confer substantial risk for adverse health effects, including cancer and non-cancer risk, for ENDS. The overall evaluation of a new product's potential health risks, assessed as part of the APPH determination and balanced against potential benefits of a new product (e.g., reductions in lifetime cancer risk as determined in an $ELCR_c$ assessment), takes into account the potential health risks posed by these HPHC and non-HPHC constituents of the new products.

Based on the information provided in the applications, and as described in this Technical Project Lead review, I find that these PMTAs 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 that the new products are manufactured consistently. The applicant submitted sufficient chemistry and microbiology data to support a (b) (4) shelf life for the bulk e-liquid and a (b) (4) shelf life for the finished new products, for a total shelf life of (b) (4) (b) (4) from the date of manufacture. The applicant also submitted sufficient engineering data demonstrating the stability of the new products' components through the product life cycle and

proposed shelf life. The new products were compared to CC and ENDS because the applicant identified that the new products are intended for adults who currently smoke CC and adults who currently use ENDS.

The new products include tobacco- and menthol-flavored ENDS. As discussed above, the literature demonstrates that the youth risks of flavored ENDS, including menthol-flavored ENDS, are higher than those of tobacco-flavored ENDS. Thus, permitting the marketing of the new menthol products requires a showing that they provide a greater benefit to public health than that of tobacco-flavored ENDS because they present a greater level of youth initiation risk. The applicant has provided sufficient reliable and robust evidence of a benefit to adults who smoke CC and completely switch from, or significantly reduce, CC that outweighs the risk of appeal, initiation, and continued use by youth for the tobacco-flavored new products (PM0000874.PD1, PM0000876.PD1, PM0000878.PD1). Specifically, the applicant submitted an observational longitudinal study (ADJUSST Study) to evaluate switching rates from CC to the use of the new products (i.e., PM0000872.PD1, PM0000876.PD1, PM0000878.PD1) over a two-year follow-up period that demonstrates switching rates for the new products of 38.4-51.9%. These switching rates are substantially higher than switching rates reported for unaided quitting (5-6%) as well as for those using nicotine replacement therapy (8-9%), thus indicating a substantial benefit to public health. The applicant also provided sufficient reliable and robust evidence of an added benefit to adults who smoke CC and completely switch from, or significantly reduce, CC that outweighs the risk of appeal, initiation, and continued use by youth for the Menthol-flavored new products (PM0000864.PD1, PM0000872.PD1, PM0000878.PD1). The ADJUSST study presented relative switching data for the menthol-flavored new products when compared to the tobacco-flavored new products. Across a two-year follow-up, these study data show that the Menthol-flavored new product (PM0000872.PD1, PM0000878.PD1) is associated with a higher switching probability than the Virginia Tobacco-flavored new product (PM0000876.PD1, PM0000878.PD1) in adjusted analyses, regardless of the modeling method used (aRR = 1.11 to 1.15, depending on the methodology used: intent-to-treat, empirical imputation, and non-missing observations); the applicant adequately bridged these results to the 3.0% Virginia Tobacco- and Menthol-flavored new products (PM0000874.PD1, PM0000864.PD1) with PM0000878.PD1. In addition, the applicant provided data indicating that users of non-mentholated CC had higher rates of switching when using the Menthol-flavored new product compared to the Virginia Tobacco-flavored new product (aRR = 1.22 to 1.28, depending on the methodology used). The relative increase in switching demonstrated by the Menthol-flavored new products is considered in the evaluation of risks and benefits to public health.

The assessment of risks to public health, in addition to the potential for youth initiation, begins with the applicant-submitted clinical studies demonstrating that the new products' abuse liability is comparable to UB CC in adults who currently smoke. This suggests that the new products may be a suitable substitute for CC among adults who smoke CC and who want to quit. Based on the data available from experienced CC users, people who have not used tobacco products and initiate use of the new products are likely to obtain nicotine exposures comparable to CC as they gain experience with the new products, thus leading to progression to regular use of the new products. Additionally, BOE data from the applicant-sponsored study PROT-00030 found that switching from UB CC use to exclusive ad libitum use of the new products for six days resulted in significant reductions in the urinary and blood BOE similar in magnitude to the reductions in participants who abstained from CC smoking. Specifically, NNAL, 3-HPMA, MHBMA, S-PMA, COHb, NNN, HMPMA, CEMA, 1-OHP, o-toluidine, 2-NA, and 4-ABP significantly decreased following use of the new products. Chemical evaluation of the new products' aerosols suggests that the new products have fewer and lower

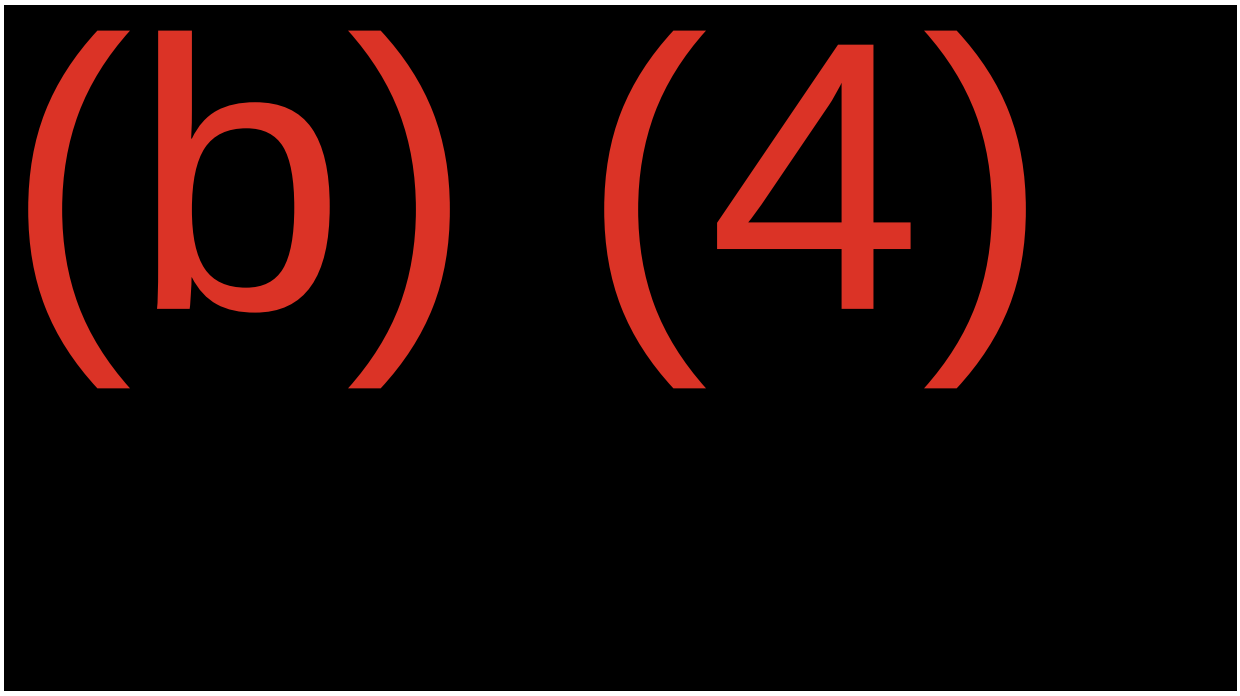
levels of many HPHCs compared to CC. A toxicology evaluation predicts that the new products' estimated $ELCR_c$ is significantly lower than the ELCR in adults who smoke CC, as all calculated $ELCR_c$ values for all new products are less than 5% of the $ELCR_c$ for the 1R6F CC. While there may be a potentially higher cancer risk associated with completely switching from some CTP-authorized ENDS to the new products, the benefit of adult smokers switching from CC to the new products is significant and outweighs the risk of substituting these new products for some alternative CTP-authorized ENDS.

There is uncertain non-cancer risk associated with two leachable constituents (i.e., the newly reassigned leachable [previously (b) (4) However, based on the amount of the leachables present in the aged e-liquid, I conclude that these leachables are unlikely to significantly change the total non-cancer risk of the new products. Also, the information submitted for the new products shows that the non-cancer hazard to users of the new products is likely to be lower than CC from a toxicological perspective, although there is uncertainty as to how much lower. I also acknowledge that conclusions in future evaluations could change as additional information becomes available.[42]

Additionally, FDA systematically evaluated AE data included in applicant-sponsored studies, in the published literature, and reported by the public to FDA's SRP and/or the new products' customer service center. Data pertaining to AEs of special interest (i.e., lung injury, seizures) were also analyzed. In general, the frequency of AEs in applicant-sponsored studies was low and there were no unexpected AEs, deaths, or reports of either seizures or lung injury. Regarding AEs reported in the published literature, the majority of citations selected for review corroborated the applicant's conclusion that the new products are well tolerated, and that the reported associated AEs are inconsequential. Regarding AEs reported by the public, twelve reports on AEs associated with the new products were submitted to the FDA's SRP between December 2018 and April 2025. These AEs were either not associated with significant health effects, were unable to be validated as bona fide medical events definitively linking these reported AEs to the new products, or were already known and reported effects of ENDS and did not introduce new health effects. As such, the review of reported AEs does not raise concerns with issuing MGOs for the new products. Furthermore, as TPL, I note the relatively small number of AEs reported regarding serious/significant adverse health outcomes. Considering the length of time that the products have been marketed, this is somewhat encouraging information with respect to the uncertain non-cancer risk presented by the products. In addition, the manufacturer's post-market reporting obligations will allow FDA to continue to monitor and assess reported AEs that may be related to the two leachable constituents.

The applicant also proposed marketing plans that include restrictions beyond those required with PMTA authorization. The Office of Health Communication and Education (OHCE) determined the proposed plans may help further limit youth exposure to the new products, the products' labeling, advertising, marketing, and/or promotion, and the potential for youth initiation. For example, the applicant proposes to (b) (4)

[42] In the time since the June 23, 2022, MDOs were administratively stayed in July of 2022, CTP's views as to the appropriate toxicology evolution framework, including non-cancer risks, has evolved. This has been documented in the following: 1) the Summary of Key Points in the Evolution of OS's Approach to Reviewing Toxicological Information, as Applicable to PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1, PM0000879.PD9, and AP0000166, signed June 4, 2024; 2) the Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications memorandum, signed June 3, 2024, and 3) the Calculating Excess Lifetime Cancer Risk in ENDS memorandum, signed June 3, 2024.



The risk posed to public health by the potential for youth initiation of the new products, is weighed against the potential for health benefits to adult users of CC. Taken together, the available evidence suggests that although the menthol-flavored new products pose risks to youth, the potential of the new products to promote CC cessation and provide significantly lower health risks than CC in adults outweighs that risk to youth. The tobacco-flavored new products also demonstrate adult benefit in terms of complete switching from CC use, with study results showing high rates of complete switching to PM0000876.PD1 at 24-month of follow-up. These tobacco- and menthol-flavored new products also present a lower risk alternative to CC use, as evidenced by toxicology's evaluation, as all calculated $ELCR_c$ values for the new products are less than 5% of the $ELCR_c$ for the 1R6F CC. Along with the applicant-proposed marketing plans and restrictions, the applicant-provided data for the new products are sufficient to demonstrate a public health benefit for adults who smoke CC that outweighs the potential for youth initiation of the new products.

Overall, the risks posed to public health by the new products, including the potential for youth initiation, uncertainty posed by the non-cancer risk of the two leachable constituents (i.e., the newly reassigned leachable [previously (b) (4) and the potentially higher cancer risk associated with use of the new products versus some CTP-authorized ENDS, is outweighed by the significant benefit of adult smokers switching from CC to the new products. Additionally, for the menthol-flavored new products, the additional potential for youth initiation is outweighed by the significant added benefit of adult smokers switching from CC to the new products.

Thus, based on the information provided in the subject PMTAs and the available evidence, as TPL, I find that permitting the marketing of the new products, as described in the applications and specified in Appendix B, Table 4 is appropriate for the protection of the public health. The issuance of these MGOs 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 new products, in accordance with the marketing order requirements outlined in the MGOs.

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

MGOs should be issued for the new products that are the subjects of this review, as identified on the cover page of this review.

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7. APPENDICES

Appendix A. Acronyms and abbreviations

Table 3. Acronyms and abbreviations

Acronym, abbreviation, term	Use
1-OHP	1-hydroxypyrene
2-NA	2-aminonaphthalene
3-HPMA	3-hydroxypropyl mercapturic acid
4-ABP	4-aminobiphenyl
aw	water activity
APPH	appropriate for the protection of the public health
AE	adverse experience
aRR	adjusted risk ratio
AUC	area under the curve
BCP	behavioral and clinical pharmacology
BIMO	bioresearch monitoring
BLOD	below the level of detection
BLOQ	below the level of quantification
BOE	biomarkers of exposure
BOPH	biomarkers of potential harm
CC	combusted cigarette
CEMA	cyanoethyl mercapturic acid
C_{max}	time to reach maximum concentration
COA	certificate of analysis
COHb	carboxyhemoglobin
CPD	cigarettes per day
CPM	cigarettes per month
EA	environmental assessment
ELCR	excess lifetime cancer risk
$ELCR_c$	cumulative ELCR
ENDS	electronic nicotine delivery system
EPA	Environmental Protection Agency
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHC	harmful and potentially harmful constituent
HPMA3	3-hydroxypropylmercapturic acid
IARC	International Agency for Research on Cancer
ISO	International Organization of Standards
IUR	Inhalation Unit Risk
JLI	JUUL Labs Inc.
LCS	longitudinal cohort study
LOD	level of detection
LOQ	level of quantification
MGO	marketing granted order
MHBMA	Monohydroxybutenylmercapturic acid
MDO	marketing denial order

Acronym, abbreviation, term	Use
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone
(b) (4)	(b) (4)
NNN	**N-nitrosonornicotine**
NRT	nicotine replacement therapy
NYTS	National Youth Tobacco Survey
OCE	Office of Compliance and Enforcement
OHCE	Office of Health Communication and Education
PG	propylene glycol
pg	picogram
PHI	public health impact
PK	pharmacokinetics
PMTA	premarket tobacco product application
RRA	remote regulatory assessment
RCT	randomized controlled trial
S-PMA	S-phenylmercapturic acid
SRP	Safety Reporting Portal
(b) (4)	(b) (4)
TPL	technical project lead
TPMF	tobacco product master file
TSNAs	tobacco-specific nitrosamines
TTC	threshold of toxicological concern
UB	usual brand
VG	vegetable glycerin
VOCs	volatile organic compounds
w/w	weight per weight

Appendix B. New products

Table 4. New products subject to Granted Orders

Common Attributes[43,44,45,46]	
Submit date	July 29, 2020
Receipt date	July 29, 2020
Applicant	JUUL Labs Inc.
Product manufacturer	JUUL Labs Inc.
Product category	Electronic Nicotine Delivery Systems (VAPES)
Attributes	**New Tobacco Product**
STN	**PM0000864.PD1**
Product name	JUULpods (Menthol 3.0%)
Product subcategory	Closed E-Liquid
Package type	Cartridge
Package quantity	1 Cartridge
Characterizing flavor	Menthol
E-liquid volume	0.7 milliliter (mL)
Nicotine concentration	3.0%
Nicotine source	Tobacco
PG/VG ratio	30/70
Additional property	Blister Pack
STN	**PM0000872.PD1**
Product name	JUULpods (Menthol 5.0%)
Product subcategory	Closed E-Liquid
Package Type	Cartridge
Package Quantity	1 Cartridge
Characterizing Flavor	Menthol
E-liquid volume	0.7mL
Nicotine concentration	5.0%
Nicotine source	Tobacco
PG/VG ratio:	30/70
Additional property:	Blister Pack

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

STN	PM0000874.PD1
Product name	JUULpods (Virginia Tobacco 3.0%)
Product subcategory	Closed E-Liquid
Package Type	Cartridge
Package Quantity	1 Cartridge
Characterizing Flavor	Tobacco
E-liquid volume	0.7 mL
Nicotine concentration	3.0%
Nicotine source	Tobacco
PG/VG ratio:	30/70
Additional property:	Blister Pack
STN	**PM0000876.PD1**
Product name	JUULpods (Virginia Tobacco 5.0%)
Product subcategory	Closed E-Liquid
Package Type	Cartridge
Package Quantity	1 Cartridge
Characterizing Flavor	Tobacco
E-liquid volume	0.7 mL
Nicotine concentration	5.0%
Nicotine source	Tobacco
PG/VG ratio:	30/70
Additional property:	Blister Pack
STN	**PM0000878.PD1**
Product name	JUUL Device
Product subcategory	Closed E-Cigarette
Package Type	Box
Package Quantity	1 ENDS Device
Characterizing Flavor	None
Nicotine source	None
Length	80.69 millimeter (mm)
Diameter[47]	Not provided
Wattage	6.5 W
Battery Capacity	200 milliampere-hour (mAh)
E-liquid volume	0.7 mL
Additional property	Depth 7.00 mm Color Slate Universal Serial Bus (USB) Charging Dock

[47] Applicant provided depth as an alternative for diameter given the product proportions.

Appendix C. Amendments and additional submissions received

Table 5. Amendments

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
November 30, 2020	November 30, 2020	All STNs.PDs	Yes	Response to November 9, 2020, FDA Information request
June 22, 2021	June 22, 2021	All STNs.PDs	Yes	Response to March 26, 2021, Deficiency letter
August 30, 2024	August 30, 2024	All STNs.PDs	Yes	Response to June 6, 2024, Deficiency letter
October 23, 2024	October 23, 2024	All STNs.PDs	Yes	Response to FDA October 22, 2024, information request

Table 6. Additional submissions

Submission Date	Receipt Date	Reviewed	Brief Description
July 29, 2022	July 29, 2022	Yes	Appeal of June 23, 2022, Marketing Denial Order (MDO) letter
August 1, 2022	August 1, 2022	Yes	Amendment to Appeal of June 23, 2022, MDO letter to update table of contents
November 6, 2023	November 6, 2023	Yes	Amendment to Appeal of June 23, 2022, MDO letter to include new studies and an expert opinion