FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review[1]	
STNs	PM0000616.PD1, PM0000617.PD1
Common Attributes	
Submission date	March 10, 2020
Receipt date	March 10, 2020
Applicant	NJOY LLC
Product manufacturer	NJOY LLC
Application type	Standard
Product category	Electronic Nicotine Delivery Systems (ENDS) (VAPES)
Product subcategory	Closed E-Liquid
Cross-Referenced Submissions	
All STNs	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	• Equivalent Testing for SE Evaluation (February 24, 2017; Addendum, April 16, 2019) • Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products (March 2019) • Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications (June 3, 2024) • Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications (June 3, 2024)
Recommendation	
Issue marketing granted orders for the new tobacco products subject to this review.	

Technical Project Lead (TPL):

Megan J. Schroeder, Ph.D.
Supervisory Pharmacologist
Division of Individual Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Matthew Farrelly, Ph.D.
Director
Office of Science

[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.

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1. EXECUTIVE SUMMARY

This Technical Project Lead (TPL) review relates to premarket tobacco product application(s) (PMTA(s)) 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 application(s) 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") is appropriate for the protection of the public health (APPH) (*subject to certain marketing restrictions*) and that none of the 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 premarket tobacco product application (PMTA) marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute places the burden on the applicant to make the required showing by providing that FDA "shall deny an application" for a product to receive a PMTA marketing authorization if, "upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product," FDA finds that "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." Section 910(c)(2)(A).

The statute further specifies that, in assessing 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 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 smoking of CC. In order to show that the marketing of an ENDS is APPH, an applicant must show that the benefits,

including those to adults who use CC, outweigh the risks, including those to youth, resulting in a net benefit to the public health. As the known risks of the product increase or decrease, the burden of demonstrating a substantial enough benefit likewise increases or decreases.

Current scientific literature demonstrates that ENDS are generally likely to have 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 use 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 use CC outweigh that risk. For tobacco-flavored ENDS the risk to youth is lower compared to flavored ENDS; accordingly, a lesser showing of benefit may suffice.

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 use CC comparable options for complete switching or significant CC reduction bears on the extent of the public health benefit that the subject flavored 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 use 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.[2] 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 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.

FDA's evaluation of these PMTAs determined that they contain sufficient information to characterize the new products' composition and design, and that there are adequate process controls and quality assurance procedures to help ensure the new products are manufactured consistently. The applicant submitted sufficient chemistry and microbiology data to support a (b)(4) product shelf life for both new products. We compared the new products to CC and other 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 are 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. Nationally representative 2023 National Youth Tobacco Study (NYTS) data show that the most popular ENDS flavors used by middle school and high school students who currently use ENDS were fruit (63.4%); candy, desserts, or other sweets (35.0%); mint (27.8%); and menthol (20.1%), while tobacco-flavored ENDS were used by 6.4% of youth who currently use ENDS (Birdsey et al., 2023). The applicant provided low prevalence estimates of the new products in youth; however, these estimates were not reliable due to small sample

[2] *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").

sizes. Meanwhile, nationally representative 2023 NYTS data show that NJOY products (of which there are many sub-brands) are the 10th most-reported brand used in the past 30 days among middle and high school students. The literature demonstrates that the risk of menthol-flavored ENDS is higher than tobacco-flavored ENDS, yet lower than some other flavors (e.g., fruit).

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 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 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)[3] or longitudinal cohort study (LCS),[4] although FDA evaluates other types of evidence on a case-by-case basis to determine if 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 tobacco-flavored ENDS in facilitating complete switching away from or significantly reducing CC smoking among adults who smoke CC.

The applicant submitted data and analyses from an online, observational LCS (NJOY User Study) that assessed rates of complete switching (i.e., cessation of CC with continued ENDS use, as well as cessation of CC and ENDS) when adults were using new product PM0000617.PD1 (NJOY ACE POD Menthol 5%) and tobacco-flavored NJOY ACE products (not subject to this PMTA review) over six months. These data demonstrated that NJOY ACE products have higher rates of absolute switching from CC (ranging from (b) (4)%) than other ENDS in general. In addition to NJOY ACE products' robust absolute switching rates ranging from (b) (4)%, these data provide robust and reliable evidence that the menthol-flavored PM0000617.PD1 is associated with statistically significant and substantially higher rates of complete switching than tobacco-flavored NJOY ACE ENDS (not subject to this PMTA review). Since the data from PM0000617.PD1 can be bridged to PM0000616.PD1, both new products provide a significant and substantial added behavioral benefit (i.e., OR range (b) (4)) compared to Classic Tobacco flavor NJOY ACE ENDS among adults who quit smoking CC.

[3] A randomized controlled trial (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.

[4] A longitudinal cohort study (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 users of non-tobacco-flavored ENDS compared with users of tobacco-flavored ENDS).

The applicant-submitted clinical studies with new product PM0000617.PD1 demonstrate that the new product's abuse liability is similar to CC among adults who are experienced with ENDS use, suggesting that the new product may be a suitable substitute for CC among adults who smoke CC and who want to quit. Additionally, the applicant's biomarker data from the NJOY User Study suggests that adults who exclusively use the new products will have lower HPHC exposures compared to adults who dually use CC and 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 excess lifetime cancer risk (ELCR) is significantly lower than the ELCR in adults who 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 as compared to adults who continue to use CC exclusively.

Based on the information provided in the PMTAs and the available evidence, I find that permitting the marketing of the new products, subject to certain marketing restrictions, is APPH. The PMTAs contain sufficient evidence to show that the new products have the potential to benefit adults who smoke CC and who switch completely or significantly reduce their CC use.

The applicant also proposed robust 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 product, the products' labeling, advertising, marketing, and/or promotion, and the potential for youth initiation. For example, the applicant proposes to limit youth exposure to the new products by not engaging in social media promotions, limiting human portrayals to models who are over the age of 45, and prohibiting the sale of NJOY ACE ENDS on third-party websites.

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 A, sold under the brand name NJOY.

The new products are prefilled NJOY ACE pods containing Menthol-flavored e-liquids in two nicotine concentrations: 2.4% nicotine (PM0000616.PD1) and 5% nicotine (PM0000617.PD1). The new products are intended to be used with a complete NJOY ACE ENDS, which is composed of a rechargeable Power Unit (not subject to this PMTA review) and an accessory USB charger for the power unit. The power unit and cartridge settings are not adjustable by the user.

2.2. REGULATORY ACTIVITY

On March 10, 2020, FDA received two PMTAs from NJOY LLC. FDA completed an acceptance review and issued an Acceptance letter to the applicant on March 17, 2020. FDA issued a Filing letter to the applicant on March 26, 2020. FDA issued a Deficiency letter to the applicant on July 29, 2020. FDA issued a Major Amendment letter to the applicant on February 10, 2023.

Refer to Appendix B 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.

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Regulatory Review	Not Assigned	N/A	Tishelle Ogunfiditimi	6/13/2023
Engineering	Nashaat Rasheed	7/27/2020	Pritesh Darji	6/17/2024
Chemistry	Selena Russell	7/27/2020	Youbang Liu	6/14/2024
Microbiology	David Craft	7/27/2020	Prashanthi Mulinti	6/14/2024
Toxicology[5]	Kamau Peters	7/28/2020	Kamau Peters	1/30/2024
Behavioral and Clinical Pharmacology	Babita Das/ Marzena Spindle	7/27/2020	Arit Harvanko	6/12/2024
Medical	Edna Termilus	7/27/2020	Candrea Smith	6/14/2024
Epidemiology	Rebecca Jackson	7/27/2020	Maria Cooper	6/14/2024
Social Science	Elisabeth Donaldson	7/27/2020	Lisa Lagasse	6/13/2024
Environmental Science	Rudaina Alrefai-Kirkpatrick	7/27/2020	Ron Edwards	6/11/2024
OCE – BIMO	Carlos Carmona	4/13/2020	Not Assigned[6]	N/A
OCE – Manufacturing/Lab	Jiali He	4/8/2020	Not Assigned[6]	N/A

Table 2. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Statistics[7]	Christopher Ellison	1/25/2021	Christopher Ellison	3/13/2024
OCE – DPAL	Rohit Mathew	7/2/2020	Not Assigned[6]	N/A
OHCE	Emily Talbert	4/29/2020	Allison O'Donnell	3/14/2022
TPST[8]	Susan Rudy	4/7/2020	Vy Nguyen	3/7/2023

[5] Toxicology addendum was completed on June 14, 2024, by Md Almamun.
[6] Second cycle review was not necessary because there was no new information or data to review for this discipline.
[7] An additional second cycle statistics consult was completed on March 15, 2024, by Christopher Ellison.
[8] An additional second cycle TPST consult was completed on February 8, 2024, by Vy Nguyen.

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

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

Per the engineering review:

- The applicant compared the authorized NJOY ACE device with the new products (menthol-flavored pods) to Vuse Alto ENDS (Original, Menthol, Rich Tobacco and Mixed Berry). NJOY ACE and Vuse Alto products have comparable design parameters such as e-liquid volume (mL), e-liquid pH, battery cell capacity (mAh), atomizer resistance (Ω), and the same atomizer type. Although not all design parameters are comparable with the comparison products, the applicant's rationale for selection of these comparison products is acceptable from an engineering perspective.

Per the chemistry review:

- The applicant measured aerosol constituent concentrations of the comparison product Vuse Alto Original 5%. This is a tobacco product in the same product category and subcategory as the new product that contains nicotine salts like the new products.
- The chemistry review also compared constituent yields from the new products' aerosols to the mainstream smoke (MSS) yields from 50 commercially available CC (FDA50). The applicant's rationale for selection of the comparison product and data from the additional comparison with CCs is acceptable from a chemistry perspective.

Per the microbiology review:

- ENDS comparison product (Vuse Alto in Original, Menthol, Mixed Berry, and Rich Tobacco) stability information was not provided for the PMTAs. Therefore, a comparison of how product characteristics affect stability, when compared to similar ENDS, could not be completed. However, based on the stability data (pH, moisture contentment, total aerobic microbial counts [TAMC], total yeast and mold counts [TYMC] and Bacterial Endotoxin [BET]) over the shelf life of the new products, the lack of stability data for the ENDS comparison products is acceptable from a microbiology perspective.
- Furthermore, the applicant submitted a literature review to establish acceptable levels of microbial content in non-sterile inhalation solutions and endotoxin levels in sterile inhalation water solutions. The new products have microbial content and endotoxin content below FDA and USP guidelines established for nonsterile products and/or for medical products.

Per the toxicology review:

- The applicant provided comparisons between the new products and CC. The applicant used the average CC MSS concentration data from the peer-reviewed scientific literature to represent the CC category. The applicant's rationale for this comparison is based on the premise of reduction of risk of overall adverse health effects for adults who smoke CC and switch completely to the new products. The rationale and selection of average CC data is an appropriate representative of the

CC category because the studies were peer-reviewed, recently published, measured many of the same HPHCs, included CC that are currently on the market, and tested them using common puffing protocols (e.g., International Organization of Standardization [ISO], Health Canada Intense [HCI]) across the studies. An additional analysis by chemistry compared HPHC yields from aerosol from the new products to MSS concentration data from FDA50. Chemistry's analysis using FDA50 showed similar HPHC profiles (i.e., the same HPHCs, with similar concentrations) to HPHC concentrations from the applicant's comparison product, average CC MSS. Therefore, from a toxicological perspective the applicant's rationale for using CC as a comparison product is acceptable, and the use of average CC data from the published toxicology literature is an acceptable representative of the CC category.

- The applicant provided in vitro mutagenicity, cytotoxicity, and genotoxicity studies that used the Kentucky Reference 1R6F CC as a comparison product. Several studies comparing other Kentucky reference CC (e.g., 1R4F, 1R5F, 3R4F) to commercially-marketed CC have shown similar HPHC profiles, and similar toxicological effects for in vitro cytotoxicity and mutagenicity, and an in vivo 90-day inhalation study (Patskan et al., 2008; Roemer et al., 2004; Vu et al., 2015). Therefore, from a toxicological perspective, the applicant's rationale for using the Kentucky Reference 1R6F CC as a comparison product in the in vitro studies is adequate to represent HPHC content in a CC.
- The applicant compared HPHC yields from the new products to an ENDS comparison product, Vuse Alto Original with 5% nicotine, to assess the range of potential HPHC exposures among users of ENDS. The rationale for this comparison was that, like the NJOY ACE system, Vuse Alto is also a closed-system ENDS with a rechargeable battery and single-use pod that is filled by the manufacturer with nicotine salt-containing e-liquid. The applicant also stated that Vuse Alto flavors (e.g., Original, Menthol) and nicotine content (5% nicotine) are similar to the new products (Menthol; 2.4% and 5% nicotine). From a toxicological perspective, the applicant's rationale for using Vuse Alto Original 5% as a comparison product is acceptable and its similarities to the new products make it a useful ENDS comparison product.
- The applicant compared HPHC yields from the new products to other ENDS (i.e., cig-a-like, fixed pods, variable pods, fixed tanks, variable tanks) to assess the range of potential HPHC exposures among users of ENDS. The applicant used the average nicotine-adjusted aerosol concentration data from peer-reviewed scientific literature to represent the other ENDS category. The applicant stated that the rationale for using this comparison was to give insight into HPHC comparisons between the new products and other ENDS, and to allow for the consideration of possible HPHC exposures for non-users who may initiate use of the new products or other ENDS. From a toxicological perspective, the applicant's rationale for using average nicotine-adjusted HPHC levels from other ENDS as a comparison product is adequate because the comparison represents a variety of ENDS, which may be considered as alternatives to the new products or may be used in conjunction with the new products.

Per the medical review:

- The applicant used NJOY DAILY Rich Tobacco 4.5%, NJOY DAILY Rich Tobacco 6%, NJOY Loop Rich Tobacco 4.5%, JUUL Virginia Tobacco 5% and participants' usual brand (UB) CC as comparison products in the submitted clinical studies to collect data on adverse experiences (AE) and health effects. All ENDS comparison products

are in the same product category as the new products and contain generally similar amounts of nicotine. It is acceptable to compare ENDS to CC because CC provide AE and health effects data on products that represent the current tobacco market.

Per the social science review:

- The applicant-submitted studies included comparisons of the new products to CC. Based upon available data on perceptions and curiosity about and intentions to try the new products, the likely users of the new products will include adults who currently use CC.

Per the epidemiology review:

- The applicant's menthol-specific analysis of the NJOY User Study (see Section 3.4.) included adults who use CC. Based on the information provided, adults who currently use CC are among the intended user populations for these new products. Therefore, comparisons between the new products and CC may assist FDA's determination of whether permitting the marketing of the new products is APPH because adults who use CC are a likely user population.

Per the BCP review:

- The applicant used UB CC as the comparison product in one key clinical study that provided data on abuse liability, nicotine exposure, subjective effects, and puff topography. The data and rationale to support the applicant's chosen comparison product (UB CC) was appropriate for comparison to the new products because adults who smoke CC are one of the applicant's stated intended users of the new products and applicant-submitted survey data show that adults who smoke CC and adults who dually use CC and ENDS are likely to use the new products.
- The applicant used closed-system ENDS containing nicotine salt formulations (i.e., NJOY DAILY, Rich Tobacco; NJOY Extra, Rich Tobacco; NJOY Loop, Rich Tobacco; JUUL, Virginia Tobacco) as the comparison products in one key clinical study that provided data on abuse liability, nicotine exposure, subjective effects, and puff topography of NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review), which was bridged to PM0000617.PD1. All products used were of the same product category as the new products and contained generally similar amounts of nicotine. BCP determined that these comparison products were appropriate as adults who use ENDS are also the applicant's stated intended users, and likely to use the new products.

3.1.2. Synthesis

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

The applicant compared the new products with Vuse Alto ENDS (Original, Menthol, Rich Tobacco and Mixed Berry flavors) for engineering parameters. The applicant also provided comparison data for aerosol constituent concentrations between the new products and Vuse Alto Original with 5% nicotine, an ENDS in the same product category and subcategory that also contains nicotine salts. For in vitro mutagenicity, cytotoxicity, and genotoxicity studies, the applicant used the Kentucky Reference 1R6F CC as a comparison product.

In their clinical studies, the applicant used participants' UB CC and NJOY DAILY Rich Tobacco 4.5%, NJOY DAILY Rich Tobacco 6%, NJOY Loop Rich Tobacco 4.5%, and JUUL Virginia Tobacco 5% as comparison products to collect data on AE, health effects, abuse liability, nicotine exposure, subjective effects, and puff topography. All comparison ENDS were of the same product category as the new products and contained generally similar amounts of nicotine as PM0000617.PD1, although they differed in e-liquid flavor. Thus, the comparison products are also similar (except in nicotine concentration) to new product PM0000616.PD1. In their online survey studies on product perceptions, appeal, and behavioral intentions, the applicant compared the new products to CC as well as to other ENDS.

The applicant used peer-reviewed scientific literature to calculate the average CC MSS concentration and the average nicotine-adjusted aerosol concentration from other ENDS (i.e., cig-a-like, fixed pods, variable pods, fixed tanks, variable tanks). These data were compared to that of the new products for HPHC comparisons between the new products and comparison products.

As TPL, I agree with engineering, chemistry, microbiology, toxicology, medical, social science, epidemiology, medical, and BCP conclusions that CC and other ENDS are appropriate as comparison products because the applicant's stated intention is to market the new products to adults who currently use tobacco products, including those who currently smoke CC and those who currently use ENDS. I also agree that the applicant provided adequate data to support the comparison between the new products and the chosen comparison products. For the purposes of the overall APPH assessment, I consider CC to be the primary comparison products since the applicant's studies demonstrate that their products are primarily used by adults who smoke CC (or use both CC and ENDS) and because the largest public health benefit associated with the new products is among adults who smoke CC and completely switch to ENDS or use the new products to quit all tobacco products. In addition, because the new products are flavored ENDS, they are also compared to tobacco-flavored ENDS to determine whether the products are associated with sufficient adult benefit, as discussed in Section 1.1.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

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

3.2.1.1. Product design and composition

Per the engineering review:

- The applicant submitted the design parameters of the new products. The applicant provided the target specifications and upper and lower range limits for all of the design parameters for the new products.
- The information submitted regarding the heating element of the NJOY ACE PODS is acceptable from an engineering perspective.

Per the chemistry review:

- The applicant provided sufficient details of the single chemical ingredients for all the e-liquids and structural materials to characterize the new products' composition. PM0000616.PD1 contains (b) (4) w/w% nicotine and (b)(4) (b) (4) and (b) (4) (b) (4) PM0000617.PD1 contains (b) w/w% nicotine and (b) (4) or (b) (4) (b) (4) , (b) (4) (b) (4) and (b) (4) These e-liquids contain nicotine salts. The information submitted regarding the new products' composition is acceptable from a chemistry perspective.

Per the microbiology review:

- The new products contain humectants (b) (4) that may impact microbial activity during the new products' proposed shelf life. However, microbiology stability data discussed in Section 3.2.1.3. addresses these concerns, indicating that the new products have low risk for microbial growth.
- The new products have microbial content and endotoxin content below FDA and USP guidelines.
- A literature review was provided to establish acceptable levels of microbial content in non-sterile inhalation solutions and endotoxin levels in sterile inhalation water solutions.

3.2.1.2. Manufacturing

Per the engineering review:

- The applicant submitted the manufacturing process for the new products, including nicotine manufacturing, (b) (4) manufacturing, bulk e-liquid manufacturing, and finished product (device [not subject to this PMTA review], PM0000616.PD1, and PM0000617.PD1) manufacturing and packaging. The applicant also provided the manufacturing processes and control strategies for the NJOY ACE PODS as well as the validation process for the NJOY ACE PODS. The information submitted regarding the manufacturing process is acceptable from an engineering perspective.

Per the chemistry review:

- The applicant provided manufacturing procedures and quality control measures for both e-liquid products to ensure the new products are manufactured in a consistent manner that minimizes variability in product quality.
- The applicant provided representative ingredient Certificate of Analysis, raw ingredient quality control test results, batch verification, liquid properties, pH, and constituent measurements. All the provided data are within the acceptance criteria indicating product batch consistency. Therefore, the information submitted regarding product manufacturing is acceptable from a chemistry perspective.

Per the microbiology review:

- The bulk e-liquid manufacturer, (b)(4) conducts e-liquid blending and filling operations in an International Organization for Standardization (ISO) Class 8 clean room.
- (b)(4) is an A2LA ISO 17025:2005 certified laboratory that performs release testing on the bulk e-liquids used in the new products.
- The information submitted regarding the manufacturing of the new products is acceptable from a microbiology perspective.

3.2.1.3. Product stability

Per the chemistry review:

- The applicant seeks a (b) (4) shelf life for the finished new tobacco products of PM0000616.PD1 and PM0000617.PD1. However, the applicant provided only (b) (4) of finished product stability data under ambient conditions (b) (4) % relative humidity [RH]) and (b) (4) of stability data under accelerated conditions (b) (4) RH) without statistical analysis to extrapolate to ambient storage time of at least (b) (4). The data provided support a (b) (4) product shelf life from the chemistry perspective.
- The applicant requested a (b) (4) bulk e-liquid shelf life for PM0000616.PD1 and PM0000617.PD2, but only provided bulk e-liquid stability data for NJOY ACE POD Rich Tobacco 5% (not subject to this PMTA review). However, based on the (b) (4) bulk e-liquid stability study at ambient conditions ((b) (4) RH), comprehensive stability studies for the two new finished e-liquid products (PM0000616.PD1, PM0000617.PD1), e-liquid formulation similarity, and comparable photostability results for the two new products, bridging the (b) (4) bulk e-liquid shelf life from NJOY ACE POD Rich Tobacco 5% (not subject to this PMTA review) to the bulk e-liquid shelf life of the new products (PM0000616.PD1, PM0000617.PD1) is adequate from a chemistry perspective.

Per the microbiology review:

- Microbial stability data are necessary for the proposed shelf life as bacterial communities change as a function of storage time (Chopyk et al., 2017; Djordjevic, 1993). Increased microbial growth over time can impact stability of the product and may result in an increased risk to public health as the product sits in storage. The applicant provided microbial data (TAMC and TYMC) over (b) (4) of shelf life for the new products. Over shelf life, the TAMC and TYMC were not detected or <1 colony forming unit (cfu)/mL. The stability data for TAMC and TYMC are acceptable from a microbiology perspective.
- The applicant provided BET measured at the beginning of shelf life. The new products contain BET levels below the method detection limit of (b) (4) EU/mL. Based on the TAMC and TYMC data, further increases in BET beyond time zero are unlikely. Therefore, the lack of BET beyond time zero of shelf life of the new products is acceptable from a microbiology perspective.
- pH and moisture content data over (b) (4) of shelf life were provided for the new products. pH and moisture content of these new products are within the design specifications established by the applicant. The pH values and the moisture changes over shelf life could potentially affect microbial growth but based on the TAMC and total yeast and mold count TYMC data discussed above, the pH values and the moisture changes observed in the new products are acceptable from a microbiology perspective.

3.2.1.4. Product test data

Per the engineering review:

- The applicant submitted test data for all the required design parameters and the test data adequately demonstrate new product consistency.

Per the chemistry review:

- All analytical methods and method validation are sufficient to support this review.
- Most constituents' aerosol yields are lower in the new products compared to the CC and Vuse Alto Original 5% nicotine comparison products. The constituents with higher yields are discussed in Section 3.5.1.
- The applicant also provided HPHC yield data for the product puff lifecycle for PM0000617.PD1. Although there is some HPHC variability between puff blocks, the results show no significant trends of increasing aerosol HPHC concentrations over the product puff lifecycle. Moreover, due to similarity in e-liquid formulations and similar aerosol HPHC profiles between the 2.4% and 5% nicotine e-liquids (except for the higher nicotine concentrations), the risk of higher levels of aerosol HPHCs during product puff lifecycle of the 2.4% nicotine e-liquids (PM0000616.PD1) is unlikely to be meaningfully different from the data for the 5% nicotine e-liquids (PM0000617.PD1) and is therefore acceptable from a chemistry perspective.

3.2.2. Synthesis

As TPL, I agree with the engineering conclusions that these PMTAs contain sufficient information on the target specifications, upper and lower range limits, manufacturing processes, and validation process for all the new products' design parameters. The applicant's test data adequately demonstrates that the new products meet the manufacturer's specifications and are produced consistently.

As TPL, I agree with the chemistry conclusions that these PMTAs contain sufficient ingredient information to characterize the new products' composition. In addition, the applicant implemented manufacturing procedures and quality control measures for all e-liquids to ensure the new products are manufactured in a consistent manner. The NJOY ACE device (not subject to this PMTA review) is a closed ENDS with no adjustable parameters. It uses sealed, pre-filled, and non-refillable NJOY ACE pods (e.g., PM0000616.PD1 and PM0000617.PD1). HPHC data show that the new products' aerosols have fewer HPHCs than CC MSS and many of the HPHCs present in the aerosols have comparatively lower potencies (i.e., lower magnitude or severity of toxicological effect at a given dose or exposure level) than those present in CC smoke (see Section 3.5.1.).

The applicant proposed a (b) (4) shelf life for the e-liquids, but only provided (b) (4) of finished product chemical stability data under ambient conditions. In addition, the applicant provided (b) (4) of microbial stability data for the e-liquids in PM0000616.PD1 and PM0000617.PD1. Because the microbial stability data is acceptable and indicates that the new products are low risk for microbial growth over the period tested and because there are no other stability concerns, the lack of chemical stability data through (b) (4) do not preclude an APPH finding for the new products. Therefore, although the applicant proposed a (b) (4) shelf life, a marketing authorization for PM0000616.PD1 and PM0000617.PD1 should note that the submitted stability data support that the new products will remain stable for (b) (4).

3.3. ABUSE LIABILITY

The applicant submitted two clinical study reports and two literature reviews to address outcomes related to abuse liability. Clinical study "m5-2-1-01-study-npk-019-accc" assessed abuse liability

measures (including nicotine pharmacokinetics [PK], puff topography, and subjective effects) associated with the use of PM0000617.PD1 among adults who are inexperienced with ENDS use. Clinical study "m5-2-2-05-study-nj[1]007-lact" assessed nicotine PK and pharmacodynamics (PD), behavioral, and subjective effects of NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) in adults who are experienced with ENDS use.

3.3.1. Discipline key findings

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

3.3.1.1. Current tobacco users

- 'Abuse liability' refers to the ability of the product to promote continued use, and the development of addiction and dependence. This can be relevant to determining the likelihood that addicted users of one nicotine product would switch to another. For example, if a new tobacco product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted. Abuse liability evaluations include nicotine PK assessments and consider the addictiveness and abuse potential of the tobacco products and the exposure to nicotine during product use.
- The new products contain nicotine salts and have nicotine concentrations that are in the middle (2.4%) or high (5%) range of ENDS currently sold in the U.S. (Romberg et al., 2019). Higher nicotine concentration has been associated with higher nicotine exposure (Goniewicz et al., 2019; Hajek et al., 2020), which suggests the new products may have higher abuse liability than ENDS with lower nicotine concentration. Further, the presence of nicotine salts can reduce harshness accompanying high nicotine concentrations, which would make the new products more palatable (Leventhal et al., 2021) and increase abuse liability further.
- The applicant-submitted clinical study among adults inexperienced with ENDS demonstrates that the abuse liability (i.e., nicotine exposure, subjective ratings of desirable effects) of NJOY ACE POD Menthol 5% (PM0000617.PD1) is comparable to NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review). Thus, in this study, the menthol flavor did not have a significant impact on abuse liability.
    - Among adults inexperienced with ENDS, the nicotine exposure associated with PM0000617.PD1 is significantly lower than UB CC. However, nicotine exposure may be underestimated by short use duration (i.e., 10 minutes) because ENDS use that extends beyond 10 minutes of use (e.g., 30 to 90 minutes of ad libitum use) may increase nicotine exposure to levels that can meet or exceed those of a CC (Dawkins et al., 2016; Farsalinos et al., 2015; Hiler et al., 2017; Spindle et al., 2017).
    - Among adults inexperienced with ENDS, UB CC produced comparable reductions in Urge to Smoke and Urge to Use Study Product as PM0000617.PD1. CC produced higher scores for Satisfaction, Psychological Reward, Relief, Aversion (e.g., nausea, dizziness), Liking, and Concern for Dependency scores than PM0000617.PD1.
    - Adults who smoke CC who are inexperienced with ENDS took similar individual puff durations and puff volumes of PM0000617.PD1 and their UB CC; adults who smoke CC took longer total puff durations when using

PM0000617.PD1 compared to smoking CC. Compared with adults who smoke CC and are inexperienced with ENDS, adults who are experienced with ENDS may take significantly larger/longer puffs and thereby obtain more nicotine from the same ENDS (Farsalinos et al., 2015; Hiler et al., 2017).

- New product PM0000616.PD1 was not tested in the applicant-submitted clinical studies. Data from adults inexperienced with ENDS who used other similar products (e.g., PM0000617.PD1 (b)(4) [redacted] however, suggest that the abuse liability of PM0000616.PD1 will be lower or comparable to CC among adults inexperienced with ENDS.
- Although the applicant-submitted studies did not assess the abuse liability of the new products (PM0000616.PD1, PM0000617.PD1) among adults who are experienced with ENDS, the applicant provided scientific rationale and justification to inform this evaluation. Specifically, the applicant provided product-specific information to inform the abuse liability of NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) in adults with and without ENDS experience. The applicant also derived a multiplication factor from these values and then applied that factor to nicotine PK values measured from products that were only evaluated among inexperienced users to estimate PK values that would be reasonably be expected among experienced users. Using this approach, new product PM0000617.PD1 would be associated with lower indices of abuse liability (i.e., lower nicotine PK) than NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review), although this relationship was not evaluated statistically. BCP further considered the relationship between NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) and new product PM0000617.PD1 in adults without ENDS experience to inform the new products' abuse liability among adults who are experienced with ENDS (a subset of the current tobacco user population). Because new product PM0000617.PD1 was associated with lower indices of abuse liability (i.e., lower nicotine PK) than NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) among adults without ENDS experience, BCP expects NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) and new product PM0000617.PD1 will have comparable abuse liability among adults who are experienced with ENDS. In the applicant-submitted study among adults who are experienced with ENDS, NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) demonstrated abuse liability comparable to what is typically seen for CC. BCP determined that the totality of information is reasonable to support bridging to new product PM0000617.PD1 and BCP estimates that the abuse liability of new product PM0000617.PD1 will also be comparable to CC in adults who are experienced with ENDS.
- Based on evidence from the applicant-submitted studies, BCP concludes that the abuse liability of PM0000617.PD1 is lower than or comparable to CC for adults inexperienced with ENDS, and comparable to CC for adults experienced with ENDS.
- New product PM0000616.PD1 was not tested in any of the applicant-submitted clinical studies. Data evaluating the abuse liability of NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) among adults experienced with ENDS were not adequately bridged to PM0000616.PD1. As such, there are insufficient data to make

conclusions about the abuse liability of PM0000616.PD1 for adults experienced with ENDS.

- The menthol flavor in the new products may facilitate more frequent use compared to CC, thereby increasing nicotine exposure and increasing the likelihood of progressing to regular use of nicotine and subsequent dependence. While adults who smoke CC took significantly more puffs from PM0000617.PD1 than from UB CC in an applicant-submitted study, nicotine exposure from PM0000617.PD1 did not exceed UB CC among adults who smoke CC and who are inexperienced with ENDS. Furthermore, the applicant submitted sufficient evidence and rationale to suggest that the menthol flavor in the new products does not impact the new products' abuse liability compared to the tobacco-flavored comparison products.
- Published literature shows that e-liquids with nicotine salts can reach or exceed nicotine exposures associated with CC (Goniewicz et al., 2019; Hajek et al., 2020) and other ENDS with free-base nicotine formulations (Boykan et al., 2019; O'Connell et al., 2019; Yingst et al., 2019). However, based on data from the applicant-submitted clinical studies, the abuse liability of the new products is lower than or comparable to CC among adults inexperienced with ENDS and the abuse liability of PM0000617.PD1 is comparable to CC among adults experienced with ENDS. Thus, there is little concern of greater nicotine exposure (addiction potential) than CC. Although there was insufficient information to determine the nicotine exposure of new product PM0000616.PD1 among adults who are experienced with ENDS use, the nicotine exposure of PM0000616.PD1 is not expected to exceed that of a CC in this population given its lower nicotine concentration relative to PM0000617.PD1 (5% nicotine). As such, PM0000616.PD1 (2.4% nicotine) would be expected to be associated with similar, or slightly lower, nicotine exposure compared to PM0000617.PD1 (5% nicotine) and CC.

3.3.2. Synthesis

The applicant provided product-specific information to inform the abuse liability of PM0000617.PD1 in adults who are inexperienced with ENDS use and NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) in adults with and without ENDS experience. Although product-specific information was not provided for PM0000617.PD1 among adults who are experienced with ENDS, BCP utilized the relationship between data from NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) and new product PM0000617.PD1 in adults who are inexperienced with ENDS as well as the relationship between these different populations with NJOY ACE POD Classic Tobacco 5% (not subject to this PMTA review) to inform the abuse liability in PM0000617.PD1 in adults experienced with ENDS. Together, the applicant's clinical studies and the appropriate bridging approaches suggest that among adults who are inexperienced with ENDS use, new product PM0000617.PD1 has lower abuse liability than CC. Furthermore, among adults who are experienced with ENDS, PM0000617.PD1 has a similar abuse liability as CC.

Although the applicant-submitted data did not assess the abuse liability of PM0000616.PD1 among adults who are inexperienced with ENDS use, I agree with the BCP review conclusions that the information submitted in the PMTAs suggests that the abuse liability data and conclusions from PM0000617.PD1 can be bridged to support conclusions in

PM0000616.PD1 among adults who are inexperienced with ENDS use. Thus, per the BCP review, the applicant-submitted data demonstrate that, among adults who are inexperienced with ENDS use, the new products are associated with a lower, or comparable, abuse liability than CC. An adult who is inexperienced with ENDS use or an adult who does not use tobacco products may not initially achieve maximum plasma nicotine concentrations similar to CC. However, among adults who are experienced with ENDS use, the submitted data suggest that new product PM0000617.PD1 has a similar abuse liability as CC. Although the BCP review concluded there was insufficient information to determine the abuse liability of new product PM0000616.PD1 among adults who are experienced with ENDS use, it is important to note that the abuse liability of PM0000616.PD1 is not expected to exceed that of a CC in this population. Given its lower nicotine concentration relative to PM0000617.PD1 (5% nicotine), PM0000616.PD1 (2.4% nicotine) would be expected to have a similar, or slightly lower, abuse liability than PM0000617.PD1 (5% nicotine) and CC. Therefore, as TPL, I conclude that the applicant provided sufficient information to determine that the abuse liability of PM0000616.PD1 will not exceed that of CC among adults who are experienced with ENDS use.

As discussed further in Section 3.4.2., the literature suggests that flavored ENDS are rated as more satisfying than tobacco-flavored ENDS among adults, adults will work harder for and take more puffs of flavored ENDS compared to tobacco-flavored ENDS, and flavors can increase nicotine exposure by potentially influencing the reinforcing effects of e-liquids. However, the BCP review concluded that abuse liability (e.g., subjective experience, nicotine exposure) was similar between the NJOY ACE POD Menthol 5% (PM0000617.PD1) and Classic Tobacco 5% (not subject to this PMTA review) ENDS (although the study was not statistically powered to evaluate differences between ENDS). Thus, these product-specific data suggest that the new products' menthol flavor does not significantly impact the abuse liability, and that the new products' abuse liability does not exceed that of a CC.

Both new products have a nicotine salt formulation which makes ENDS use more palatable, facilitates ease of use, and is often associated with high (and comparable to CC) nicotine exposures in the literature. As discussed further in Section 3.4.2., the comparable abuse liability to CC and the nicotine salt formulation of the new products also suggest that the new products may serve as a suitable substitute to CC among adults who smoke CC and want to quit smoking; thus, the new products may facilitate complete or partial switching from CC.

3.4. USER POPULATIONS

The BCP review relied on data from two applicant-submitted clinical studies (see Section 3.3.) to inform these outcomes. The epidemiology and social science reviews relied on applicant-submitted studies, including two adult and five youth observational studies, to inform user population outcomes.

The applicant-submitted "A Prospective Longitudinal Online Survey Evaluating the Effectiveness of NJOY ACE Electronic Nicotine Delivery System (ENDS) on Reduction, Abstinence, and Switching from Conventional Cigarette Use in a National Purposive Sample of U.S. Adults Aged 21 Years and Over" is herein referred to as the "NJOY User Study" and evaluated complete

switching behaviors among adults who use NJOY ACE ENDS over three months. The applicant also submitted an amendment "Primary and Secondary (Six-Month) Outcomes Report and Additional Analyses (Appendix A) Showing the Role of NJOY ACE and Flavors on Complete Switching" with six month outcome data and "Appendix A – Additional Flavor Analysis" that compared outcome data between tobacco- and other flavored products. The applicant also submitted an amendment "Amendment Report- Menthol-flavored NJOY ACE" that included additional analyses of the outcome data comparing tobacco- and menthol-flavored products. Switching outcomes were evaluated in the epidemiology review. Perceptions about harmfulness and addictiveness were evaluated in the social science review.

"An Online Survey Assessment of Prevalence, Perceptions, and Intentions to Use NJOY ENDS in a National Probability Sample of US Adult Current, Former, and Never Smokers of Conventional Cigarettes" and its supplemental analysis is herein referred to as the "Adult Prevalence Study" and assessed perception, prevalence of use, and intentions to use NJOY products in adults. These outcomes were evaluated in the epidemiology and social science reviews.

"An Online Survey of US Adolescents' Perceptions of the Risks and Intentions to Use NJOY Vapor Products" is herein referred to as the "2021-2022 Youth Perceptions Study" and evaluated prevalence, curiosity, and intent to use the new products. These outcomes were evaluated in the epidemiology and social science reviews.

"A Cross-Sectional Online Survey Assessment of the Prevalence of Use of Conventional Cigarettes, NJOY Vapor Products and Other E-Cigarettes in a National Probability Sample of US Adolescents Aged 13-17 Years (conducted Jan/Feb 2019)" is herein referred to as the "Youth Prevalence Study 1". This study was fielded in January and February 2019 and assessed U.S. adolescents' prevalence, perceptions of harm, addictiveness, curiosity, and intent to use NJOY products. These outcomes were evaluated in the epidemiology and social science reviews.

"A Cross-Sectional Online Survey Assessment of the Prevalence of Use of Conventional Cigarettes, NJOY Vapor Products and Other E-Cigarettes in a National Probability Sample of US Adolescents Aged 13-17 Years (conducted October/November 2019)" is herein referred to as "Youth Prevalence Study 2". This study was fielded in October and November 2019 and assessed U.S. adolescents' prevalence, perceptions of harm, addictiveness, curiosity, and intent to use NJOY products. These outcomes were evaluated in the epidemiology and social science reviews.

The applicant also submitted results from two independent studies (b) (4) [redacted] Study Wave #1 and Wave #2) which collected youth prevalence data by brand and flavor in 2021 and 2022. These data were evaluated in the epidemiology review.

The applicant-submitted "Label-Comprehension/Self-selection and Instructions-for-Use Comprehension (Usability) Studies of the NJOY ACE and NJOY DAILY Vaping Devices" assessed consumers' ability to understand product labeling. This outcome was evaluated in the social science review.

3.4.1. Discipline key findings

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

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

Per the social science, epidemiology, and BCP reviews:

- The applicant stated that the intended user population is "current adult users of nicotine-containing products who cannot or choose not to discontinue use of nicotine, particularly current CC users and ENDS users."

3.4.1.2. Current tobacco users

Per the social science review:

- Applicant-submitted data from the Adult Prevalence Study demonstrated that curiosity about using the new products was low among current adult smokers (5%) but was greater than curiosity among former smokers (2%) and never smokers (1%). There was no variation in curiosity about the new menthol-flavored NJOY ACE products compared to the tobacco-flavored NJOY ACE products (not subject to this PMTA review). A similar proportion of current adult smokers were curious about the Classic Tobacco and Rich Tobacco NJOY ACE flavors (10-14%; not subject to this PMTA review) compared to the Menthol-flavored (7%) new products. However, there are significant limitations related to adult curiosity in ENDS. Curiosity is best understood as an indicator of youth initiation of tobacco products. Seminal research on the role and measurement of curiosity established curiosity as an independent predictor of future CC use among adolescents (Pierce et al., 2005). Recent research demonstrates an association between youth curiosity and ENDS initiation (Evans-Polce et al., 2018; Han et al., 2022; Pierce et al., 2005). Curiosity is less informative for understanding adult use of ENDS without additional measures of motivations for use, as there is no significant evidence to suggest behavioral outcomes associated with adult endorsement of curiosity to try ENDS.
- Applicant-submitted data from the Adult Prevalence Study demonstrated that intention to try the new products in the next year was low among adult current smokers (4%) but was greater than intention to try among former smokers (1%) and never smokers (1%). There was no variation in intention to try flavored NJOY ACE products relative to the tobacco-flavored NJOY ACE products (not subject to this PMTA review). Similar proportions of current adult smokers intended to try Classic Tobacco 5% (11.1%), Classic Tobacco 2.4% (5.9%) and Rich Tobacco 5% (7.8%) flavors (not subject to this PMTA review) compared to the Menthol 5% (10.2%) and Menthol 2.4% (4.7%) flavored new products.
- In summary, based on ratings of curiosity and intentions to use, the applicant's data suggest that current adult smokers do not differentially prefer Menthol-flavored NJOY ACE ENDS compared to the tobacco-flavored NJOY ACE ENDS.

Per the epidemiology review:

- The prevalence of NJOY ACE products use in general was approximately 0.4% among adults in the Adult Prevalence Study. The proportion of adult CC users who reported use of NJOY products was 2.3% and for NJOY ACE products it was 1.6%. Overall, 4.1% of respondents reported using any ENDS, slightly higher than, but similar to, estimated national prevalence of adult ENDS use in the 2018 National Health Interview Survey (3.2%) (Bao et al., 2020). Similar to the published literature, more current and former smokers (compared to never tobacco users) used ENDS generally and the new products specifically. The applicant reported that most ENDS initiation in adults occurred after CC initiation, and current or former CC smokers

were more likely to initiate ENDS use than never tobacco users. However, some of these outcomes could be due to cohort effects or product generational differences in the ENDS marketplace.

- In the applicant's NJOY User Study, (b)(4)
- (b)(4)
- These results are robust across different model specifications, as they demonstrate that, after adjusting for a wide range of covariates as well as using ITT methods to account for potential bias associated with loss-to-follow-up, Menthol as an initial flavor used was significantly associated with higher rates of past 30-day smoking cessation than Classic Tobacco (not subject to this PMTA review) at both 3 and 6 months, while Menthol use at the time of switching was significantly associated with higher rates of past 30-day smoking cessation than Classic Tobacco (not subject to this PMTA review) at 6 months.
- Some study limitations are noted to inform interpretation of the results such as: not studying PM0000616.PD1; not reporting participants' menthol CC status; and the likely inflated absolute switching rate due to the study population. However, these limitations do not undermine the validity of the research question of interest focused on the relative switching rates between the menthol-flavored new products and the tobacco-flavored comparison ENDS.
- The applicant's findings and additional analyses conducted by Statistics demonstrate a statistically significant added benefit of using Menthol-flavored NJOY ACE compared to Classic Tobacco flavor (not subject to this PMTA review) in achieving past 30-day CC smoking cessation (see Table 3 below).

Table 3. Past 30 Day PPA and Adjusted Odds Ratios for Menthol versus Classic Tobacco

Per Protocol Analysis (PP)									
Primary Predictor	**Flavor**	**3-month**				**6-month**			
		% abstain	**95% CI for % abstain**	**aOR**	**p-value**	**% abstain**	**95% CI for % abstain**	**aOR**	**p-value**
Initial Flavor at Baseline	Menthol	24.2%*	20.6%-27.8%	1.473	0.0194	38.9%*	34.5%-43.3%	1.351	0.0524
	Classic Tobacco	16.80%	13.6%-20.0%	ref	--	30.30%	26.1%-34.6%	ref	--
Most Used Flavor at Baseline	Menthol	24.7%*	20.9%-28.5%	1.497	0.0254	35.90%	31.3%-40.5%	1.212	0.259
	Classic Tobacco	17.50%	13.9%-21.2%	ref	--	30.70%	25.9%-35.4%	ref	--
Flavor at Time of Switching	Menthol	25.5%*	21.5%-29.5%	1.289	0.1703	39.0%*	34.5%-43.6%	1.328	0.0842
	Classic Tobacco	18.30%	14.5%-22.1%	ref	-	28.60%	24.1%-33.0%	ref	--
Intention to Treat Analysis (ITT)									
Primary Predictor	**Flavor**	**3-month**				**6-month**			
		% abstain	**95% CI for % abstain**	**aOR**	**p-value**	**% abstain**	**95% CI for % abstain**	**aOR**	**p-value**
Initial Flavor at Baseline	Menthol	17.5%*	14.8%-20.2%	1.563	0.0051	26.6%*	23.4%-29.7%	1.414	**0.0091**
	Classic Tobacco	11.30%	9.1%-13.5%	ref	--	19.30%	16.6%-22.1%	ref	--
Most Used Flavor at Baseline	Menthol	17.5%*	14.6%-20.3%	1.393	0.0561	24.20%	21.1%-27.4%	1.143	0.3603
	Rich Tobacco	13.00%	10.2%-15.7%	ref	--	21.60%	18.2%-25.0%	ref	--
Flavor at Time of Switching	Menthol	17.2%*	14.3%-20.0%	1.379	0.0869	27.1%*	23.9%-30.3%	1.506	0.0071
	Classic Tobacco	12.00%	9.4%-14.6%	ref	--	19.30%	16.3%-22.2%	ref	--
Notes: * indicates p<0.05.									

- The applicant stated that the NJOY User Study assessed PM0000617.PD1 only; thus, the study does not directly inform switching behaviors associated with PM0000616.PD1.
- Epidemiology assessed the study for data quality and the extent of added behavioral benefit of the menthol-flavored new products compared to tobacco-flavored ENDS and determined it was of sufficient quality, when considering study limitations and strengths. Furthermore, epidemiology concludes the absolute switching rate (17-25%) was substantial and the adjusted odds ratio (aOR=1.473) for relative switching comparing menthol- to tobacco-flavored ENDS was moderate. The added benefit to adults can be characterized as highly beneficial.
- A large number of NJOY ACE ENDS users (likely >40%) will become dual users with CC, similar to patterns of dual use reported in the literature (43.5%-54.1%) (Coleman et al., 2019; Piper et al., 2020; Stanton et al., 2020). The NJOY User Study demonstrates a substantial reduction in CC smoking among smokers who also use

NJOY ACE ENDS and evidence from the published literature on switching behavior demonstrates that switching from CC to ENDS does occur among a small proportion of users—typically through a period of dual use (Coleman et al., 2019; Piper et al., 2020; Stanton et al., 2020).

- Published literature also currently suggests that many adult dual users will discontinue ENDS use over time and only a few will transition to exclusive ENDS use-- although some may discontinue use of both products (Coleman et al., 2019; Osibogun et al., 2020; Piper et al., 2020; Stanton et al., 2020).

Per the BCP review:

- Among adults inexperienced with ENDS, abuse liability and nicotine exposures associated with the new products are lower than or comparable to CC.
- Among adults experienced with ENDS, the abuse liability and nicotine exposures associated with PM0000617.PD1 may be comparable to CC.
- Based on the applicant-submitted abuse liability data, adults who smoke CC who are inexperienced with ENDS will likely not switch completely to the new products because of their lower abuse liability and nicotine exposure relative to CC. Some adults who smoke CC will likely try the new products but discontinue their use and resume exclusive CC use (which are rated higher in terms of liking and satisfaction), while others may continue using the new products in addition to maintaining CC use (i.e., dual use).
- There are no product-specific abuse liability data for the new products among adults experienced with ENDS. However, data from an applicant-submitted study on NJOY ACE PODS Classic Tobacco 5% can be bridged to PM0000617.PD1 and suggests that some adults who smoke CC who become experienced with PM0000617.PD1 may find it an adequate substitute for CC and switch completely. Those who find PM0000617.PD1 to be an adequate substitute to CC, however, will likely also maintain a comparable level of dependence on the new product as they did with CC.

3.4.1.3. Tobacco non-users (including youth)

Per the social science review:

- Overall, reported curiosity and intention to try NJOY ACE products was low (<2%) among adult never and former smokers. These data suggest that former and never smoking adults are not interested in trying the new products.
- There was not a meaningful difference in curiosity or behavioral intentions among youth or adults for the Menthol-flavored NJOY ACE new products compared to the tobacco-flavored NJOY ACE products (not subject to this PMTA review).
    - In the 2021-2022 Youth Perceptions Study, a similar proportion of youth overall endorsed curiosity in menthol-flavored (Menthol 2.4% = (b) (4) and Menthol 5% = (b) (4) and tobacco-flavored (not subject to this PMTA review) NJOY ACE (Classic Tobacco 2.4% = (b) (4) Classic Tobacco 5% = (b) (4) Rich Tobacco 5% = (b) (4) products. Differences in curiosity were not statistically significant.
    - A similar proportion of youth overall reported intent to try menthol-flavored (Menthol 2.4% = (b) (4) and Menthol 5% = (b) (4) and tobacco-flavored (not subject to this PMTA review) NJOY ACE (Classic Tobacco 2.4% = (b) (4) Classic Tobacco 5% = (b) (4) Rich Tobacco 5% = (b) (4) products.

Differences in intentions to try the Menthol and Rich Tobacco (not subject to this PMTA review) flavored products were not statistically significant.

- There is an abundance of literature about precursors to use of flavored ENDS, in general; however, the literature does not separate findings for menthol from flavors such as dessert and fruit, making it difficult to draw conclusions regarding youth perceptions and appeal of menthol-flavored ENDS, in particular.
- The literature on precursors to use of menthol-flavored ENDS among youth is sparse. Of the two studies identified with menthol-specific precursors to use data, adolescents demonstrate a slight preference for menthol- versus tobacco-flavored ENDS. One study found that adolescents were more likely to report interest in trying an ENDS offered by a friend if it were fruit-flavored (12.8%), candy-flavored (9.3%), or menthol-flavored (8.3%) compared with tobacco-flavored (2.2%) ENDS (Pepper et al., 2016). Another study of youth and adults found that adolescents slightly preferred mint- (9.1%) or menthol- (9.8%) compared to tobacco- (4.8%) flavored ENDS; however, these differences were not statistically significant (Morean et al., 2018).
- According to NYTS 2023 data, among youth who currently use ENDS, 90.3% of high school students and 87.1% of middle school students reported using a flavored ENDS (Birdsey et al., 2023). Fruit- (63.4%), candy - (35.0%), mint- (27.8%), and menthol- (20.1%) flavor categories were commonly reported among youth who were current ENDS users; 6.4% of youth reported using tobacco-flavored ENDS. (Birdsey et al., 2023). Overall, the literature substantiates that pre-filled cartridge ENDS in non-tobacco flavors, including menthol, pose risks to youth. Specifically, the scientific evidence demonstrates that menthol-flavored ENDS pose a risk of youth appeal. Importantly, youth use of menthol ENDS is greater than tobacco flavor, but lower than other flavors such as candy, desserts, and sweets.
- Among youth ENDS users, cartridge and pod-based products (like the new products) are the second most commonly used device type (high school = 16.0%; middle school = 16.7%) (Birdsey et al., 2023), and therefore new products PM0000616.PD1 and PM000617.PD1 (independent of e-liquid flavor) may pose a moderate risk to youth.

Per the epidemiology review:

- The applicant submitted results from their (b) (4), which is two waves of a nationally representative cross-sectional survey of U.S. youth aged 13 to 17 years collected in 2021 and 2022. The applicant finds a low prevalence of youth use of ENDS overall in their (b) (4) Wave #1 (past 30-day prevalence: 4.92%) and Wave #2 (past 30-day prevalence: 6.73%). The applicant also finds a low prevalence of NJOY ENDS use among adolescents (past 30-day prevalence was 0.49% in Wave #1 and 0.42% in Wave #2 for all NJOY ENDS) and NJOY ACE ENDS use among adolescents (past 30-day prevalence was 0.36% in Wave #1 and 0.35% in Wave #2). These estimates, however, are lower than estimates from the literature from the same time period, likely due to differences in survey methodology, including sampling design and data collection procedures. The (b) (4) Study Wave #1 and Wave #2 had small sample sizes and thus were not able to provide reliable prevalence estimates of menthol-flavored NJOY ACE use among youth. Moreover, the (b) (4) Study may be outdated. As such, the conclusions from the applicant's (b) (4) Study should be interpreted with caution. The most recent data from the 2023 NYTS show

that NJOY was the 10th most-reported brand used in the past 30 days (i.e., 7.5% of current ENDS users) among middle and high school students (Birdsey et al., 2023).

- Close to 90% of youth currently using ENDS reported using flavored ENDS in 2023 NYTS, and 21.4% of these youth reported use of menthol-flavored ENDS (internal FDA analyses).
- According to internal analysis of the most recent data from the PATH Study (2021-2023), among youth (aged 12-17 years) who reported using ENDS in the past 30 days, the prevalence of exclusive mint/menthol use showed no statistically significant change between Wave 6 (17.93%) and Wave 7 (15.31%).
- Prevalence data in the literature suggest flavored ENDS are popular across all age groups, especially among youth and young adults. While NYTS data on the use of flavored ENDS by brand is not available, analysis of the 2023 NYTS shows that the majority of high school and middle school current ENDS users reported use of flavored ENDS (89.4%) (Birdsey et al., 2023). In Wave 3 (2015-2016) of the Population Assessment of Tobacco and Health (PATH) Study, among past 30-day youth ENDS users, menthol/mint ENDS flavors were more prevalent than tobacco ENDS flavors (10.8% versus 5.1%) (Schneller et al., 2019). Therefore, the menthol-flavored NJOY ACE products may pose risks for youth initiation.
- The applicant's 2021-2022 Youth Perceptions Study suggests that among youth who reported ever using ENDS (n=1,070), 18.0% started with tobacco-flavored ENDS, 41.5% started with menthol or mint, and 40.5% started with "something other" than tobacco or mint/menthol flavors. Among youth who reported ever using NJOY ACE ENDS (n=440), 14.7% reported starting with Classic Tobacco (not subject to this PMTA review), 39.8% reported starting with Blueberry or Watermelon (not subject to this PMTA review) flavor, and 36.3% reported starting with menthol-flavored NJOY ACE ENDS. The 2021-2022 Youth Perceptions Study also showed that among youth who reported using NJOY ACE in the past 30-days (n=169), 47.2% report using the menthol flavor most often and 15.2% report using Classic Tobacco (not subject to this PMTA review) most often.

Per the BCP review:

- The applicant did not submit behavioral and clinical pharmacology information for people who do not use tobacco. Therefore, the assessment on this population is based solely on published literature.
- The new products are flavored, pod-style ENDS. These product characteristics appeal to youth and may facilitate initiation; youth and people who do not use tobacco who initiate use of the new products are at risk for progression to regular ENDS use and subsequent nicotine dependence due to high nicotine exposures from pod-style ENDS.
- The new products contain nicotine salt formulations which may be easier (i.e., less irritating) to inhale at high nicotine concentrations (Caldwell et al., 2012; Omaiye et al., 2019; Prochaska et al., 2019; Talih et al., 2019), thereby facilitating initiation and use of ENDS with high amounts of nicotine. However, based on data from the applicant-submitted clinical studies, the abuse liability of PM0000616.PD1 and PM0000617.PD1 among youth who are inexperienced with ENDS may be somewhat lower than, or comparable to, CC, mitigating concern of greater addiction potential than CC.

- Youth users of pod-style ENDS report more symptoms of nicotine dependence than non-pod-ENDS users (Martinez et al., 2020; Morean et al., 2019).
- While ENDS with non-tobacco flavors and high nicotine delivery may help adults who smoke switch from CC to ENDS, these same characteristics may facilitate initiation and continued nicotine use by youth.

3.4.1.4. Vulnerable populations (other than youth)

Per the social science review:

- Based on the applicant's submitted data, it is possible that there are gender and race/ethnicity differences in the intention to try NJOY ACE ENDS. Data from the Adult Prevalence Study suggest that males were more likely to intend to try NJOY products than females. In addition, White and Black non-users were less likely to intend to try NJOY products than Hispanic and "other" race non-user respondents. However, the modeling methods were not well described and included intention to try any NJOY ENDS rather than NJOY ACE ENDS. Therefore, it is unclear whether these findings indicate meaningful differences in NJOY ACE ENDS use by gender and race/ethnicity.

Per the epidemiology review:

- Evidence from the published literature indicates that all age groups with substance use or mental health issues are more likely to use ENDS compared to those without (Cho et al., 2018; Conway et al., 2018; Riehm et al., 2019). Additionally, the prevalence of ENDS use is higher among other populations (e.g., pregnant persons and lesbian, gay, and bisexual individuals) (Azagba et al., 2019; Hawkins et al., 2020; Obisesan et al., 2020; Wheldon et al., 2019). While the evidence indicates that some populations experience disproportionate ENDS use, there is a lack of currently available evidence to show whether the new products would help facilitate CC smokers from different populations (i.e., groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation) to switch or reduce cigarettes per day.
- The applicant did not provide information specific to different populations in their PMTAs.

Per the BCP review:

- No clinical studies were provided or reviewed by the applicant addressing use of the new products among different populations. An applicant-submitted clinical study indicates the new products may have a similar or lower abuse liability relative to CC among adults who smoke CC who are inexperienced with ENDS, which suggests the new products may not pose greater risk of progression to regular use and addiction among different populations other than youth compared to CC. Nevertheless, these studies did not specifically assess different populations, and there is insufficient available information in the currently available scientific literature to conclude that the new products' impact would differ for different populations other than youth. Therefore, the impact of the new products on abuse liability and product use behavior in different populations is unknown.

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

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

- The applicant did not provide robust product-specific data on the degree to which its labeling, advertising, marketing, and promotion may influence youth perception, youth appeal, and the likelihood of youth initiation of tobacco use.
- The applicant describes an approach to market the new products to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion.
- The applicant summarized several measures directed toward limiting youth exposure to the new products' marketing materials and activities for which OHCE is supportive:
    - Not utilizing the following marketing practices
        - Broadcast or digital radio advertising,
        - Television advertising,
        - Outdoor advertising,
        - Print advertising,
        - Search engine advertising,
        - Online display advertising,
        - Paid or unpaid product placements,
        - Public relations or earned media,
        - In-person engagements or activations,
        - Social media promotions,
        - Partners, sponsors, influencer, bloggers, or brand ambassadors,
        - Referral or affiliate programs, or
        - Product sampling;
    - Prohibiting the use of cartoon images or characters, fruit or food-related images, or imagery of any kind that is intended, designed, or otherwise likely to appeal to minors;
    - Limiting human portrayals to only depictions of models who are or appear to be over age 45;
    - Limiting the use of NJOY-owned social media properties to the sole purpose of receiving inbound customer service communications, and utilizing all available platform-native age-gating functionality to restrict access to adults;
    - Maintaining Distributor and Retailer Policies that govern the selection and oversight of tobacco retailers that carry NJOY ACE products;
    - Prohibiting the sale of NJOY ACE products on third-party websites;
    - Limiting the number of products that can be purchased in a given time period or transaction;
    - Using competent and reliable third-party sources to verify the age and identity of users against public records before granting access to product website or conducting online sales;
    - Requiring retailers to only place NJOY ACE products in non-self-service areas of the store; and
    - Conducting quarterly audits of point-of-sale signage located in retail chains that carry NJOY to determine whether only NJOY-approved trade marketing materials are being utilized.

- 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 their proposed approaches to limit youth exposure to its products' labeling, advertising, marketing, and/or promotion.

Per the social science review:

- Social science reviewed these PMTAs, including all applicant-proposed marketing restrictions and mitigation measures to determine whether there are novel and materially different proposed measures that might mitigate the substantial risk to youth from flavored ENDS sufficiently to decrease the magnitude of adult benefit required to show APPH. As part of the marketing plan, the applicant provided measures to restrict youth access and limit youth exposure, including prohibiting use of cartoons and models who appear to be under age 45 years in advertising; maintaining distributor and retailer policies that govern the selection and oversight of tobacco retailers that carry NJOY ACE products; limiting number of products that can be purchased in a given time period or transaction; and other measures. These marketing restrictions are likely to further limit youth use but do not change the required showing for flavored ENDS.

3.4.1.6. Labeling and advertising

Per the social science review:

- OCE noted that the applicant includes general categories of statements they "may make…as substantiated" including, for example, "statements about transitioning from CC (or other nicotine-containing products) to NJOY products or substituting NJOY products for CC (or other nicotine-containing products)." The applicant did not provide any specific statements. Based on the general categories of statements described in the PMTA, social science cannot conclude that the proposed labeling is false or misleading in any particular way. However, depending on the nature of the specific statements, they may be considered explicit or implicit modified risk claims. The MGO letter should communicate that no modified risk claims (either explicit or implicit) can be made without a modified risk tobacco product (MRTP) order, and no cessation claims can be made without going through the drug approval process.

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.

For the marketing of a new product to be found to be APPH, any risks posed by a new product to youth 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 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 adults who use cigarettes 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 cigarettes. 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.

Previously, FDA excluded menthol products from application decisions to allow more time to consider whether any factors unique to menthol would affect the APPH assessment. Among other things, FDA considered the potential significance of the fact that menthol-flavored CC currently remain on the market, unlike other non-tobacco characterizing flavors that are prohibited in CC. FDA conducted a thorough examination of the peer-reviewed scientific literature on this subject to determine whether it established that menthol-flavored ENDS provide a sufficient benefit for adults who use CC relative to that of tobacco-flavored ENDS.

As discussed in the section entitled "*Impact of Menthol-flavored ENDS on Adults,"* 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 does not demonstrate that menthol-flavored ENDS differentially facilitate completely switching or significant cigarette reduction, and this is the behavioral outcome measurable with available methods that most directly and most robustly determines the potential benefit to users. In addition, flavored ENDS, including menthol-flavored ENDS, pose substantial risk of youth appeal and use. 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 their menthol-flavored ENDS products provide an added benefit for adults who use cigarettes 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 an at risk population for various reasons, including that the majority of tobacco use begins before adulthood (U.S. Department of Health and Human Services, 2012) and thus youth are particularly susceptible to tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Almost 90 percent of adults who use CC daily started smoking by the age of 18 (U.S. Department of Health and Human Services, 2014). Adolescents who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood (Apelberg et al., 2014). On the other hand, youth and young adults who reach the age of 26 without ever starting to use 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 2023, 10.0% of high school students and 4.6% of middle school students reported current ENDS use. The majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time (Cullen et al., 2019). In the 2014 NYTS, 65.1% of high school and 55.1% of middle school current (past 30 day) e-cigarette[9] users reported using a flavored e-cigarette (Corey et al., 2015). By the 2023 NYTS, the percentage of youth who currently use e-cigarettes reporting using a flavored product[10] was up to 90.3% of high school users and 87.1% of middle school users (Birdsey et al., 2023). In 2023, among youth who currently used flavored e-cigarettes, the most commonly used flavor type was fruit (63.4%), followed by candy, desserts, and other sweets (35.0%), mint (27.8%), and menthol (20.1%) (Birdsey et al., 2023) . The published literature shows that, compared to adults who use ENDS, youth who use ENDS are more likely to use flavored ENDS. In the PATH study Wave 5.5 from 2020, 67.4% of youth using ENDS aged 13 to 17 reported using fruit, followed by 53.8% for mint/menthol, 23.4% for candy/dessert/other sweets, and 13.3% for tobacco flavor (internal analysis[11]). In the 2020

[9] We use “e-cigarette” here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.
[10] Flavored product use in these studies means use of flavors other than tobacco.
[11] 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.

PATH Adult Telephone Survey, 51.5% of adult using ENDS 25 and older used fruit, 30.4% used mint/menthol, 24.1% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal analysis[12]). 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, in Wave 1 of the PATH Study from 2013-2014, over 81% of youth aged 12-17, 71% of young adults 18-24, and 53% of adults 25 and older reported that the first e-cigarette that they used was flavored (Villanti et al., 2019). In another PATH study, 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 from 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 who ever use ENDS aged 25 and older (Rostron et al., 2020b).

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 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. 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 (18-24 years), 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 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[13] such as flavored cartridge-based or pod-based ENDS, use for 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 reported use of flavored products, with fruit, mint, candy, and menthol among the most commonly used. Disposable use and

[12] Data generated from PATH Wave 5.5 PATH-ATS Public Use Files (PUF) released in October 2022, available at https://www.icpsr.umich.edu/web/NAHDAP/studies/37786/datadocumentation#.

[13] 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

flavor use continued to be high in 2021 among ENDS users. In 2023, disposable ENDS continued to be the most widely used type of ENDS among middle and high school students with 65.2% of high school e-cigarette users and 47.9% of middle school e-cigarette users using disposable ENDS (Birdsey et al., 2023). 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 use of ENDS.

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. The 2023 NYTS data clearly demonstrate that youth use of menthol-flavored ENDS (20.1% of past 30-day flavored ENDS users) is similar to that of flavors such as mint (27.8%) and candy/desserts/sweets (35.0%) (Birdsey et al., 2023). Indeed, the literature described above substantiates that menthol-flavored ENDS pose a known and substantial risk to youth.[14]

Type of Evidence Needed to Outweigh the Risk to Youth[15]

Given the known and substantial risk to youth of the new products, 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 cigarettes to completely switch or significantly reduce their cigarette 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 comparator 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

[14] 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 separately. 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. By contrast, the 2022 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 20.1% of middle-and high-school users of flavored ENDS, which is similar to the use rates for mint (27.8%) and candy/desserts/sweets (35.0%) (Birdsey et al., 2023).

[15] 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 that permitting the marketing of the new products would be APPH. See Section 3.4.1.5. for details.

evidence could be generated from (1) an RCT or (2) a LCS. 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 comparator product tobacco-flavored ENDS and flavored products on tobacco use behavior over time among adults who use CC[16], 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.[17] 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 use CC: (1) complete switching from cigarettes to exclusive use of the new product or (2) significant reduction in cigarettes per day.

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 adults who use 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

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

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 flavored subject products outweighs the clear risks to youth.

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 cigarette 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.

Impact of Menthol-flavored ENDS on Adults

In addition to reviewing the applicant-submitted information (see Section entitled "*Evidence Provided in the PMTAs"*), and in light of the fact that menthol-flavored CC currently remain on the market unlike other non-tobacco flavored CC that are prohibited, FDA conducted a thorough examination of the peer-reviewed scientific literature on this subject.[18] FDA evaluated whether that literature established that menthol-flavored ENDS provide a sufficient benefit for adults who smoke relative to that of tobacco-flavored ENDS.

The peer-reviewed literature supports that adults who use menthol CC indicate more enjoyment, satisfaction, and intent to use menthol-flavored ENDS compared to tobacco-flavored ENDS after trying ENDS (DeVito et al., 2020; Goldenson et al., 2020; Rosbrook et al., 2016; Voos et al., 2020). In addition, the peer-reviewed literature supports that menthol/mint-flavored ENDS are more likely to be used by adults who use menthol CC than by adults who use non-menthol CC, including by those who have completely switched from CC to ENDS (Rostron et al., 2020a). Behavioral economics experiments suggest that adults who use menthol CC will most commonly use menthol ENDS as a substitute for menthol CC—in scenarios where menthol ENDS are available—compared to other tobacco products,

[18] In May 2022, FDA proposed a product standard to prohibit menthol as a characterizing flavor in cigarettes. Tobacco Product Standard for Menthol Cigarettes, 87 Fed. Reg. 26454 (May 4, 2022). That rulemaking proceeding remains pending and not yet in effect. As such, considerations such as a final rule going into effect in the future and whether it would have any impact on the assessment of menthol-flavored ENDS did not factor into the analysis at this time.

including tobacco-flavored ENDS (Denlinger-Apte et al., 2021; Shang et al., 2020). Together, these data demonstrate that adults who use menthol CC prefer menthol-flavored ENDS over tobacco-flavored ENDS. However, actual product use is critical in the evaluation of product switching because the ability of a product to promote switching among adults who use 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.

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 adults who currently use CC (including adults who use menthol CC) (Goldenson et al., 2022; Goldenson et al., 2021; Nollen et al., 2022). 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.[19]

Evidence Provided in the PMTAs

The applicant submitted brand-specific data from an online, observational study that contained evidence to suggest that the menthol-flavored new products will promote switching or CC reduction among adults who smoke CC relative to tobacco-flavored ENDS. This evidence is considered 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 tobacco products would have a net benefit to public health based upon the risks and benefits to the population as a whole.

<u>Youth Appeal and Prevalence</u>
Although the applicant submitted youth prevalence estimates for NJOY ENDS and NJOY ACE products, these data were collected in 2021-2022 and may no longer reflect current youth use. Nationally-representative data from the 2023 NYTS show that NJOY (of which there are many sub-brands, including ACE) was the 10th most-reported brand used in the past 30 days (i.e., 7.5% of current ENDS users) among middle and high school students (Birdsey et al., 2023).

Data from the applicant's 2021-2022 Youth Perceptions Study suggest that youth are not more curious about or have greater intent-to-use the Menthol-flavored new products compared to the tobacco-flavored NJOY ACE products, but data from the same study demonstrates that youth initiated NJOY ACE use with the Menthol-flavored new products more than with the Classic Tobacco flavor (not subject to this PMTA review) and more youth

[19] 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 CC in terms of completely switching or significantly reducing CC use beyond that of a tobacco-flavored ENDS.

used the NJOY ACE Menthol products (compared to the Classic Tobacco flavor [not subject to this PMTA review]) within the past 30 days. Furthermore, and consistent with the general ENDS literature (Cooper, 2022; Rose et al., 2020), fewer youth initiated with and used the Menthol-flavored NJOY ACE products than fruit-flavored NJOY ACE products (not subject to this PMTA review). Additionally, 2023 NYTS estimates suggest that among current ENDS users, although approximately 90% of youth use flavored ENDS, 20% of that population use menthol-flavored products. These 2023 NYTS data, and other data discussed elsewhere, suggest that the menthol-flavored new products pose a risk to youth. I also acknowledge that use of the flavored new products by youth who use ENDS might change, depending on the availability of other products on the market. As discussed in Section 3.4.1.5., but not considered in the APPH assessment, the applicant's marketing plan is robust and is expected to limit youth exposure to the new products and the products' labeling, advertising, marketing, and/or promotion.

Adult Use

I agree with the BCP and epidemiology reviews that the new products will be most commonly used with CC (i.e., dually used). The epidemiology review noted that more than 40% of NJOY ACE users (any flavor) are likely to be dual users; such estimates are consistent with the general literature. Importantly, the NJOY User Study suggested that, as is consistent with the literature (e.g., (Carpenter et al., 2023)), dual use of the new products and CC (i.e., adults who smoke CC and did not completely switch to NJOY ACE products) is associated with decreased CC consumption compared to levels when they were smoking CC exclusively. As described in Section 3.5.1.2., biomarkers of exposure (BOE) are generally similar among adults dually using ENDS and CC compared to adults who exclusively smoke CC, suggesting this population is unlikely to experience health benefits.

However, 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. A recent Cochrane review evaluated tobacco cessation rates with various smoking interventions (e.g., ENDS, NRT, pharmacotherapy) and identified the most effective smoking cessation method as nicotine-containing ENDS (Lindson et al., 2023), like the new products. The review provides additional evidence and concludes with "high-certainty evidence" that nicotine-containing ENDS are more effective at promoting smoking cessation than NRT (Lindson et al., 2024). These data indicate that ENDS, in general, have an adult benefit to public health by facilitating complete switching from CC.

As described in the epidemiology review, the applicant submitted data from an online, observational study (NJOY User Study) with evidence demonstrating that absolute rates of complete switching (i.e., cessation of CC with continued ENDS use, as well as cessation of CC and NJOY ACE ENDS) associated with specific NJOY ACE products (including products not subject to this PMTA review) are higher than nationally representative estimates of ENDS in general.

That NJOY ACE products (in general) have higher rates of absolute switching than ENDS in general is also supported by BCP review conclusions because PM0000617.PD1 may facilitate complete switching more than ENDS with freebase nicotine and lower abuse liabilities. Indeed, the applicant-submitted clinical data suggest that PM0000617.PD1 has an abuse liability similar to CC in certain populations (see Section 3.3.1.1.), which may facilitate more

complete switching (i.e., CC cessation) compared to other ENDS with lower abuse liability. Furthermore, the new products' nicotine salt formulation also suggests that the new products may be substitutable to CC given their more similar nicotine delivery patterns to CC. Thus, the higher switching rates observed in the applicant's NJOY User Study compared to rates from the general ENDS literature may be reflective of the new products' capacity to offer users a similar use experience to CC (i.e., greater substitutability).

The applicant's data also evaluated the extent to which Menthol-flavored new product PM0000617.PD1 is likely to promote complete switching (measured by 30-day PPA) more than the NJOY ACE Classic Tobacco ENDS (not subject to this PMTA review) in terms of its impact on tobacco use behavior among adults who smoke CC. The applicant's models presented several variables (i.e., initial flavor used at baseline, most used flavor at baseline, flavor at time of switching), durations of follow-up (i.e., 1, 2, 3, and 6 months), and types of analyses (e.g., per-protocol and ITT) to address complete switching, but the epidemiology review noted several gaps in the applicant-provided analysis. While these gaps did not affect the epidemiology conclusions, they limited the confidence with which I, as TPL, was able to draw conclusions about the extent of the adult benefit associated with the Menthol-flavored new products compared to the tobacco-flavored NJOY ACE product and the robustness of these data. Thus, I submitted a statistical consult to address these analysis gaps.

The statistical consult dated August 16, 2023, and the associated epidemiology review conclusions, suggest that the applicant's NJOY User Study presents reliable and robust data indicating that NJOY ACE POD Menthol 5% ENDS are associated with significantly higher rates of complete switching than tobacco-flavored NJOY ACE ENDS (not subject to this PMTA review). For example, the statistical consult concluded that "flavor at the time of switching" (which the epidemiology review characterized as the most proximate measure for ENDS flavor) was a significant predictor of 30 day PPA (i.e., complete switching) in ITT analyses (which the epidemiology review characterized as the most conservative estimate of switching), where adults who used menthol flavored NJOY ACE ENDS "demonstrated significantly lower odds of smoking … than Classic Tobacco use at 3-month[20] and 6-month time points, respectively." Similar outcomes were also demonstrated for other switching estimates, including per protocol analyses and "initial flavor used at baseline" measures. Furthermore, after adjusting for a wide range of covariates, as well as using ITT methods to account for potential bias associated with loss-to-follow-up, menthol-flavored (as an initial flavor used) NJOY ACE products were significantly associated with higher rates of past 30-day tobacco cessation than Classic Tobacco (not subject to this PMTA review) NJOY ACE ENDS at both 3 and 6 months. Additionally, menthol-flavored NJOY ACE use at the time of switching was significantly associated with higher rates of past 30-day PPA than Classic Tobacco (not subject to this PMTA review) NJOY ACE ENDS at 6 months.

The majority of the primary (3-month) and secondary (6-month) cessation estimates for 30-day PPA among adults who used the menthol-flavored NJOY ACE new products (ITT range: (b) (4) ; per-protocol range: (b) (4)) were significantly higher than the estimates

[20] Although the statistical consult requested by the TPL concluded that the 3-month cessation data was significant (p=0.09), the epidemiology review states they "will not describe the final models' odds ratios with p-values greater than 0.05 as statistically significant."

for adults who used NJOY ACE Classic Tobacco products (not subject to this PMTA review, ITT range: (b) (4) ; per-protocol range: (b) (4)). Therefore, the totality of evidence provided by the applicant suggests that the Menthol-flavored PM0000617.PD1 is associated with significantly higher smoking cessation rates than tobacco-flavored NJOY ACE products and epidemiology concluded that the new products are highly beneficial to adults who smoke CC.

The epidemiology review determined that the NJOY User Study was of sufficient quality. It is important, however, to interpret these findings regarding adult benefit in the context of study limitations and study design factors. For example, the NJOY User Study was conducted with 5% nicotine products (including new product PM0000617.PD1 and NJOY ACE POD Classic Tobacco 5% [not subject to this PMTA review]). The literature, however, suggests that ENDS with higher nicotine content (including nicotine salts) are associated with greater nicotine exposure and, presumably, abuse liability. Thus, because it contains a higher nicotine content, it is likely that PM0000617.PD1 has a somewhat greater abuse liability than PM0000616.PD1, and PM0000617.PD1 therefore may be a more effective substitute for CC smoking. Since participants in the NJOY User Study used PM0000617.PD1 (with 5% nicotine), and not PM0000616.PD1, the absolute switching rate estimates for PM0000616.PD1 (and NJOY ACE PODS Classic Tobacco 2.4% [not subject to this PMTA review]) may be somewhat lower than those in the NJOY User Study. Nevertheless, both menthol-flavored new products may offer adults who dually use CC and ENDS a distinct behavioral benefit compared to the Classic Tobacco flavored (not subject to this PMTA review) NJOY ACE products of equivalent nicotine concentration.

Furthermore, participants' CC status (i.e., menthol or regular) was not reported in the NJOY User Study. While many adults who smoke menthol CC report lower cessation outcomes than adults who smoke non-menthol CC (e.g., Cook et al., 2022), the literature suggests that adults who smoke menthol CC may prefer to use menthol-flavored ENDS. It is possible, therefore, that the availability of a preferred ENDS flavor (i.e., menthol) may lead to greater success quitting menthol CC smoking when using menthol-flavored ENDS compared to tobacco-flavored ENDS (Rostron et al., 2021). Thus, the switching rates in the NJOY User Study may underestimate actual switching rates when assessing quit rates among adults who smoke menthol CC and use menthol-flavored NJOY ACE products.

The epidemiology review also notes that the study population (i.e., adults who currently use NJOY ACE ENDS) may inflate the absolute switching rates reported in the NJOY User Study. The applicant recruited a convenience sample of adults who recently purchased NJOY ACE products to capture the impact of starting to use NJOY products on CC smoking. Recruitment of a new user population may, however, result in a study population that is generally more likely to quit smoking CC than general ENDS users. While this study population may inflate the absolute cessation rates in the NJOY User Study, as TPL, I believe the study population is appropriate to assess how NJOY ACE products may affect CC cessation among adults who want to quit CC smoking. Furthermore, the analytical question of focus, whether the *relative* switching rate differs between adults who use Menthol versus Classic Tobacco (not subject to this PMTA review) NJOY ACE products, is not impacted by this lack of external validity.

Overall, the epidemiology review determined that the evidence is acceptably strong and the added benefit of these new products to adults is highly beneficial to public health.

To further evaluate the flavored new products' potential risk to youth, FDA examined the applicant's marketing plans and restrictions. The OHCE consult determined that the applicant's approach to marketing may help further limit youth exposure to the new products. 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 their proposed marketing plans.

Regarding product labeling, packaging, and advertising, I agree with the social science review and conclude that the labels and statements do not contain misleading or false information. Because the applicant included claims that they "may make … if substantiated", I recommend that the MGO letter remind the applicant that no modified risk claims (either explicit or implicit) can be made without an MRTP order.

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 added adult behavioral benefit associated with these new products. Indeed, the applicant submitted robust and reliable data that demonstrate added benefit of using Menthol-flavored compared to Classic Tobacco flavored (not subject to this PMTA review) NJOY ACE in achieving past 30-day smoking cessation – a showing 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 menthol-flavored new products have the potential to benefit adults who smoke CC, who switch completely or significantly reduce their CC use, that outweighs the risk to youth.

3.5. TOXICANT EXPOSURE

The BCP review relied on limited clinical biomarker data from a subsample of the NJOY User Study population to inform these outcomes.

The 2nd cycle toxicology review evaluated applicant-submitted whole smoke and whole aerosol nonclinical data (cytotoxicity and genotoxicity) for the new products, CC, and an ENDS comparison product. In addition, toxicology qualitatively assessed the risks and hazards (cancer and noncancer) related to HPHCs and leachables that were observed in aerosol.

An addendum to the 2nd cycle toxicology review reflects toxicology's consideration of all sources of aerosol-based cancer risks, including ingredients, as well as HPHCs and leachables. The conclusions in the addendum update some of the information provided in Section 3.1.5 (Toxicant exposure) of the 2nd cycle review to include cancer risk evaluations for the new products related to ingredients, HPHCs, and leachables, as well as associated risk estimations relative to other tobacco products. The overall risk assessment from the toxicology addendum (described in Section 3.5.1.1.) and the risk assessment conclusions from the 2nd cycle toxicology review are consistent. Based on current thinking regarding the overall cancer risk from all potential cancer hazards, toxicology estimated an $ELCR_C$ for the new products and then

compared it to the associated risk of CC as well as Center for Tobacco Product (CTP)-authorized ENDS.[21]

3.5.1. Discipline key findings

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

3.5.1.1. Toxicity

Per the 2nd cycle toxicology review:

- Overall, aerosol HPHCs were lower when tested using the NJOY ACE e-liquids (PM0000616.PD1 and PM0000617.PD1) stored for up to 9 months compared to CC comparison data under both non-intense and intense puffing regimens. In comparisons of CC smoke HPHC concentrations to aerosol HPHC concentrations from the new products, CC smoke has more HPHCs and many of the HPHCs present in CC smoke have comparatively higher potencies (i.e., higher magnitude or severity of toxicological effect, at a given dose or exposure level) than HPHCs in the aerosols of the new products. Higher (b) (4) propylene glycol, and nickel of the new products aerosols are outweighed by lower levels of other respiratory toxicants (e.g., acetaldehyde, diacetyl, acetyl propionyl, acrolein, butyraldehyde, formaldehyde, furfural and ethylene glycol) in the CC comparison products, therefore, are unlikely to raise toxicology concerns for users of the new products in comparison to average CC yields. Observed (b) (4) PG, and nickel levels are comparable to levels seen in other ENDS market comparisons.

Per the toxicology addendum:

- The risk assessment process used by toxicology summarizes and integrates toxicity and exposure information to estimate and characterize overall cancer risk due to HPHCs, leachables, and ingredients, both in quantitative expressions and qualitative statements.
    - The main metric of risk assessment 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.
    - As described in Memorandum: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications (June 3, 2024), the ELCR approach is a consistent way to estimate cancer risk resulting from individual ingredients, HPHCs, and leachables measured in the new products, and it allows for a robust comparative analysis to other tobacco products assessed the same way.
    - As described in Memorandum: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications (June 3, 2024), all individual ELCRs in a given product are added together to obtain a $ELCR_C$ and compared to the $ELCR_C$ for 1R6F Kentucky research CC, which is representative of CC, and to the median $ELCR_C$ of CTP-authorized ENDS[21].

[21] ENDS that have received marketing granted orders as of February 2024.

- The new products contain ingredients, leachables, and HPHCs for which their estimated exposures exceed a screening threshold associated with a cancer prevalence of 1 case of cancer per 100,000 users and as such could add to the cumulative cancer risk.
- As described in Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications (June 3, 2024), individual constituents of the new products are evaluated and placed into tiers, depending on the information available for the constituent.
    - Tier 1-3 constituents have been evaluated by the International Agency for Research on Cancer (IARC) or Environmental Protection Agency (EPA) for carcinogenicity which increases toxicological certainty in the associated Tier 1-3 constituents contributing to cancer risk.
    - Placement into Tier 4 is primarily based 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 4 constituents contributing to cancer risk.
    - For Tier 4 constituents, future chemical-specific studies and methodologies could provide data that facilitate updated chemical tiering.
- For these new products, when the risk assessment is limited to Tier 1-3 constituents, PM0000616.PD1 has an $ELCR_C$ that is 0.25% of the 1R6F $ELCR_C$ and PM0000617.PD1 has an $ELCR_C$ that is 0.12% of the 1R6F $ELCR_C$. The associated $ELCR_C$ of both new products (including Tier 1-3 constituents) is lower than the median $ELCR_C$ for marketed ENDS.
    - The $ELCR_C$ based on Tier 1-3 constituents is driven by acrolein, nickel, and formaldehyde which are established HPHCs and classified by EPA/IARC into Tiers 1-3.
    - However, limiting the assessment to only the most well studied and understood carcinogens (i.e., Tiers 1-3) when evaluating a new and emerging product portfolio, can result in an underestimation of cancer risks due to a lifetime of exposure to the new products because there are other constituents to which potential users of the new products will be exposed. These additional and potential cancer risks are due to constituents identified as Tier 4—chemicals that have one or more positive results in a genotoxicity assay or mixed results that limit the confirmation or ruling-out of carcinogenicity.
- When the risk assessment includes Tier 1-4 constituents, PM0000616.PD1 has an $ELCR_C$ that is about 11% of the 1R6F $ELCR_C$ and PM0000617.PD1 has an $ELCR_C$ that is 5% of the 1R6F $ELCR_C$. The new products' $ELCR_C$s are higher than the median for CTP-authorized ENDS when considering Tier 1-4 constituents. The median $ELCR_C$ of the current CTP-authorized ENDS is 118 excess cancer cases per 100,000 users. The marketplace median, however, will change over time and reflects only those products authorized as of February 2024.
    - The ELCR based on Tiers 1-4 constituents is driven by (b) (4) [redacted] acrolein, nickel, and formaldehyde.

- Sixteen unknown leachables also exceeded the analytical exposure threshold of 1.5µg/day, assuming 100% transfer from e-liquid to aerosol. Given these ingredients are without data to support a positive (or negative) relationship with cancer outcomes (i.e., Tier 4E per Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications [June 3, 2024]), they were not included in the $ELCR_C$ assessments. These unknowns add to the uncertainty of the current risk assessment.

- This cancer risk assessment indicates that if users completely switch from CC to the new products and their nicotine consumption does not significantly change when changing products their risk of cancer is lower when using the new products than when using CC.
- Based on assessment of chemicals in Tiers 1-4, the new products are associated with higher risk relative to CTP-authorized ENDS, specifically regarding users who either initiate with these new products (versus another CTP-authorized ENDS) or switch from a CTP-authorized ENDS.
- Overall, when considering the cancer risk assessment, the Tier 1 – 3 assessment represents the lower estimate of risk based solely on chemicals for which there is the greatest certainty of carcinogenicity and the Tier 1 – 4 assessment represents a conservative estimate of carcinogenicity that includes constituents for which there is evidence of carcinogenic potential, but for which there is more uncertainty regarding carcinogenic potential. Synergistic interactions (and antagonistic) between multiple carcinogens are a further uncertainty in this analysis that cannot be ruled out.

3.5.1.2. Biomarkers of exposure

Per the BCP review:

- Biomarker data submitted from the applicant-submitted NJOY User Study found that participants who had recently used only NJOY ACE ENDS, which may have included the new products, had lower levels of many BOE (e.g., CO, cotinine, CEMA, 3-HPMA, NNAL) relative to adults who recently dually used NJOY ACE ENDS and CC. These data suggest that exclusive use of the new products may be associated with lower levels of BOE compared to concurrent use with CC.
- Published studies suggest that cotinine levels (i.e., nicotine exposures) in adults who use pod-style ENDS are comparable or higher than the levels of adults who smoke CC (Goniewicz et al., 2019) and adults who use non-pod-ENDS (Boykan et al., 2019).
- In youth, cotinine levels increase over time, particularly with increases in ENDS use frequency (Vogel et al., 2019).
- Adults who smoke CC will likely experience significant reductions in volatile organic compound (VOC) exposure upon complete switching to the new products (Goniewicz et al., 2017; Oliveri et al., 2020; Round et al., 2019).
- Adults who dually use ENDS and CC will likely have comparable levels of tobacco-specific nitrosamine (TSNA) and VOC BOE as adults who smoke CC, or they may experience low to modest reductions in these BOE (Pulvers et al., 2018).
- Adults who exclusively use the new products will likely be exposed to greater levels of TSNA and VOC BOE compared with adults who do not use tobacco products.

- Based on published literature, heavy metal exposure is likely to stay the same or decrease upon complete switching to the new products (Goniewicz et al., 2018; Jain, 2019; Prokopowicz et al., 2019).

3.5.2. Synthesis

The 2nd cycle toxicology review concluded that the new NJOY ACE products' aerosols have lower levels of some HPHCs, and as such lower noncancer risk, compared to the CC comparison products. This conclusion is based on the qualitative observation that higher risk of adverse noncancer health effects due to higher levels of (b) (4) PG, and nickel in the new product aerosols, are likely offset by the lower risk of adverse health effects due to the lower levels of other respiratory toxicants (e.g., acetaldehyde, diacetyl, acetyl propionyl, acrolein, butyraldehyde, formaldehyde, furfural, ethylene glycol) in the new products compared to CC.

The toxicology addendum to the 2nd cycle toxicology review estimated the $ELCR_C$ of the new products and characterized the new products' cancer risk based on two levels of hazard certainty (i.e., including constituents in Tiers 1-3 and those in Tiers 1-4; see Section 3.5.1.1.). With uncertainty in hazard identification being the main difference between the Tier 1-3 ELCR and the Tier 1-4 ELCR, the latter represents a conservative estimate which is the most appropriate when considering whether the new products are appropriate for the protection of the public health in this TPL review. The toxicology addendum compared the new products to both CC and the CTP-authorized ENDS as of February 2024. However, the number of CTP-authorized ENDS is small and does not provide a robust ELCR assessment based on the small sample size, rendering this comparison incomplete for the purposes of this TPL review. Thus, for the purposes of this TPL review, the most appropriate toxicological assessment for the new products is Tier 1-4 $ELCR_C$ compared to CC. The toxicology addendum identified several constituents with some uncertainty as to their genotoxic hazard identification and associated risks. In comparative terms, the estimated Tier 1-4 $ELCR_C$s indicate that PM0000616.PD1 and PM0000617.PD1 are about 11% (i.e., estimated to carry a risk of 1 case of cancer for every 97 users) and about 5% (i.e., estimated to carry a risk of 1 case of cancer for every 222 users), respectively, of the $ELCR_C$ of CC (i.e., estimated to carry a risk of 1 case of cancer for every 10 users)[22]. While the overall estimated $ELCR_C$ due to exclusive use of the new products is substantially lower than the estimated $ELCR_C$ due to the use of CC (estimated to be less than 12% the 1R6F $ELCR_C$), these estimates are based on chemical exposure information, for which a reduction in exposure may not be directly proportional to a reduction in cancer risk. Thus, there is uncertainty in how much risk will decrease 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 a CC still results in a significant risk compared to adults who have never used tobacco products or adults who formerly used tobacco products.

[22] These are estimations of the potential cancer risks based on Tiers 1-4 constituents from the toxicology perspective and should not be interpreted as observed cancer incidences.

It is also important to consider the potential cancer risks associated with switching from a CTP-authorized ENDS to the new products given that adults who currently use ENDS are one of the applicant's intended populations (see Section 3.4.1.1.). Additionally, the epidemiology review noted that approximately 40% of adults using the new product will be using both ENDS and CC (see Section 3.4.1.2.). The conservative Tier 1-4 $ELCR_C$ (which considers constituents with greater uncertainty to their toxicological profile) suggests the new products' calculated cancer risk is higher than the median risk of CTP-authorized ENDS, posing a moderate level of concern of cancer risk. These results must be interpreted while considering the limitation (i.e., small sample size of CTP-authorized ENDS) associated with the CTP-authorized ENDS $ELCR_C$ calculations. The sample size for the CTP-authorized ENDS calculation is small and does not represent the full ENDS market; thus, this comparison is incomplete and not meaningful at this time. Nevertheless, although there may be a higher risk associated with completely switching from another CTP-authorized ENDS to the new products, as TPL, I believe that the comparison of the new products to CC for cancer risk provides a more compelling consideration in the APPH assessment at this time.

While these toxicology cancer risk estimations assume that adults who smoke CC (or use ENDS) will completely switch from CC (or marketed ENDS) to the new products, as TPL, I acknowledge that the new products are most likely to result in dual use with CC (see Section 3.4.1.2.), and the lower cancer risks may not be as significant in that population.

The BCP review concluded that the applicant-submitted data demonstrated that adults who exclusively use the new products are expected to have lower levels of several BOE (e.g., CO, cotinine, CEMA, 3-HPMA, NNAL) compared to people who dually use CC and the new products. Thus, as TPL, I agree with the toxicology and BCP conclusions that adults who smoke CC and completely switch or significantly reduce CC consumption with the new products may reduce overall exposures to HPHCs compared to adults who smoke CC.

These data are consistent with the literature on other ENDS and may indicate a likely relative health benefit associated with exclusive use of the new products compared to exclusive use of CC (see Section 3.6.). As discussed in Sections 3.4.2., the new products facilitate complete switching (i.e., CC cessation) at rates above those in the general ENDS literature (which may be due to the new products' high abuse liability in some populations), 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

The toxicology addendum conclusions cited in Section 3.5.1.1. replace the genotoxicity conclusions provided in Section 3.1.6 (Health effects) of the 2nd cycle toxicology review.

3.6.1. Discipline key findings

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

3.6.1.1. Toxicology

Per the toxicology review:

- The new products and the ENDS comparison product, Vuse Alto Original 5%, aerosols demonstrated no cytotoxicity (neutral red uptake [NRU] assay) at the concentrations and under the conditions tested. The new product PM0000617.PD1 (NJOY ACE POD Menthol 5%) was tested in this assay because it was similar to the ENDS comparison product (Vuse Alto Original 5%). The test data from PM0000617.PD1 can be bridged to PM0000616.PD1. Overall, under the test conditions, the applicant's results did not exhibit cytotoxicity, while the CC comparison product (1R6F reference CC) showed statistically significant cytotoxicity in Chinese hamster ovary CHO-WBL (IVGT) cells.
- The applicant provided supporting data from published in vitro and in vivo toxicology literature on respiratory effects, carcinogenicity, cardiovascular effects, mutagenicity and genotoxicity effects, reproductive/developmental effects, immunotoxicity, neurotoxicity effects, and other systemic effects (such as skin sensitization, hepatotoxic and nephrotoxic effects). The applicant claims that although data gaps remain on the health effects of ENDS, the current state of the science supports that "health effects (if observed) from exposure to ENDS are less severe than health effects associated with combusted cigarette smoke." (Appendix C, pg. 43, m4-5-risk-assess-rpt-app-c.pdf).

3.6.1.2. BIMO inspection findings

Per the medical review:

- BIMO inspection was not conducted by FDA because the reported AEs did not raise clinically significant concerns.

3.6.1.3. Addiction as a health endpoint

Per the BCP review:

- Clinical study data submitted by the applicant suggests that, based on subjective effects and nicotine exposure, PM0000617.PD1 and PM0000616.PD1 (by bridging from PM0000617.PD1) have a somewhat lower or comparable addiction potential than CC among adults inexperienced with ENDS.
- People who currently smoke CC (i.e., one of the applicant's stated intended user populations), who switch partially or completely to PM0000617.PD1, are initially likely to achieve somewhat lower or comparable nicotine exposures and likely will maintain their nicotine addiction. After some period of experience with the new products, however, nicotine exposure from PM0000617.PD1 may become comparable to CC.
- Adults who dually use CC and ENDS are likely to achieve slightly lower or comparable nicotine exposures from PM0000617.PD1 as adults who exclusively smoke CC; some adults who smoke CC may titrate, over time, to their preferred nicotine exposures (St Helen et al., 2020). Adults who dually use CC and ENDS are likely to maintain nicotine addiction, as with people who exclusively smoke CC.
- Based on published literature and the applicant-submitted survey study, adults who dually use CC and the new products likely will reduce their CC consumption; however, published literature is mixed on whether dual-use of ENDS and CC is associated with a decrease in CC use (Carpenter et al., 2023).

- E-liquids with nicotine salts are easier (i.e., less irritating) to inhale at high nicotine concentrations (Caldwell et al., 2012; Omaiye et al., 2019; Prochaska et al., 2019; Talih et al., 2019) and may facilitate use and progression to regular use by naïve users such as youth. Published literature suggest that youth who initiate use of nicotine salt-containing pod-style ENDS may have comparable or higher nicotine exposures compared with youth who smoke CC and non-pod-ENDS users. Youth who use nicotine salt-containing pod-style ENDS may experience increased cotinine levels over time which may correspond with increases in nicotine dependence and progression to regular use.

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

Per the medical review:

- Overall, the applicant provided data to evaluate the short-term health effects of the new products and, based on the provided information, no safety concerns were identified.
- Limitations of the applicant's literature review include a lack of new product-specific data and inclusion of ENDS with various chemical compositions and testing methods.
- Based on the applicant-submitted literature review, the impact of ENDS use on cardiovascular disease, cancer, respiratory outcomes, developmental, and reproductive health outcomes, oral health, mental health, and other health topics is largely inconclusive. Risk of injury and poisonings have been consistently reported in the literature; however, the literature did not report these outcomes specifically with the use of the new products.
- Applicant-submitted clinical studies did not identify short-term health effects of concern specific to Menthol-flavored NJOY ACE products. The submitted clinical studies have limitations, including small sample sizes and relatively short durations of new product exposure, thereby limiting the generalizability of the health effects data to a larger user population and extrapolation of the long-term health effects of the new products. Based on the information reviewed, including the clinical studies, published literature, consumer reports, and adverse experiences, the short-term health effects of the new products are expected and consistent with those reported for this class of products.

Per the epidemiology review:

- *Users vs. Never Users:* The applicant provided limited data on observational health outcomes. In the NJOY User Study, participants were asked seven questions regarding respiratory symptoms, fatigue, and subjective health in the past 12 months. At each follow-up time point, the average number of self-reported respiratory symptoms, fatigue, and subjective health was reported by NJOY use status and CC smoking status. However, these results should be interpreted with caution due to the short duration, potential loss to follow-up bias, and the fact that most results are unadjusted for potential confounding factors. Due to these limitations, the published literature provides a better source of information on potential health effects. There is currently some epidemiologic evidence suggesting positive associations between ENDS use and some health outcomes (e.g., cardiovascular diseases, respiratory diseases, oral health); however, these studies are limited by the lack of ability to discern temporality and the fact that most ENDS

users included were former smokers whose past smoking might be related to these increased health risks, even after accounting for smoking status in multivariable models. Several cross-sectional Behavioral Risk Factor Surveillance System studies in ENDS users who never smoked CC found associations between ENDS and respiratory outcomes. There is strong evidence that ENDS use is linked with ENDS battery explosion related burns and e-liquid nicotine poisoning. ENDS users have higher exposure to constituents such as VOCs than do non-tobacco users.

- *Dual Use:* In general, data from the biomarker literature suggests that dual users may have higher levels of certain BOEs 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 CC smokers.
- *Switching:* Goniewicz et al. (2017) found levels of total nicotine and some polycyclic aromatic hydrocarbon metabolites did not change after switching from CC to ENDS, but levels of all other biomarkers significantly decreased after one week of using ENDS (Goniewicz et al., 2017). Further, the literature also suggests that exclusive ENDS users have lower levels of exposure to some constituents including TSNAs than CC smokers (Anic et al., 2022). Nicotine levels among exclusive ENDS users are usually somewhat lower or comparable to levels among CC smokers.

3.6.1.5. Likelihood and effects of product misuse

Per the medical review:

- The applicant did not report any serious health outcomes related to misuse. Although reports of ENDS-related poisonings among adults and children are documented in the literature, the closed-system nature of the new products' pods may mitigate the risk of accidental exposure. The majority of ENDS-related injuries among children and adults have been minor with more extensive injuries related to lithium batteries which are a power source for devices; however, no serious AEs related to lithium battery use were reported by the applicant.
- CTP has received reports of seizures in youth and young adults associated with ENDS. To further study any potential relationship between ENDS and seizure, periodic reporting to evaluate seizures and other neurological symptoms may be warranted.

Per the BCP review:

- The applicant did not provide any information regarding mitigating features that prevent tampering or refilling of pods and use of non-authentic or counterfeit pods.
- The applicant-submitted clinical studies and literature review did not provide data evaluating the likelihood of misusing the new products. Despite the lack of clinical data assessing product misuse (i.e., using the product in ways other than intended such as product modifications, dripping, stealth use), the likelihood of misuse is low for the new products because they are closed-system pod-style ENDS. NJOY ACE device power settings are non-adjustable, and the e-liquid is enclosed in a pod, thereby reducing chances that users may manipulate ENDS settings and e-liquid constituents, including nicotine levels, which may influence exposure to nicotine and other HPHCs in the aerosol.

3.6.1.6. Adverse experiences

Per the engineering review:

- The applicant evaluated the failure modes of the pods, device, and the complete system by calculating a Risk Priority Number to establish a standard risk scale.
- Engineering reviewed the Tobacco Product Surveillance Team (TPST) search reports. AE0001804 cited concerns related to “leaking”, “non-functional” pods. However, the applicant reported no concerns regarding leakage during manufacturing process. The applicant provided manufacturing processes which are followed by visual inspection to ensure compliance with specifications before the packaging process as indicated in m2-3-2-prdt-manuf-sum.pdf. The finished pods undergo various tests to ensure they meet the acceptance criteria as mentioned in 2.4.1 of m2-3-3-sum-pdt-cntrl.pdf (pages 46-49). Due to these quality assurance steps, from an engineering perspective, it appears that adequate tests are in place to avoid leaking of pods. From an engineering perspective, the applicant has adequately addressed this issue.

Per the medical review:

- There were no deaths or other serious AEs reported in the two applicant-submitted clinical studies. The clinical studies did not include use of PM0000616.PD1.
- Nineteen AEs were reported in the clinical studies and assessed as at least possibly related to NJOY ACE products (including those not subject to this PMTA review). The AEs reported were either mild or moderate in severity, with the majority being mild. Two headache AEs associated with PM0000617.PD1 were reported in an applicant-submitted clinical study and reported as probably related; medical agrees with this assessment. One report of dizziness with PM0000617.PD1 was reported as unlikely or unrelated to the new product; however, medical believes the new product may be related to the AE reported given the temporal relationship to product administration and biological plausibility of the AE after exposure to PM0000617.PD1.
- The most commonly reported AEs across the clinical studies and among all NJOY ACE products (including those not subject to this PMTA review) were gastrointestinal (nausea, vomiting, dyspepsia, and stomachache) followed by neurological (dizziness and headache). All AEs resolved prior to the end of the study.
- The four categories in the applicant’s Adverse Experiences Summary Report (including products not subject to this PMTA review; from September 25, 2019, through January 12, 2020) containing the highest number of AEs were Respiratory System (n=71), Digestive System (n=48), General (n=30), and Nervous System (n=11). The top four AEs across all organ systems were Sore Throat (n=23), Mouth Irritation (n=22), Cough/Sputum (n=19), and Feeling Sick (n=17).
- The reports of gastrointestinal and neurological effects in clinical studies and in the Adverse Experiences Summary Report could indicate the potential for health effects of this nature when generalized to a larger population. These effects could potentially lead to further health complications or exacerbate underlying medical conditions in subpopulations of users (e.g., immunocompromised, diabetic, cardiac disease, respiratory disease).
- In the applicant-submitted literature review on ENDS, AEs reported in published studies included cough, dry or irritated mouth or throat, dizziness or lightheadedness, headache or migraine, shortness of breath, change in or loss of

taste, nausea, tight chest, and congestion. Several of these AEs were reported in the applicant-sponsored clinical studies.

- Due to the limited information provided for the two cases classified as serious and unexpected AEs in the applicant-submitted Summary Report from NJOY- Quarter 1 2020 Update, including whether the implicated NJOY products were the new products, it is difficult to assess whether the reported AEs are related to the use of the new products other than being related temporally. In the absence of competing causes, such as underlying comorbidities and because these AEs resolved, they do not raise product-specific concerns.
- Three TPST searches were conducted on April 7, 2020, March 7, 2023, and February 8, 2024. Six AE reports were associated with health effects. Despite these AEs, information in the Safety Reporting Portal (SRP) data is limited, making it difficult to identify potential trends in AEs for the new products in order to draw conclusions regarding health risk. Because of the limitations in SRP data (e.g., reports are voluntary, TPST reported events do not imply causation, reported information is often incomplete, and reported information is generally not verifiable), it is not possible to determine if clinically relevant trends exist for the new products based on the SRP reports.
- FDA is aware of several health issues regarding the use of ENDS, specifically seizures, overheating/fire/explosion-related thermal burn injuries (OH/F/Exp), and lung injury.
    - OH/F/Exp is a potential risk with all ENDS. Although the new products do not contain batteries, they contain heating elements that connect to a battery during product use. All ENDS batteries pose a risk for OH/F/Exp. There were no reports of OH/F/Exp in the applicant's clinical studies the literature or SRP.
    - There were no seizures reported as an AE in the applicant-submitted clinical studies. While there were four seizures associated with ENDS reported to the SRP, none could be causally attributed to the new products.
    - There were no reports of lung injury in the applicant's clinical studies.
    - If the new products receive a marketing authorization, medical recommends post-market reporting to monitor the occurrence and potential relation of the new products to neurological events, OH/F/Exp incidents, and lung injury.

3.6.2. Synthesis

As TPL, I agree with the BCP conclusions that the new products have a lower or comparable addiction potential than CC. Thus, adults who currently smoke CC and who switch partially or completely to the new products will likely maintain their nicotine addiction. As described in the epidemiology review, the health risks of all ENDS are more significant than the health risks to never users; however, the social science review concluded that adults who do not use tobacco products and adults who formerly used tobacco products report low curiosity and intent to use the new products (see Section 3.4.1.3.). I also agree with the epidemiology and medical conclusions that the data regarding short- and long-term health effects of ENDS are largely inconclusive. However, the data do suggest that adults who smoke CC and who switch to the new products (either completely or with a significant reduction in CC

consumption) could benefit from reduced risk of cancer associated with exposure to toxicants as described in Section 3.7.1.1. A qualitative noncancer assessment also suggests that adults who smoke CC and completely switch have similar or lower noncancer risks relative to not switching from CC (see Section 3.5.1.1.). The nonclinical studies using whole aerosol and whole smoke also support this conclusion.

3.7. POPULATION AND PUBLIC HEALTH

The epidemiology review evaluated the applicant's population modeling approach called NJOY-PopMod to estimate the potential population health effects of NJOY ACE ENDS in "Impact of NJOY ACE Electronic Nicotine Delivery System (ENDS): Population Health Modeling Report."

The toxicology addendum conclusions replace the information provided in Sections 3.1.7 (Population health) of the 2nd cycle toxicology review.

3.7.1. Discipline key findings

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

3.7.1.1. Toxicology

Per the toxicology addendum:

- The overall risk assessment indicates that if users completely switch from CC to the new products and their nicotine consumption does not significantly change when changing products, their risk of cancer is lower. Conversely, the new products may be associated with higher cancer risk relative to CTP-authorized ENDS, specifically regarding users that either initiate with this product (e.g., versus a marketed product) or switch from a currently marketed ENDS.

3.7.1.2. Population health impact (PHI) model

Per the epidemiology review:

- The data inputs used in the applicant's population health modeling scenarios for both ENDS generally and NJOY ACE ENDS specifically present significant methodological and substantive challenges. Switching rates were calculated from cross-sectional, instead of longitudinal, data and may overestimate actual switching from CC smoking to exclusive ENDS use. The scenarios also did not consider the possibility of ENDS use among young people, even though such use is a considerable public health concern. Given these limitations, the population modeling projections are not informative to the overall assessment. Despite these limitations, the prevalence rates and behavioral data related to users and non-users provided in the PMTAs was sufficient to inform an assessment of the new products from the epidemiology perspective.

3.7.2. Synthesis

As TPL, I agree with the toxicology addendum's conclusions that switching completely from CC smoking to the new products will result in lower cancer risks. Further, I acknowledge that adults who smoke and initiate use of the new products are most likely to dual use the

products with CC (see Section 3.4.1.2.), and the lower cancer risk may not be as significant in that population.

I also agree with the epidemiology review on the limitations of the applicant's population health modeling methodology, including overestimations of actual switching rates from CC smoking to exclusive ENDS use and overlooking scenarios of ENDS use among young people. Therefore, given the limitations associated with the model inputs described in the epidemiology review, the applicant's population model is not informative in the evaluation of whether marketing of the new products would be APPH.

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 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[23]

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

3.8.3. Labeling

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

3.8.4. Product standards

There are no applicable product standards for these PMTAs.

4. ENVIRONMENTAL DECISION

4.1. DISCIPLINE FINDINGS

Environmental science concluded that the environmental assessments for all PMTAs contain sufficient information to determine whether the proposed actions may significantly affect the quality of the human environment. As TPL, I agree with this conclusion.

4.2. ENVIRONMENTAL CONCLUSION

A finding of no significant impact (FONSI) was signed by Luis Valerio on 6/14/2024. The FONSI was supported by a programmatic environmental assessment prepared by FDA on 6/14/2024.

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

5. CONCLUSION AND RECOMMENDATION

Section 910 of the FD&C Act requires that, for a product to receive a PMTA marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute specifies that, in assessing whether the marketing of the new products would be APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products. Section 910(c)(4). 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).

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 the new products are manufactured consistently. The applicant submitted sufficient chemistry and microbiology data to support a (b) (4) product shelf life for both new products. The new products were compared to CC and ENDS because the applicant identified that the new products are intended for adults who currently smoke CC and adults who currently use ENDS.

The new products are 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. Nationally representative 2023 NYTS data show that the most popular ENDS flavors used by middle school and high school students who currently use ENDS were fruit (63.4%); candy, desserts, or other sweets (35.0%); mint (27.8%); and menthol (20.1%), while tobacco-flavored ENDS were used by 6.4% of youth who currently use ENDS (Birdsey et al., 2023). The applicant provided low prevalence estimates of the new products in youth, however, these estimates were not reliable due to small sample sizes. Meanwhile, nationally representative 2023 NYTS data show that NJOY products (of which there are many sub-brands) are the 10th most-reported brand used in the past 30 days among middle and high school students. The literature demonstrates that the risk of menthol-flavored ENDS is higher than tobacco-flavored ENDS, yet lower than some other flavors (e.g., fruit).

Thus, permitting the marketing of the new products requires a showing that the products would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth. The PMTAs present 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. The applicant submitted data and analyses from

an online, observational LCS (NJOY User Study) that assessed rates of complete switching (i.e., cessation of CC with continued ENDS use, as well as cessation of CC and ENDS) when adults were using new product PM0000617.PD1 (NJOY ACE POD Menthol 5%) and tobacco-flavored NJOY ACE products (not subject to this PMTA review) over six months. These data demonstrated that NJOY ACE products have higher rates of absolute switching from CC (ranging from 17-27%) than other ENDS in general. In addition to NJOY ACE products' robust absolute switching rates ranging from 17-27%, these data provide robust and reliable evidence that the menthol-flavored PM0000617.PD1 is associated with statistically significant and substantially higher rates of complete switching than tobacco-flavored NJOY ACE ENDS (not subject to this PMTA review). Since the data from PM0000617.PD1 can be bridged to PM0000616.PD1, both new products provide a significant and substantial added behavioral benefit (i.e., OR range 1.41-1.56 at 3 and 6 months) compared to Classic Tobacco flavor NJOY ACE ENDS among adults who quit smoking CC.

Furthermore, applicant-submitted clinical studies with new product PM0000617.PD1 demonstrate that the new product's abuse liability is similar to CC among adults who are experienced with ENDS use, suggesting that the new product may be a suitable substitute for CC among adults who smoke CC and who want to quit. Additionally, the applicant's biomarker data from the NJOY User Study suggests that adults who exclusively use the new products will have lower HPHC exposures compared to adults who dually use CC and 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 of the new products' ELCR predicts that adults who exclusively use the new products will have significantly lower concerns of cancer risks than adults who smoke CC. The applicant, therefore, has demonstrated the potential for these new products to benefit adults who smoke CC as compared to those who continue to use CC exclusively.

Together, the available evidence suggests that although the menthol-flavored new products pose risks to youth, the potential of the new products to promote cessation and provide significantly lower health risks than CC outweighs that youth risk.

Thus, based on the information provided in the PMTAs and the available evidence, I find that permitting the marketing of the new products, as described in the applications and specified in the Appendix, Table 4 is appropriate for the protection of the public health. The issuance of these marketing granted orders confirms that the applicant has met the requirements of section 910(c) of the FD&C Act and authorizes marketing of the new products. Under the provisions of section 910, the applicant may introduce or deliver for introduction into interstate commerce the new products, in accordance with the marketing order requirements outlined in the marketing granted orders.

The applicant also proposed robust marketing plans that include restrictions beyond those required with PMTA authorization. OHCE has 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 limit youth exposure to the new products by not engaging in social media promotions, limiting human portrayals to models who are over the age of 45, and prohibiting the sale of NJOY ACE ENDS on third-party websites.

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

Marketing granted orders should be issued for the new products subject to this review, as identified on the cover page of this review.

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7. APPENDIX

Appendix A. New products

Table 4. New tobacco products subject to Granted Orders

Common Attributes[24,25,26,27]	
Submit date	March 10, 2020
Receipt date	March 10, 2020
Applicant	NJOY LLC
Product manufacturer	NJOY LLC
Product category	Electronic Nicotine Delivery Systems (ENDS) (VAPES)
Product subcategory	Closed E-Liquid
Attributes	**New Tobacco Product**
STN	**PM0000616.PD1**
Product name	NJOY ACE POD Menthol 2.4%
Package type	Cartridge
Product quantity	2 Cartridges
Characterizing flavor (CF)	Menthol
Nicotine source	Tobacco
E-liquid volume	1.9 milliliters (mL)
Nicotine concentration	2.4% weight per weight (w/w)
PG/VG ratio	0.86
Nicotine source	Tobacco
Additional property	Length: 34.75 millimeters (mm) Thickness: 11.57 mm Width: 29.59 mm

[24] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.
[25] Product name is brand/sub-brand or other commercial name used in commercial distribution.
[26] 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.
[27] Attributes in Appendix A may display converted values.

STN	PM0000617.PD1
Product name	NJOY ACE POD Menthol 5%
Package type	Cartridge
Product quantity	2 Cartridges
Characterizing flavor (CF)	Menthol
Nicotine source	Tobacco
E-liquid volume	1.9 mL
Nicotine concentration	5% w/w
PG/VG ratio	0.77
Nicotine source	Tobacco
Additional property	Length: 34.75 mm Thickness: 11.57 mm Width: 29.59 mm

Appendix B. Amendments and additional submissions received

Table 5. Amendments

Submit Date	Receipt Date	Applications being amended[28]	Reviewed	Brief Description
June 16, 2020	June 16, 2020	All	Yes	Technical update to new adverse experiences reporting, updated user survey, and updated population model
August 11, 2020	August 11, 2020	All	Yes	Response to July 29, 2020, Deficiency Letter
August 26, 2020	August 26, 2020	All	Yes	Follow up phone call for July 29, 2020, Deficiency Letter
September 30, 2020	September 30, 2020	All	Yes	Response to July 29, 2020, Deficiency Letter
December 17, 2020	December 17, 2020	All	Yes	Notification of new/current literature to support PMTA applications
December 2, 2022	December 2, 2022	All	Yes	Additional clarifying information including longitudinal studies, perception data and prevalence data

Table 5. Additional submissions

Submit Date	Receipt Date	Reviewed	Brief Description
June 10, 2020	June 10, 2020	Yes	Temporary Change in Address
August 31, 2023	August 31, 2023	Yes	Authorized POC update
September 7, 2023	September 7, 2023	Yes	Authorized POC update
October 20, 2023	October 20, 2023	Yes	Temporary Authorized POC update
November 29, 2023	November 29, 2023	Yes	Letter of Authorization for TPMF
January 11, 2024	January 11, 2024	Yes	Response to Wages and White Lion Investments, LLC v. FDA decision
January 11, 2024	January 11, 2024	Yes	Form 4057a and response to Wages and White Lion Investments, LLC v. FDA decision
February 6, 2024	February 6, 2024	Yes	Letter of Authorization for TPMF
April 29, 2024	April 29, 2024	Yes	Address update

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