U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review[1]	
STNs	PM0000628.PD1 and PM0000629.PD1
Common Attributes	
Submission date	March 30, 2020
Receipt date	March 30, 2020
Applicant	NJOY LLC
Product manufacturer	NJOY LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	Closed E-Cigarette
Cross-Referenced Submissions	
All STNs	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	• Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications (June 3, 2024). • Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications (June 3, 2024). • Normalization of HPHC Yields between new and comparison products in ENDS PMTAs (September 10, 2020)
Recommendation	
Issue marketing granted orders for the new tobacco products subject to this review.	

Technical Project Lead (TPL):

Yanling Chen, Ph.D.
Supervisory Toxicologist
Division of Nonclinical Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

[1] Product details, amendments, and dates are provided in the Appendix. PMTA means premarket tobacco application. STN means submission tracking number.

Matthew Farrelly, Ph.D.
Director
Office of Science

TABLE OF CONTENTS

LIST OF TABLES

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 other denial grounds specified in section 910(c)(2) apply. Accordingly, I recommend that marketing granted orders (MGOs) be issued for the new products, subject to the marketing restrictions and post-market requirements.

1.1. APPH STANDARD

Section 910 of the FD&C Act requires that, for a product to receive a 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 product or significantly reducing smoking of CC. In order to show that marketing of an ENDS is APPH, an applicant must show that the benefits,

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

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 such 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 PMTAs to determine whether they contain sufficient evidence of the type described above to demonstrate that marketing of the products would be APPH.

The new products are a closed, non-rechargeable, non-serviceable ENDS that minimizes potential risk of poisoning during handling or use of the products. FDA's evaluation of these PMTAs determined that they contain sufficient information to characterize the new products' composition and design, and that there are adequate process controls and quality assurance procedures to help ensure the new products are manufactured consistently. The applicant submitted sufficient chemistry and microbiology data to support a (b) (4) product shelf life for the new products. The applicant did not report any serious health outcomes related to misuse of the new products. In addition, the applicant-submitted clinical studies did not have serious human adverse experiences (AEs) or death with the new products. No definitive AEs related to the new products were found in FDA's Safety Reporting Portal.

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 flavors used by middle school and high school current ENDS users 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 current youth ENDS users (Birdsey et al., 2023). The applicant provided low prevalence estimates of the new products in

[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").

youth, however, these estimates were not reliable due to small sample sizes. Meanwhile, nationally representative 2023 National Youth Tobacco Study (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 use that could outweigh that risk to youth. To effectively demonstrate this benefit in terms of product use behavior, the PMTAs generally need to provide product-specific evidence from a randomized controlled trial (RCT)[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 CC 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 both CC and ENDS) when adults were using the menthol-flavored new products and tobacco-flavored NJOY DAILY products (not subject to this PMTA review) over a six months period (3-month as the primary outcome cohort). The applicant's data suggested a higher rate of absolute switching for the NJOY DAILY products (21-32%), comparing to the estimates for ENDS in general in the literature. Additionally, the applicant's comparison analyses suggest that the menthol-flavored NJOY DAILY ENDS products were associated with statistically significant and substantially higher rates (32-43%) of complete switching than the rate (21-37%) of the tobacco-flavored NJOY DAILY ENDS products (not subject to this PMTA review) at 3 or 6 months. Additional statistical analyses using covariable-adjusted odds ratio (aOR)demonstrated that

[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).

switching for menthol flavor was statistically significantly higher than that of tobacco flavor (aOR range 1.24-1.50) at 3 months. Therefore, these comparison analyses demonstrated a 24%-50% substantial added benefit from the menthol-flavored NJOY DAILY ENDS products relative to that of the tobacco-flavored NJOY DAILY ENDS in facilitating complete switching away from or significantly reducing CC smoking among adults who smoke CC.

The applicant-submitted clinical studies demonstrated that the new products' abuse liability is similar to CC among adults who are experienced with ENDS use, suggesting that the new products 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 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 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 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 DAILY 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 TOBACCO PRODUCTS

The applicant submitted information for the new products listed in Appendix A, sold under the brand name NJOY. The new products are disposable ENDS products with a reservoir containing prefilled menthol flavored e-liquid. The new products, PM0000628.PD1 and PM0000629.PD1, contain 4.5% and 6% nicotine, respectively. The devices are powered by a lithium-ion, non-rechargeable battery. The power unit and cartridge settings are not adjustable by the user.

2.2 REGULATORY ACTIVITY

On March 30, 2020, FDA received two PMTAs from NJOY LLC. FDA completed an acceptance review and issued an Acceptance letter to the applicant on April 8, 2020. FDA issued a Filing

letter to the applicant on April 21, 2020. FDA issued a Deficiency letter to the applicant on December 17, 2020.

Refer to the 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	
	Reviewers	**Review Date**	**Reviewers**	**Review Date**
Regulatory	Not Assigned	N/A	Liam Garven	6/8/2023
Engineering	Jim Melchiors	12/17/2020	Jim Melchiors	6/9/2022
Chemistry	Tianrong Cheng	12/14/2020	Tianrong Cheng	6/7/2022
Microbiology	Wen Lin	12/14/2020	Kristy HuynhNgo	6/9/2022
Toxicology[5]	Prince Awuah	12/16/2020	Prince Awuah; Toyin Ajao	6/9/2022; 6/14/2024
Behavioral and Clinical Pharmacology	Tyler Nighbor	12/14/2020	Steven Meredith	6/13/2024
Medical	Kathy Jackson	12/17/2020	Candrea Smith	6/13/2024
Epidemiology	Arpi Terzian	12/16/2020	Amy Gross	6/14/2024
Social science	Dannielle Kelley	12/16/2020	Dannielle Kelley	6/13/2024
Environmental science	Dilip Venugopal	12/16/2020	Dilip Venugopal	6/8/2022 6/14/2024
OCE-BIMO[6]	Tara Singh	11/23/2020	Not assigned[6]	N/A
OCE-Manufacturing/Lab	Hiwot Kesi	11/19/2020	Hiwot Kesi	04/30/2021

Table 2. Consultations

Discipline or Office	**Cycle 1**		**Cycle 2**	
	Reviewer(s)	**Review Date**	**Reviewer(s)**	**Review Date**
Statistics	Not assigned	**N/A**	Sapna Thakur; Christopher Ellison	05/06/2021; 02/16/2023; 12/05/2023; 03/01/2024
OCE-DPAL	Adeola Obajemu	11/5/2020	Not assigned[6]	N/A
OHCE	Emily Talbert	10/14/2020	Emily Talbert	02/24/2022
Tobacco Product Surveillance Team	Susan Rudy	09/30/2020	Vy Nguyen	09/30/2020; 02/15/2023; 02/06/2024

[5] Toxicology addendum was completed on 06/14/2024, by Toyin Ajao.

[6] A second cycle review was not necessary as there was no new information or data to review for this discipline.

3. SCIENTIFIC REVIEW

3.1 COMPARISON PRODUCTS

3.1.1 Discipline key findings

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

- Chemistry:
  - The applicant provided aerosol constituent concentrations for Leap Go Smooth Tobacco 5% as a comparison product. Leap is a prefilled disposable tobacco flavored e-cigarette containing 5% nicotine salt and is in the same product category and subcategory compared to the new products.
- Toxicology:
  - All PMTAs provided aerosol constituent concentrations (generated from the applicant conducted testing) for Leap Go Smooth Tobacco 5% as a comparison product. Leap is a prefilled disposable tobacco flavored ENDS containing 5% nicotine salt. The rationale for this comparison was that Leap Go Smooth is also a disposable closed system ENDS with a non-rechargeable battery and single-use pod that is filled by the manufacturer with nicotine salt-containing e-liquid. From a toxicological perspective, the applicant's rationale for using Leap Go Smooth Tobacco with 5% nicotine salt is adequate and the product similarities make it a useful ENDS comparison product.
  - The applicant compared the aerosol of the new products to the MSS of CC. The applicant used the average CC MSS concentration data from peer-reviewed scientific literature to represent the CC. This comparison was present in the harmful and potential harmful constituents (HPHC) data evaluation (Section 2.3 in cycle 1 Toxicology review that referenced Chemistry data and analysis). The applicant's rationale for this comparison is based on the premise of potential reduction of risk of overall adverse health effects from CC smokers switching completely to the new products. The selection of average CC data as representative of the CC is appropriate because the studies were peer-reviewed and selected studies that were recently published measured many of the same HPHCs, included cigarettes that are currently on the market, and were tested using common puffing protocols (e.g., ISO and HCI) across the studies. Because the selected comparison product is representative of the CC, and the applicant's stated intended user population includes adult cigarette smokers, the applicant's rationale for using CC as a comparison product is appropriate, and the use of average CC data from the published toxicology literature is an appropriate representative of the CC from a toxicological perspective.
  - Because the applicant also identified CC to compare to the new products, toxicology obtained data (from the chemistry review) and compared constituent yields from the new product aerosols to the mainstream smoke (MSS) yields of 50 commercially available CC (FDA50 products).
  - The applicant provided in vitro mutagenicity, cytotoxicity and genotoxicity studies that used the Kentucky Reference 1R6F cigarette as a comparison product. Kentucky Reference 1R6F cigarette was designed to be used as an

analytical standard and therefore its generalizability to commercially marketed CC is unclear, however, several studies comparing other Kentucky reference cigarettes (e.g., 1R4F, 1R5F and 3R4F) to commercially marketed cigarettes 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 cigarette as a comparison product in the in vitro studies is adequate to represent the overall content of HPHCs in a combusted tobacco product.

- The applicant provided comparisons between the new products and an ENDS comparison product, Leap Go Smooth Tobacco 5% nicotine, which is also a closed-system ENDS with a rechargeable battery and single-use pod containing nicotine salt e-liquid. This comparison was presented in the HPHC data and in the in vitro mutagenicity, cytotoxicity, and genotoxicity studies. The applicant also states that Leap Go Smooth Tobacco 5% nicotine contents (i.e., nicotine salt, 5% w/w) are similar to the new products (4.5% and 6% nicotine salt, w/w) in that they both contain nicotine salt. The new products contain (b) (4) Given that the levels of (b) (4) is more than 370 fold lower than established toxicity reference values, and considering that (b)(4) is naturally occurring in the human body, the presence of (b) (4) at the indicated levels is acceptable from a toxicological perspective. From a toxicological perspective, the applicant's rationale for using Leap Go Smooth Tobacco with 5% nicotine salt is adequate.
- The applicant provided comparisons between the new products and other ENDS products (i.e., cig-a-like, fixed pods, variable pods, fixed tanks and variable tanks). The applicant used the average nicotine-adjusted aerosol concentration data from peer-reviewed scientific literature to represent the other ENDS products (i.e., cig-a-like, pods, and tank systems). This comparison was present in the nicotine-adjusted HPHC data. The applicant states that the rationale for using this comparison was to give insight into HPHC comparison between the new products and other ENDS products and to allow for the consideration of possible HPHC exposures for current non-users who may initiate use of the new products or other ENDS products. From a toxicological perspective, the applicant's rationale for using average nicotine-adjusted HPHC levels from other ENDS products as a comparison product is adequate because this would allow for a ingredient normalized comparison since there are ingredient and design differences between the different ENDS products and the new products.

- Engineering:
  - STIG Cubano and STIG Mighty Mint are similar products to the new products with respect to the product design and are disposable ENDS like the new products; the applicant included these as comparator products. The engineering review indicates that the applicant provided limited information on the STIG Cubano and STIG Mighty Mint. They have the same wick material and coil resistance as the new products, although the

comparator products are slightly bigger, with 34% more e-liquid at 1.2 mL and 30% more battery at 260 mAh. Per engineering review conclusions, these are appropriate comparators to the new products with respect to the product design.

- Epidemiology:
  - The applicant's menthol-specific analysis of the NJOY User Study included CC smokers. Based on the data provided and the peer-reviewed literature, it is likely that current CC smokers are the target population for these new products. However, some non-tobacco users will also likely use the product, especially youth and young adults. Therefore, comparisons between the new products and CC are acceptable from an epidemiology's perspective because CC smokers are a likely user population.
- Medical:
  - The medical review indicated that the comparison products in the applicants' clinical studies (NJOY ACE Tobacco 5%, NJOY LOOP Rich Tobacco 4.5%, and JUUL Virginia Tobacco 5%) were the same category (ENDS) as the new products and contained similar nicotine concentrations. The applicant reviewed ENDS literature as a general category without reviewing literature specific to the new products and did not adequately bridge to the new products. However, based on the totality of the data reviewed, including the clinical studies, published literature, and adverse events, medical finds that the health effects identified in the clinical studies and other submitted data are consistent with those previously described with ENDS and are acceptable.
- Microbiology:
  - The applicant provided stability information for the new products, but not for the ENDS comparator product (Leap Go Smooth Tobacco 5%). Therefore, a comparison of how product characteristics affect shelf life, when compared to similar ENDS tobacco products, could not be completed. However, based on the stability data (pH, moisture content, total aerobic microbial counts (TAMC), total yeast and mold counts (TYMC) and bacterial endotoxin content (BET)) over shelf life of the new products, the lack of stability data for the comparison products is acceptable from a microbiology perspective.
  - All new products have microbial content below the FDA and USP guidelines (TYMC(b) (4) cfu/mL, TAMC(b) (4) cfu/mL).
- Social Science:
  - The applicant-submitted studies included comparisons of the new products to CC, as well as to non-NJOY ENDS and nicotine replacement therapies (NRTs). Based upon available data on perceptions, curiosity about, and intentions to try the new products, the likely users of the new products will include adults who currently smoke CC. Some non-tobacco users may also use the new products, such as youth and young adults. Overall, the comparisons of the new products made by the applicant to CC, non-NJOY ENDS, and NRTs are appropriate from a social science perspective because

the intended user populations are users of nicotine-containing products, particularly adults who currently smoke CC and adult ENDS users.

- Behavioral & Clinical Pharmacology (BCP):
  - The applicant-submitted survey data shows that CC smokers and dual users of CC and ENDS are likely to use the new products.
  - From BCP perspective, the data and rationale to support CC as a comparison product was appropriate because CC smokers are the applicant's stated intended users of the new products. Additionally, the data and rationale to support other ENDS (e.g., NJOY ACE; JUUL) as comparison products was appropriate as ENDS users are also the applicant's stated intended users.

3.1.2 Synthesis

The applicant used CC, other ENDS products in the same category as the new products, and a variety of other products in different product categories as comparison products. As TPL, I agree with the Toxicology, Chemistry, Microbiology, Engineering, Medical, Behavioral and Clinical Pharmacology (BCP), Epidemiology, and Social Science conclusions that the comparison products selected by the applicant, the rationale for selection, and the data from these products are appropriate for each discipline's comparison analyses in the PMTAs. For the purposes of the overall APPH assessment, as TPL, I consider the primary comparison products to be CC and ENDS products of the same category with similar flavors and ENDS design as the new products. The rationale for the selection of the comparison products is appropriate because the intended user populations for the new products are current users of nicotine-containing products, including current users of CC and ENDS users. In addition, because the new products are flavored ENDS, they are compared to tobacco-flavored ENDS to determine whether the products are associated with sufficient adult benefit (discussed in Section 1.1). To compare the toxicity profile of the new products to that of the selected comparison products, the applicant compared the aerosol HPHCs in the new products to those in the MSS of CC or the aerosol of other ENDS products. As TPL, I note that comparison of HPHCs in isolation from the ingredients and leachables that are present in the e-liquid and aerosols provides only a limited perspective on the toxicity considerations of these products; therefore this comparison is useful, but is not a complete assessment (see Section 3.5.1.1). Nevertheless, the applicant provided adequate justification, rationale, and data to support the selections of the comparison products and comparisons made between the new products and the chosen representative comparison products.

3.2 PRODUCT CHARACTERIZATION

3.2.1 Discipline key findings

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

3.2.1.1 Product design and composition

- Engineering:
  - Each new product is of the product category ENDS (Vapes) and subcategory closed e-cigarette. The new products are disposable and non-rechargeable. The new products are not serviceable by the user for any purpose,

including, but not limited to, customizing the atomizer, or modifying or refilling the e-liquid.

- When the user draws air through the device, the pressure differential activates an airflow sensor that triggers the heating of the coil by the non-rechargeable lithium-ion battery cell, which heats an e-liquid (consisting of (b) (4) to yield 3 to 5 mg of inhalable aerosol (for a 3-second puff). The airflow sensor limits the maximum puff duration to (b) (4) seconds; for longer than that period of time, a user must take multiple puffs. When airflow stops, the device returns to standby mode. When the battery cell is depleted (b) (4) to (b) (4) V), the device is no longer usable.
- The new products (b)(4) This risk is being monitored by the applicant and is minimal from an engineering perspective.
- The new products have a coil resistance between (b) (4) Ω and (b) (4) Ω with a target of (b) (4) Ω. The overall atomizer resistance is the same (b) (4) Ω to (b) (4) Ω which is a reasonable design of the atomizer. The applicant does provide data that demonstrates that the coil resistance meets the specification.
- The device always remains on in standby mode with activation controlled by the Application Specific Integrated Circuit (ASIC} residing in the airflow controller waiting to detect airflow. The ASIC in the new products does not require software or firmware, as the required logic is integrated into the device. It has no user-adjustable parameters and stores no data. The device cannot be accessed, altered, or adjusted through any external connection.
- Specifications were provided for all of the components of the new products to adequately characterize the new products. From an engineering perspective, the information submitted regarding design and principles of operation fully characterize the new products.
- The new products have UL 1642 Certification for the battery cell to demonstrate reduced risk of fire and explosion. The devices also have short circuit protection. The battery presents a minimal risk from an engineering perspective.
- The design minimizes the risk of accidental exposure to e-liquid by containing the e-liquid in a manner that results in the e-liquid being inaccessible through customary or reasonably foreseeable handling or use, consistent with the Child Nicotine Poisoning Prevention Act of 2015. In addition, the e-liquid quantity is only 0.94 mL and it is contained in a sponge and is not free-flowing. There is a low risk of poisoning from an engineering perspective.
- The new products have small packaging components that could present a choking hazard if not disposed of properly. They have a silicon end tip side cap and silicon mouthpiece side cap that are 9.2 mm in diameter. This risk is being monitored by the applicant and no adverse experiences have been recorded.
- The applicant performed a design failure modes and effects analysis (dFMEA) for the new products. A risk assessment was completed by the applicant to identify potential risks in the design of the product including

battery rupture. The engineering review concluded that the applicant's risk assessment identified and implemented control measures that adequately mitigate foreseeable hazards.

- Chemistry:
  - The new products contain nicotine salt ((b) (4)). The source of nicotine is cross referenced to Tobacco Product Master Files (TPMFs). According to the applicant, the nicotine used is extracted from *Nicotiana tobacum* plant. Per the TPMFs (b)(4) the nicotine specifications meet those in US Pharmacopeia monograph 41.
  - The 4.5% nicotine e-liquid contains (b) (4) The 6.0% nicotine e-liquid contains (b) (4) . With regard to nicotine salts in the new products, the applicant used (b) (4) The applicant indicated the main purpose is to (b) (4) The applicant stated (b) (4) Chemistry noted the nicotine concentration and nicotine form are comparable between the new products and the comparison ENDS product (Leap Go Smooth Tobacco 5% nicotine salts). Leap Go Smooth Tobacco 5% nicotine salts is in the same category (ENDS Vapes) and subcategory (closed E-cigarette) as the new products and is, like the new products, disposable and non-rechargeable. Chemistry review found the applicant's justification for use of (b) (4) in the formulation acceptable.
  - All PMTAs included single chemical and complex ingredient information for e-liquids and the information is acceptable. All PMTAs included ingredient information and extractables and leachables (E&L) study results for the product structure materials that are in contact with e-liquids/aerosols. The ingredient information and E&L study results are acceptable from a chemistry perspective as the above provided information is sufficient and adequate for product evaluations.
  - The applicant provided uniquely identifying information for materials and ingredients for the container closure system (CCS), and the information is acceptable from chemistry perspective. For all PMTAs, the applicant provided the material/ingredient quantities in percentages without providing the absolute quantity of the materials/ingredients. This limitation does not impact the outcome of this review, because the applicant provided the time zero leachable data for all bulk e-liquids.
- Microbiology:
  - The new products are a closed ENDS device that heats an e-liquid to yield an inhalable aerosol. The device consists of two permanently connected subsystems: cartomizer and power. The cartomizer is a sealed, prefilled, non-refillable, disposable CCS containing 0.84 to 0.94 mL of e-liquid that includes an atomizer for aerosolization and an airway to transport aerosol to user.

- The new products contain humectants (b) (4)) which may impact microbial activity during product shelf life. The stability of the new products is discussed in Section 3.2.1.3 of this review.

3.2.1.2 Manufacturing

- Engineering:
  - The applicant subcontracts the manufacturing of the products to (b) (4) . The applicant provided a description of the manufacturing process at (b) (4) including the manufacturing steps, the sources of the components assembled, the packing processes, and the associated quality control (QC) and safety mechanisms that are in place. (b) (4) . Then, the assembly is completed, and the product is packaged.
  - The applicant states it audits the (b)(4) of the suppliers and contract manufacturers periodically to ensure compliance with applicable internal and external standards and regulations. The applicant supplied the relevant documentation for their (b) (4) including the (b) (4) documentation for (b) (4) The information on the manufacturing steps and the quality control measures in place demonstrate that the products meet manufacturing specifications for the new products and that the products are manufactured in a consistent manner that minimizes the variability in product quality.
  - The above information submitted regarding the manufacturing process and quality control measures is acceptable from an engineering perspective.
- Chemistry:
  - The manufacturing procedures for the new product e-liquids ((b) (4) and all e-liquids cartridge filling (by (b) (4) are acceptable from a chemistry perspective. All PMTAs included representative ingredient Certificate of Analysis (CoA) for each ingredient, raw ingredient quality control test results, batch verifications, liquid properties, and constituent measurements.
  - Quality control test data provided for all PMTAs are within the acceptance criteria indicating batch consistency with respect to the provided e-liquid properties. The applicant provided the test information (methods, validation reports, and test laboratory quality management system) for the (b) (4) in-process and batch release testing and a valid laboratory accreditation certificate for (b) (4) The applicant provided pH and density acceptance criteria and included (b) (4) as a product quality measure for the new products manufactured by (b) (4) The information provided demonstrated that each new product's quality was controlled in a consistent manner and, therefore, is acceptable from a chemistry perspective.
  - The remote regulatory assessment (RRA) did not find any significant observations. The applicant provided 22 exhibits, 14 of which address the chemistry relevant items listed in the Firm Specific Package (FSP). All 14 exhibits were acceptable from a chemistry perspective.

- The applicant provided data for in-process/batch release testing and specifications for all PMTAs and the test information (test methods, validation reports, and testing laboratory quality management system) for manufacturing batches of the new products. (b) (4) Chemistry found (b) (4) Overall, from a chemistry perspective, the data quality information in the submission on in-process/batch release testing, liquid properties, and constituent measurements demonstrates there is suitable quality, data accuracy and reliability in test results, and therefore, the data quality information provided by the applicant is acceptable from a chemistry perspective.

- Microbiology:
  - The bulk e-liquid manufacturers used by the applicant conduct e-liquid blending and filling operations by (b) (4) an A2LA ISO 17025:2005 certified laboratory, and (b) (4) an on-site laboratory, in an ISO Class 8 clean room.
  - (b)(4) perform release testing on the finished bulk e-liquids that were packaged in the new products.
  - The released finished bulk e-liquids are dispensed into (b)(4) and sealed (b)(4) and shipped to the GMP certified (b)(4) to manufacture and package into finished new products.
  - At (b)(4) (ISO 9001:2015 certified) personnel sample and test the finished new products (organoleptic testing for e-liquids only). The new products that are compliant with NJOY specifications are released for shipment. This information is acceptable from a microbiology perspective.

3.2.1.3 Product stability

- Chemistry:
  - The applicant provided complete stability study data including test data for bulk e-liquids, finished product e-liquids, and aerosols; extractables and leachables data for components and parts and CCS; the stability specifications; justifications for the specifications; and justifications for bridging the bulk e-liquid stability data from NJOY Daily Extra Rich Tobacco 6% nicotine (not subject to this PMTA review) to the new products for sealed bulk e-liquid shelf life. The applicant proposed a shelf life of (b) (4) for the finished new products, and a shelf life of (b) (4) for bulk e-liquid in all PMTAs. All stability data show that the finished products (e-liquids and aerosols) and bulk e-liquids in all PMTAs meet the stability specifications at the proposed shelf life, demonstrating that the shelf life for finished products in all PMTAs is (b) (4) whereas the shelf life for sealed bulk e-liquids is (b) (4).
  - The applicant provided homogeneity data demonstrating that the new products remain homogeneous (b) (4) This is acceptable from a chemistry perspective.

- For all PMTAs, the applicant justified bridging the bulk e-liquid shelf life of NJOY Daily Extra Rich Tobacco 6% nicotine to the new products because the nicotine content in NJOY Daily Extra Rich Tobacco is the highest (6.0%) and, therefore, is expected to generate the highest amount of nicotine related substances (NRS). This justification alone is not acceptable because the bulk e-liquid stability data show that 4.5% nicotine content bulk e-liquid of other flavors (e.g., (b) (4)) contains a higher amount of certain (b) (4)). However, the specification of total (b) (4) is lower compared to that for NJOY Daily Extra Rich Tobacco 6.0% nicotine content bulk e-liquids ((b) (4) µg/g) and thus, is acceptable.

- Microbiology:
  - The microbial stability data are necessary for the proposed shelf life as bacterial communities change as a function of storage time. 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 (Chopyk et al., 2017; Djordjevic et al., 1993).
  - The applicant provided stability testing data (water content, TAMC, and TYMC) that support (b) (4) of shelf life following new product storage at (b) (4) relative humidity (RH). Therefore, the data provided are sufficient to demonstrate the microbial stability of the finished products for (b) (4)
  - Endotoxin testing data at zero and (b) (4) were provided for all new products. All new products' endotoxin content is below the acceptable limits (≤ (b) (4) EU/mL or ≤ (b) (4) EU/device) as established by USP<161> or FDA Guidance for Industry 2012[7].

3.2.1.4 Product test data

- Engineering:
  - The product performance testing provided demonstrates conformance with the finished product release specifications set for the new products. The applicant has provided adequate information to demonstrate that the new products can be manufactured consistently and meet the applicant's pre-defined quality controls and specifications, and that they will operate consistently throughout the life of the product.
- Chemistry:
  - All analytical methods and validations for chemical characterizations (of e-liquids and aerosols) and product stability studies of all PMTAs are sufficient to support the provided test data.
  - The aerosol HPHC yields of the new products are tested under intense and non-intense regimens. There are significant reductions in HPHCs from the new products' aerosols compared to CC comparison data under intense and non-intense regimens.

[7] Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM), Center for Devices and Radiological Health (CDRH), Office of Regulatory Affairs (ORA), Food and Drug Administration, US Department of Health and Human Service. *Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers*. Compliance; June 2012. https://www.fda.gov/media/83477/download

- The aerosol generation regimens (non-intense and intense) selected for all PMTAs are appropriate and represent the range of emissions including the emissions that could occur during heavy use of the new products.
- The acceptable levels (i.e., stability specifications) of aerosol constituents of all new products at (b) (4) (b) (4) are higher than the corresponding constituents in the aerosol of comparator product when compared to the comparator product characterization test data.

- Microbiology:
  - Stability testing data (Water content, TAMC, TYMC) that supports (b) (4) of shelf life were provided at time points ((b) (4)) following new product storage at (b) (4) . From amicrobiology perspective, the provided stability testing is sufficient to demonstrate the microbial stability of the products over the applicant proposed shelf life of (b) (4) .
  - Endotoxin testing data at zero and (b) (4) were provided for all new products. All new products endotoxin content data are below acceptable limits (≤ (b) (4) EU/mL or ≤ (b) (4) EU/device) as established by USP<161> and consistent with recommendations set out in FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers, June 2012 (https://www.fda.gov/media/83477/download).
  - The information submitted regarding endotoxin content levels in the new products is acceptable from a microbiological standpoint.

3.2.2 Synthesis

As TPL, I agree with engineering, chemistry, and microbiology conclusions that these PMTAs contain sufficient information to characterize the product design and adequate manufacturing processes and controls to help ensure that the new products meet the manufacturer's specifications.

I agree with the engineering review that these PMTAs contain sufficient information to characterize the product design, composition, manufacturing, and test data. The devices were designed and tested to minimize the risk of fire, explosion, and accidental poisoning. The battery of the new products has UL1642 Certification, which suggests a low risk of overheating, fire, or explosion; the battery does not present an increased risk compared to other similar battery-powered ENDS products. Engineering review identified a potential choking hazard from small packaging components as a limitation; however, no adverse experiences related to the small packaging components have been recorded for the new products and this is being monitored by the applicant. Thus, this limitation represents a low risk and is acceptable from engineering perspective. Further, manufacturer's post-market reporting obligations will allow FDA to monitor and assess any potential issues with accidental exposure.

Chemistry review found that the applicant's materials and ingredient information was adequately described, and, as TPL, I agree with Chemistry's conclusions. Nicotine salt and (b) (4) are used for nicotine delivery in the droplet phase of the aerosol and for palatability. (b) (4) (see Section 3.1.1), resulting in less throat irritation for the user. I agree with

Chemistry and Toxicology (see Section 3.1.1) that the use of nicotine salt and (b) (4) in the new products at the indicated levels are acceptable.

I also agree that manufacturing procedures information provided by the applicant showed that the new products have consistent quality control with only negligible limitations regarding (b) (4) specification. The applicant provided adequate justifications for bridging the bulk e-liquid stability data to the new products, and the finished products (e-liquids and aerosols) in all PMTAs meet the stability specifications. The applicant's product stability data support an intended (b) (4) shelf life for the finished products and (b) (4) shelf life for sealed bulk e-liquid. Microbiological stability testing data supports a (b) (4) shelf life for the finished products.

3.3 ABUSE LIABILITY

3.3.1 Discipline key findings

3.3.1.1 Current tobacco users

- Behavioral and Clinical Pharmacology (BCP):
  - '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 tobacco product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted to the product.
  - The new products contain nicotine salts and have nicotine concentrations that are in the higher range (4.5% and 6%) of ENDS sold in the United States (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 lower nicotine concentration ENDS.
  - 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 potentially further increase abuse liability. 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 likely lower and may reach, but not likely exceed, that of CC.
  - Results from an applicant-submitted clinical study suggests that the new product in PM0000629.PD1 produces lower nicotine exposure and subjective effects than CC, suggesting lower abuse liability for this new product. Bridging information provided by the applicant for the untested

new product in PM0000628.PD1 suggests that abuse liability for this product could be as high as, but no higher than, the new product in PM0000629.PD1.

- Evidence from the peer-reviewed literature suggests flavored ENDS can modulate the sensory, preference, liking, rewarding, and reinforcing effects of e-liquids, thereby facilitating ENDS use and increasing abuse liability. Some evidence suggests that e-liquid flavors influence ENDS puffing patterns and thereby influence nicotine exposure (St Helen et al., 2017; Voos et al., 2020). Results from the applicant-sponsored study "m5-2-1-01-study-npk-019-dacc-report" also suggest puff topography measures (e.g., puff duration; puff volume) for the new product in PM0000629.PD1 may be higher than CC, suggesting users were engaging in compensatory ENDS use behavior to increase nicotine exposure. However, nicotine exposure did not exceed that of a CC as reported in this study.
- Results from an applicant-submitted clinical study involving acute exposure to new products (cross-referenced other NJOY ENDS products PM0000630 and PM0000631, not subject to this PMTA review) suggest these products may have lower nicotine exposure than comparison ENDS products. However, the applicant did not provide information to bridge these findings to the new products in PM0000628.PD1 and PM0000629.PD1; therefore, based on data from this clinical study, it is unclear how the abuse liability of these new products compares to other ENDS.

3.3.2 Synthesis

The applicant submitted data and analyses for two clinical study reports, one user survey and biomarker study, and two literature reviews to address the pharmacokinetics (PK), pharmacodynamics (PD), subjective effects, and puff topography of the new products. Clinical study "m5-2-1-01-study-npk-019-dacc-report" examined the new product PM0000629.PD1 for abuse liability and the applicant bridged the findings to the untested new product PD0000628.PD1. Clinical study "m5-2-2-01-study-nj-007-lact" examined the abuse liability and product use behavior of the cross-referenced PMTAs (cross-referenced PM0000630 and PM0000631, not subject to this PMTA review) and compared them to other ENDS products. Survey study "m6 2-4-pro00037699" examined dependence and biomarkers of exposure (BOE) of NJOY DAILY products. In the literature reviews, there were no data specific to the new products and the applicant states that information in the literature is considered to be secondary to the data provided as part of the applicant's survey study.

The applicant-submitted data analysis and BCP evaluation on the two clinical studies suggest that the new products are associated with a lower C_{max} (maximum nicotine concentration), a lower $AUC_{0\text{-}120}$ (plasma nicotine exposure measured by area under the curve over 120 minutes), and a greater T_{max} (time at which maximum concentration of plasma nicotine occurred) than CC, indicating a likely lower abuse liability of the new products compared to CC. The applicant-submitted clinical study data also suggest differences in puff topography measures (e.g., puff duration; puff volume) between the new product in PM0000629.PD1 and CC, indicating potential compensatory ENDS use behavior by the users to increase

nicotine exposure; however, nicotine exposure did not exceed that of a CC as reported in this study.

I agree with BCP evaluation and conclusions that the new products have comparable or lower abuse liability compared to CC, which potentially helps reduce smokers' urge to smoke, and therefore may facilitate smokers switching from CC to ENDS products. With experience, users might reach higher nicotine levels to satisfy the withdrawal and craving symptoms. Although the overall abuse liability of the new products may be lower than CC, it is likely sufficient to sustain dependence in already nicotine-dependent smokers. This is potentially beneficial for smokers trying to switch to ENDS as they are more likely to have satisfactory results and not resume cigarette smoking, thus being exposed to lower levels of HPHCs. Therefore, the relatively lower but comparable abuse liability of the new products to CC suggests that the new products may serve as an appropriate substitute to CC among adults who smoke CC and want to quit smoking, facilitating complete or partial switching among CC users.

3.4 USER POPULATIONS

The relevant studies submitted by the applicant include:

NJOY User Study - Study Pro00037699 entitled, "A Prospective Longitudinal Online Survey Evaluating the Effectiveness of NJOY DAILY ENDS on Reduction, Abstinence, and Switching from Conventional Cigarette Use in a National Purposive Sample of US Adults Aged 21 Years and Over." (conducted in 2020[8]) that evaluated complete switching behaviors among adults who use NJOY DAILY ENDS over three months (the CC smoking status at three months was referred to by the applicant as the Primary Outcome Cohort). The baseline (n=3634) survey for this study includes participants who completed the survey (cohort n=533) on or before January 10, 2020, with follow-up at months 1, 2, and 3, ending April 17, 2020. The applicant amended the NJOY User Study submission to include a sample size of 2,776 for the three month primary outcome cohort on July 13, 2020 (PM0000829). Further, the applicant submitted "Primary and Secondary (Six-Month) Outcomes Report and Additional Analyses (Appendix A) Showing the Role of NJOY DAILY and Flavors on Complete Switching" with 6-month outcome data for 2,533 participants and "Appendix A – Additional Flavor Analysis." (PM0004573) that compared outcome data between tobacco- and other flavored products. Furthermore, the applicant submitted "Amendment Report – Menthol-flavored NJOY DAILY" (PM0007181), which included re-analysis of the primary cohort (three month) and the secondary cohort (six month) outcome data from the NJOY User Study specific to the menthol flavored products (PM0000628.PD1-PM0000629.PD1). Switching outcomes were evaluated in the epidemiology review. Curiosity and perceptions about harmfulness and addictiveness were evaluated in the social science review.

[8] Participants filled out all required questions in both registration and baseline before January 11, 2020.

Adult Prevalence, Perception, and Intention to Use Study- Study 100134284 entitled, "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." (conducted October 30 - November 18, 2019) and supplemental analysis (referred to as the "Adult Prevalence Study"), which assessed perception, prevalence of use, and intentions to use NJOY products in adults. These outcomes were evaluated in the epidemiology and social science reviews.

Youth Perception Study- Study 0743-100134250 entitled, "An Online Survey of US Adolescents' Perceptions of the Risks and Intentions to Use NJOY Vapor Products." (conducted November 18 - December 11, 2019, referred to as the "Youth Perceptions Study"), which evaluated prevalence, curiosity, and intent to use the new products. These outcomes were evaluated in the epidemiology and social science reviews.

Youth Prevalence Study 1 - Study 100128478 (Jan) entitled, "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)" (conducted January 25 - February 4, 2019, referred to as the "Youth Prevalence Study 1), which evaluated 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.

Youth Prevalence Study 2 - Study 100128478 (Oct) entitled, "A Cross-Sectional Online Follow-Up 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)." (conducted October 17 - October 27, 2019, referred to as "Youth Prevalence Study 2"), which 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.

(b) (4) **Study Wave #1 and Wave #2** - two independent studies by (b) (4) which collected youth prevalence data by brand and flavor in 2021 and 2022. These data were evaluated in the epidemiology review.

The BCP review relied on data from the two applicant-submitted clinical studies to inform users' health 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.

3.4.1 Discipline key findings

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

3.4.1.1 Intended user population(s) (target population)

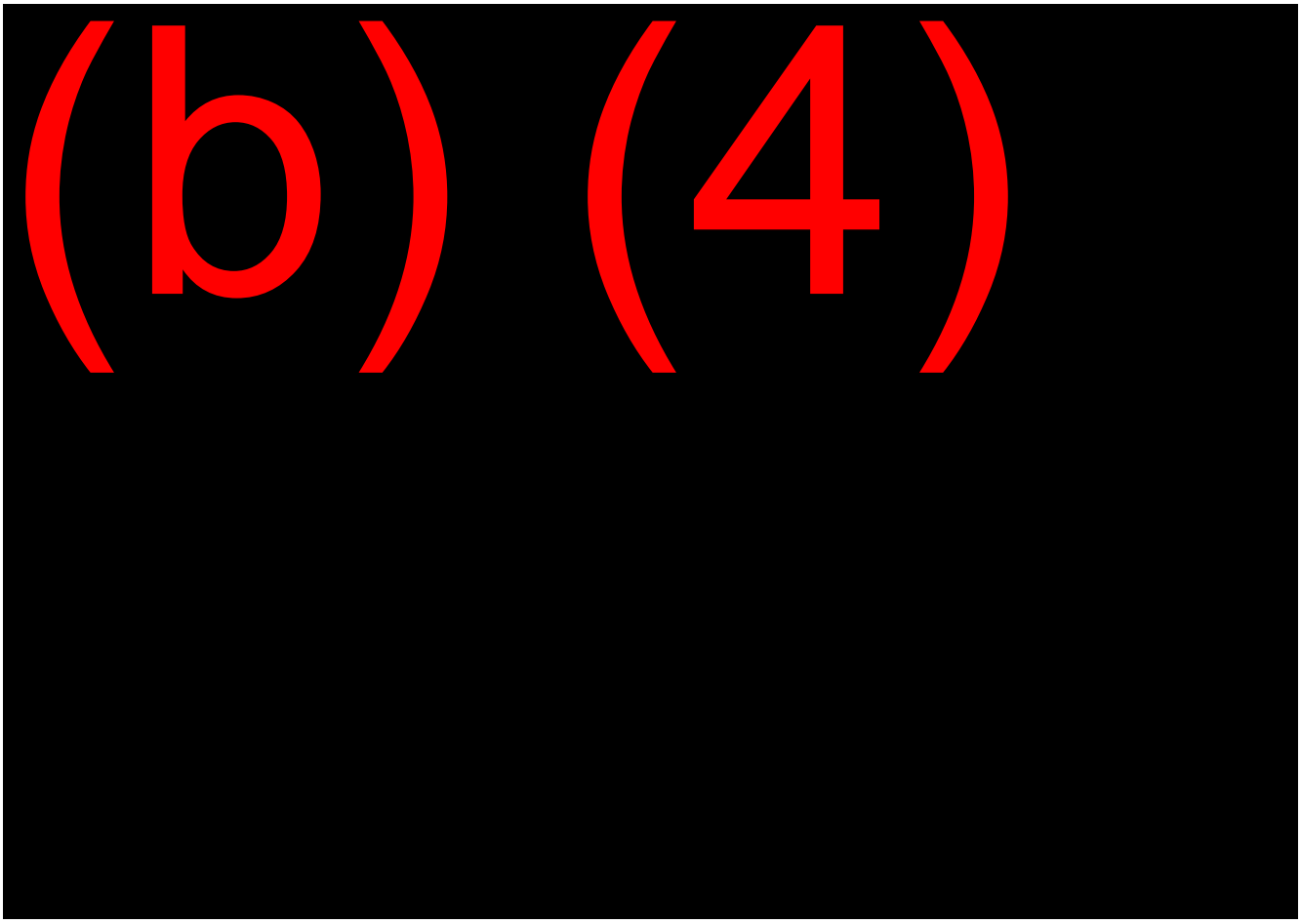
Per the social science, epidemiology, and BCP reviews:

- The applicant states that the intended users of the new products are "current adult users of nicotine-containing products who cannot or choose not to discontinue use of nicotine, particularly current combustible cigarette users and ENDS users."

3.4.1.2 Current tobacco users

- Social Science:
  - Based on the study data submitted by the applicant, current adult smokers appear to rate the new products overall as similar in terms of perceived harm and addictiveness to non-NJOY ENDS and nicotine replacement therapies. There are no concerning differences in perceptions among current smokers.
  - Applicant-submitted data suggest that curiosity about using the new products was low among current adult smokers ([redacted] but was greater than curiosity among former smokers ([redacted] and never smokers ([redacted] 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 & Son, 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 any of the new products in the next year was low among adult current smokers ([redacted] but was greater than intention to try among former smokers ([redacted] and never smokers ([redacted] There are no meaningful differences in curiosity or behavioral intentions among current tobacco users for any of the NJOY DAILY menthol-flavored variants compared to the NJOY DAILY Rich Tobacco products.
  - Amendment PM0007181 includes updated adult intentions data (not separated for adult current, former, or never tobacco users), which suggest no significant differences between overall adult intentions to use the NJOY DAILY Menthol variants and the NJOY DAILY Rich Tobacco variants.
  - The applicant did not submit data on perceptions or behavioral intentions regarding NJOY DAILY by other current tobacco user groups, including those who use non-NJOY ENDS products. Therefore, we do not know the extent to which current smokers who are also currently using other ENDS products intend to use NJOY DAILY.

- Epidemiology:
  - The prevalence of NJOY DAILY products use in general was approximately 0.3% among adults in the applicant-provided Adult Prevalence Study. The proportion of adult CC users who reported use of NJOY products was 2.3%. 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., 2019). 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 than never tobacco users. However, some of these outcomes could be due to cohort effects or product generational differences in the marketplace.
  - In the applicant's NJOY User Study (b) (4)
  - (b)(4)
  - (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 the conservative ITT analysis to account for potential bias associated with loss-to-follow-up, menthol as an initial flavor at baseline and as most used flavor at baseline both were significantly associated with higher rates of past 30-day CC smoking cessation than rich tobacco flavor(not subject to this PMTA review) at 3 months, which is the primary endpoint as proposed by the applicant. Additionally, menthol as the most used flavor at baseline was significantly associated with higher rates of past 30-day smoking cessation than rich tobacco flavor (not subject to this PMTA review) at 6 months.
- Some study limitations are noted to inform interpretation of the results (e.g., not reporting participants' menthol CC status; 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 at 3 months (PP analysis, aOR=1.24-1.50) of using NJOY DAILY Menthol ENDS products

compared to NJOY DAILY Rich Tobacco ENDS products (not subject to this PMTA review) in achieving past 30-day CC smoking cessation.

- 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 that the absolute switching rate (21-32%) was substantial and the adjusted odds ratio (aOR=1.24-1.50) for relative switching comparing menthol-to-tobacco flavored ENDS was moderate. The added benefit to adults can be characterized as highly beneficial.
- The applicant's analysis of the NJOY User Study reported on initial flavor used at baseline, as well as most used flavor at baseline. This did not include flavor use at any other timepoint (e.g. flavor use at time of switching). This information would have been valuable in evaluation of the overall application, and represents a limitation of the analyses. However, it does not prevent completion of the Epidemiology review.
- Based on the applicant's submitted data, a large number of NJOY DAILY users (likely >(b) (4) 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 DAILY ENDS. 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).

- BCP:
  - Based on a survey study provided by the applicant and findings in the literature, current tobacco users who use the new products are unlikely to switch completely to the new products, but are likely to be dual users of the new products and CC.
  - Based on the literature, current tobacco users may learn to titrate their use of the new products to their preferred nicotine exposures over time, thereby maintaining their nicotine dependence.
  - Clinical data provided by the applicant suggest the new products have abuse liability lower than, but perhaps approximating, CC among experienced ENDS users. Together with the published literature, this suggests users of the new products will maintain their nicotine dependence and have a low likelihood of complete cessation from tobacco products.

3.4.1.3 Tobacco non-users (including youth)

- Social Science:

- The data submitted by the applicant on reported curiosity and intention to try NJOY DAILY overall was low among adult never (5.1% and 0.5%, respectively) and former (3.5% and 0.8%, respectively) smokers. These data thus do not suggest that former and never smoking adults are interested in trying NJOY DAILY.
- The applicant does not include data on perceptions, curiosity, or behavioral intentions regarding NJOY DAILY menthol products specifically by tobacco use status for youth or adults (i.e., youth current smokers, youth non-smokers, adult current smokers, adult former smokers, adult non-smokers). However, the applicant does provide data from youth and adults, in general, so that is what is reported in this review.
- Amendment PM0007181 included the same data as previously submitted but added new analyses for the data. Social Science did not find a meaningful difference in curiosity or behavioral intentions among youth or adults for any of the NJOY DAILY Menthol-flavored variants compared to the NJOY DAILY Rich Tobacco flavored variants (not subject to this PMTA review).
    - A similar proportion of youth overall report curiosity in Menthol (Menthol (b) (4) (b) (4) and EXTRA Menthol (b) (4) (b) (4) and Rich Tobacco flavored NJOY DAILY products (Rich Tobacco (b) (4) (b) (4) and EXTRA Rich Tobacco (b) (4) (b) (4) Differences in curiosity between the Menthol variants and Rich Tobacco variants were not statistically significant.
    - A similar proportion of youth overall intend to try the Menthol (Menthol (b) (4) (b) (4) and EXTRA Menthol (b) (4) (b) (4) and Rich Tobacco flavored NJOY DAILY products (Rich Tobacco (b) (4) (b) (4) and EXTRA Rich Tobacco (b) (4) (b) (4) Differences in intentions to try the Menthol variants and Rich Tobacco variants were not statistically significant.

  Therefore, based on ratings of curiosity and intentions to use, the applicant's data suggest that youth do not differentially prefer the Menthol-flavored variants of NJOY DAILY to the Rich Tobacco flavored variants.

Social Science Key Findings from the Literature

- There is an abundance of literature about precursors to use of flavored ENDS, in general; however, these studies do 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 of adolescents 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). Examining flavors by device type utilizing 2023 NYTS data, fruit was the most commonly reported flavor for all device types (70.5% among disposable ENDS users), with the next most frequently reported flavors among disposable ENDS users in descending order as follows: candy, desserts, or other sweets (39.8%), mint (32.0%), menthol (18.7%), unflavored (7.8%), alcoholic drinks (7.2%), and tobacco (5.4%) (Birdsey et al., 2023). Overall, the literature substantiates that disposable 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. Youth use of menthol ENDS is greater than tobacco flavor, but lower than other flavors such as candy, desserts, and sweets.
- NYTS 2023 data indicate that among youth who use ENDS, disposables are the most commonly used device type (high school = 65.2%; middle school = 47.9%), and therefore the new products may pose a risk to youth (Birdsey et al., 2023).

- BCP:
  - Overall, the abuse liability of the new products appears to be somewhat lower than CC, mitigating concern of greater nicotine exposure and addiction potential than CC among youth. In addition, based on a survey study provided by the applicant, minimal use of the new products was observed among youth and non-tobacco users. However, menthol characterizing flavors in the new products may increase product abuse liability and initiation in youth relative to tobacco-flavored ENDS. In laboratory studies, young adult ENDS users report liking menthol flavors more than tobacco flavor (Leventhal, Cho, et al., 2019; Leventhal, Goldenson, Barrington-Trimis, et al., 2019); these flavors enhance sweetness/smoothness and may reduce the bitterness of nicotine for youth and young adults (Jackson et al., 2020; Leventhal, Cho, et al., 2019; Leventhal, Goldenson, Barrington-Trimis, et al., 2019). In addition, menthol flavors may encourage non-experienced ENDS users to continue using non-tobacco flavored ENDS (Leventhal, Cho, et al., 2019; Leventhal, Goldenson, Barrington-Trimis, et al., 2019). Furthermore, recent findings suggest that the use of disposable ENDS, like the new products, is increasing among youth (Wang et al., 2020), and ENDS that contain nicotine salt formulations 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. Thus, the presence of menthol flavors in the new products, as well as the fact that the new products are disposable ENDS containing nicotine-salt formulated e-liquids, may pose a risk of initiation across populations, including youth, young adults, and non-users.

- Based on data from the applicant submitted clinical studies, BCP concluded that the abuse liability of NJOY DAILY products is lower than or comparable to CC, mitigating concern of greater nicotine exposure and subsequent addiction relative to CC in youth and non-users.

- Epidemiology:
  - 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: (b) (4) and Wave #2 (past 30-day prevalence: (b) (4) The applicant also finds a low prevalence of NJOY ENDS and NJOY DAILY use among adolescents in their (b) (4) Wave #1 and 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) Wave #1 and Wave #2 had small sample sizes and thus were not able to provide reliable prevalence estimates of Menthol flavored NJOY DAILY use among youth. Moreover, the (b) (4) may be outdated. As such, the conclusions in the applicant's (b) (4) 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, and especially among youth and young adults. While NYTS data on the use of flavored ENDS products 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 products (89.4%) (Birdsey et al., 2023). In Wave 3 of the 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 NJOY DAILY Menthol flavored products may pose risks for youth initiation.
  - The 2019 Youth Perceptions study, a national survey of youth submitted previously by the applicant, suggests that among youth who reported ever using ENDS (n=1,070), 18.0% started with tobacco-flavored ENDS (not subject to this PMTA review), 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 DAILY ENDS, 13.3% reported starting with Rich Tobacco (not subject to this PMTA review), 45.6% reported starting with a (b) (4) and 32.8% reported starting with

Menthol. The 2019 Youth Perceptions Study also showed that among youth who reported using NJOY DAILY in the past 30-days (n=164), 40.5% report using the menthol flavor most often and (b) (4) [redacted]

3.4.1.4 Vulnerable populations (other than youth)

- Social Science
  - It is possible, based on the applicant's submitted data, that there are gender and race/ethnicity differences in intention to try NJOY DAILY among adults. The applicant summarizes what appears to be intention to try data that they call "initiation" in a logistic regression model in their Adult Perceptions Study. The model findings suggest that males were more likely to intend to try NJOY than females. In addition, White and Black non-users were less likely to intend to try than Hispanic and 'other' non-user race respondents. However, the modeling methods were not well described and included intention to try any NJOY ENDS product rather than NJOY DAILY. Therefore, it is unclear whether these findings indicate meaningful differences in NJOY DAILY use by gender and race/ethnicity from the social science perspective.
- Epidemiology:
  - 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 vulnerable populations (e.g., pregnant persons, and lesbian, gay, and bisexual individuals) (Azagba et al., 2019; Hawkins et al., 2020; Obisesan et al., 2020; Wheldon & Wiseman, 2019). While the evidence indicates that some vulnerable populations experience disproportionate ENDS use, there is a lack of currently available evidence to show whether the new products would help facilitate adult 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 (CPD).
  - The applicant did not provide information specific to vulnerable populations (i.e., groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation) in their application.
- BCP:
  - The applicant did not provide data on use of the new products among any specific vulnerable populations to examine potential differences relative to a general sample of adults who smoke CC. At this time, there is insufficient available information in the currently available scientific literature to conclude that the impact of the new products would differ for any specific vulnerable populations other than youth. Therefore, from a BCP perspective, it is unknown whether the impact of the new products on abuse liability and/or product use behavior would differ for certain

vulnerable populations (other than youth) relative to the populations studied.

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

Office of Health Communication and Education (OHCE) consult:

Office of Health Communication and Education (OHCE) has reviewed the marketing information for the new products and finalized a consult dated February 24, 2022.

- 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's stated intended audience is "current adult users of nicotine-containing products who cannot or choose not to discontinue use of nicotine, particularly current combustible cigarette users and ENDS users", and the following marketing channels are proposed by the applicant: point-of-sale signage, product displays in non-self-serve areas of retail locations, "digital messages distributed via mobile applications or email mailing list subscriptions maintained by traditional tobacco retailers" to only age-verified adults (21+) who opt-in to such communications, and a company-owned website.
- 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,
        - Direct mail advertising,
        - Search engine advertising,
        - Online display advertising,
        - Paid or unpaid product placements,
        - Public relations or earned media,
        - In-person engagements or activations,
        - Social media promotion,
        - Partners, sponsors, influencers, 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 Daily products;
- Prohibiting the sale of NJOY Daily 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 the product website or conducting online sales;
- Requiring retailers to only place NJOY Daily 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.

Social Science:

- 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 DAILY 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

Social Science:

OCE DPAL noted that the applicant lists 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 application, 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 people 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 (Birdsey et al., 2023) 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 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, Cheng, et al., 2020).

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

[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.

[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#.

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 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 products (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 substantiates that menthol-flavored ENDS pose a known and substantial risk to youth[14].

[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

[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).

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 people 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 evidence could be generated from (1) an RCT or (2) a longitudinal cohort study. Although RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity, cohort studies enable stronger generalizability because conditions are closer to real-world. FDA is aware of these trade-offs and generally does not favor one type over the other for addressing this question.

To be informative, a study using one of these two designs would measure the impact of use of the new and appropriate 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 cigarette 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.

[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.

[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)".

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 people 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. 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 & Green, 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, Chang, et al., 2020). 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, 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 people 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 people who currently use CC (including people 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

[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 here at this time.

[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.

The applicant submitted data and analyses in their original submission for five observational studies, including two adult studies and three youth studies, to assess product perceptions, appeal, and behavioral intentions from adult tobacco users and youth. The applicant also submitted amendment PM0007181 on December 21, 2022 that includes clarification information and re-analyses for the previously submitted data regarding the menthol-flavored products, focusing on adult switching, youth perceptions, and new youth prevalence data. We consider the evidence submitted by the applicant 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.

Youth Appeal and Prevalence

The applicant submitted youth prevalence estimates for NJOY ENDS and NJOY DAILY products, suggesting a finding of low overall prevalence of ENDS use, low prevalence of NJOY ENDS use, and low prevalence of NJOY DAILY use. However, these data were collected before 2022 and may no longer reflect current youth use. Nationally-representative data from the 2022 NYTS shows that NJOY (of which there are many sub-brands, including DAILY) was the 5th most-reported brand used in the past 30 days (i.e., 8.3% of current ENDS users) among middle and high school students (Cooper et al., 2022); in 2023 NJOY was ranked 10th (i.e., 7.5% of current ENDS users) (Birdsey et al., 2023).

Regarding youth curiosity, intention, and initiation, the applicant-submitted data suggest no meaningful differences in curiosity and intention to try in youth for the menthol-flavored NJOY DAILY products and tobacco-flavored NJOY DAILY products. The applicant-submitted data also show that fewer youth initiated with and used the menthol-flavored NJOY DAILY products than fruit-flavored NJOY DAILY products (not subject to this PMTA review), which is consistent with the literature on ENDS in general (Cooper et al., 2022; Rose et al., 2020). Additionally, 2023 NYTS estimates suggest that among ENDS users, approximately 90% of youth use flavored ENDS, while 20% of that population use menthol-flavored products. Nevertheless, these 2023 NYTS data and other data discussed through this TPL 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 and switching data

The applicant states that the intended users of the new products are current adult users of nicotine-containing products, particularly CC users and ENDS users, who cannot or choose not to discontinue use of nicotine. The epidemiology review noted that a large number of NJOY DAILY users (likely >40%) will become dual users with CC (i.e., adults who smoke CC and do not completely switch to NJOY DAILY products), similar to what is reported in the literature. I agree with the BCP and epidemiology reviews that the new products will be most commonly used together with CC (i.e., dually used). 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 is associated with decreased CC consumption compared to levels when they were smoking CC exclusively. While there is some evidence of modest reduction in some BOEs when adults who smoke CC switch to dual use of ENDS and CC, the conclusions from the literature are mixed, which suggest that BOEs are generally similar among adults who dually use ENDS and CC compared to adults who exclusively use CC (Arnold et al., 2021; Cohen et al., 2021; Czoli et al., 2019; D'Ruiz et al., 2016; Goniewicz et al., 2018; Jay et al., 2020; Morris et al., 2022; O'Connell et al., 2016; Polosa et al., 2014; Pulvers et al., 2018; Pulvers et al., 2020), suggesting this population is unlikely to experience health benefits.

Significant adult benefits for users of the new products are expected from complete switching from CC to ENDS, which is associated with substantial decrease in many BOE (see Section 3.5.1.2.) and may lead to complete tobacco cessation. A recent Cochrane review evaluated tobacco cessation rates with various smoking cessation 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. Additional evidence concludes with “high-certainty evidence” that nicotine-containing ENDS are more effective at promoting smoking cessation than NRT (Lindson et al., 2024). These data suggest that ENDS, in general, have an adult benefit to public health by facilitating complete switching from CC.

To demonstrate the new products’ potential to facilitate complete switching, the applicant submitted amendment PM0007181 that includes new analyses for the previously submitted data in the NJOY User Study. Per the epidemiology review, the estimated absolute rates of complete switching (i.e., cessation of CC with continued ENDS use, as well as cessation of CC and ENDS) for the NJOY DAILY ENDS products are higher than nationally representative estimates of ENDS in general. Additionally, the applicant’s analysis suggests that, among users who smoke CC at baseline, using menthol flavored NJOY Daily ENDS products was associated with significantly higher rates of switching to ENDS than using the tobacco flavored NJOY Daily products in the NJOY User Study. Specifically, the majority of the primary (3-month) and secondary (6-month) per protocol and ITT estimates for 30-day PPA (representing complete switching) among NJOY DAILY users who used Menthol flavor (per-protocol range: (b) (4) ; ITT range: (b) (4)) are significantly higher than the estimates for users who used Rich Tobacco flavor NJOY DAILY products (not subject to this PMTA review, per-protocol range: (b) (4) ; ITT range: (b) (4) (Section 3.4.1.2, Table 3).

The observed higher rates of absolute switching in users of the NJOY DAILY ENDS products than users of ENDS in general is supported by the BCP review conclusions because the abuse liability of the NJOY DAILY ENDS, which is similar to, though lower than, that of CC may facilitate complete switching (i.e., CC cessation) compared to other ENDS with lower abuse liability. Additionally, the new products’ nicotine salt formulation also suggests that the new products may be substitutable to CC, given their similar nicotine delivery patterns to CC. Thus, the abovementioned higher switching rates may be reflective of the new products’ capacity to offer users a similar use experience to CC (i.e., greater substitutability).

To evaluate the extent of promoting switching in adults who smoke cigarettes by the menthol-flavored new products (measured by 30-day PPA) relative to the tobacco-flavored NJOY DAILY products (not subject to this PMTA review), several variables were included in the applicant-submitted analysis, including initial flavor used at baseline, most used flavor at baseline, durations of follow-up (i.e., 1, 2, 3, and 6 months), and types of analyses (e.g., per-protocol and ITT). To address several gaps in the applicant-submitted analyses, a statistical consult was conducted and completed on December 5, 2023. The consult results and the associated epidemiology review suggest that the applicant's NJOY User Study presents reliable and robust data that menthol-flavored NJOY DAILY ENDS products are associated with higher rates of complete switching than tobacco-flavored NJOY DAILY ENDS products (not subject to this PMTA review). Additional statistical analyses determined an aOR value of 1.24-1.50 (aOR = 1.24-1.50) based on the switching data for menthol flavor versus tobacco flavor at 3 months, suggesting approximately 24%-50% higher switching rate in users of the menthol-flavored new products than that in users of the tobacco-flavored NJOY DAILY products (not subject to this PMTA review) (Table 3). Additionally, higher switching rates for menthol flavor compared to tobacco flavor were seen in the ITT analysis (which the epidemiology review characterized as the most conservative estimate of switching) at 3-months (aOR=1.80-2.06, ITT analysis, Table 3). Further, similar higher switching rates were seen in the comparison at 6-months time point for menthol-flavor compared to tobacco-flavor (Table 3). The totality of evidence provided by the applicant suggests that the new products are associated with significantly higher smoking cessation rates than tobacco-flavored NJOY DAILY products. The epidemiology review determined that the applicant-submitted evidence is acceptably strong and the added benefit of these new products to adults is highly beneficial to public health.

The epidemiology review determined that the NJOY User Study was of sufficient quality. It is important, however, to interpret these findings in the context of study limitations and study design factors. For example, the epidemiology review notes that the study population may inflate the absolute switching rates reported in the NJOY User Study. The applicant recruited a convenience sample of adults who recently purchased NJOY DAILY products to capture the impact of starting to use NJOY products on CC smoking. Recruitment of a population of new users may 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 DAILY products will affect CC cessation. This is because eligibility criteria for the NJOY User Study included being at least 21 years of age and having smoked 100 cigarettes throughout lifetime and smoked within the past 30 days (i.e., established adult smokers, who are the applicant's intended user population). Importantly, the comparison between menthol-flavor and tobacco-flavor NJOY DAILY products assess the same study population, and the final statistical analyses considered covariates such as "Baseline Motivation to Stop Smoking" and "Baseline Past 12m Quit Attempts". Additionally, 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 using menthol-flavored ENDS. Although the published literature has not demonstrated that use of menthol-flavored ENDS is associated with increased likelihood of CC cessation, it is possible that the availability of a menthol-flavored ENDS may lead to greater success quitting CC smoking when using menthol-flavored ENDS compared to

tobacco-flavored ENDS (Rostron, Chang, et al., 2020). Therefore, there may be additional benefit to adults who smoke menthol CC and use NJOY DAILY Menthol products.

To further evaluate the 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 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 and recommendations 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 general categories of statements 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 new menthol-flavored 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 the menthol-flavored NJOY DAILY ENDS products compared to the tobacco-flavored NJOY DAILY ENDS products (not subject to this PMTA review) 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

3.5.1 Discipline key findings

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

3.5.1.1 Toxicity

The 2nd cycle toxicology review evaluated the 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 ELCRc for the new products and then compared the associated risk to relative to CC as well as Center for Tobacco Product (CTP)-authorized ENDS[20].

Toxicology 2nd cycle review

- HPHCs in the aerosol of the new products were compared to the average HPHC yields in CC MSS. Most HPHC levels were lower in the new products relative to CC and as such the HPHCs levels in the aerosol of the new products are unlikely to raise toxicology concerns for users of the new products in comparison to average CC yields. (Note: HPHC exposure is not the only contributing factor to cancer risks – the overall genotoxic and carcinogenic risks from HPHCs, ingredients, and leachables are evaluated in the Toxicology addendum to the 2nd cycle review below and summarized in the Section 3.5.2.)
- Most of the HPHC yields were decreased in the aerosols of the new products compared to the applicant's comparison ENDS product, Leap Go Smooth Tobacco 5% flavors. Users of the new products are expected to have similar or less exposures to HPHCs compared to this ENDS comparison product from a toxicological perspective.
- All of the nicotine-adjusted HPHC yields (i.e., HPHC:nicotine ratios) in the aerosols of the new products were similar or lower compared to average HPHC:nicotine ratios for other ENDS products (i.e., cig-a-like, pod, and tank systems) at the tested conditions. Overall, users of the new products are expected to have similar or less exposures to HPHCs compared to other ENDS products from a toxicological perspective.

Toxicology addendum to the 2nd cycle review

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

- 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 characterization is an excess lifetime cancer risk (ELCR), which provides an extrapolated estimate for how many additional cases of cancer would be expected in a population exposed to a given

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

toxicant concentration and intake level for an entire lifetime based on the toxicant's carcinogenic potency.
    - As described in DNCS Memorandum (Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications; signed June 3, 2024), the ELCR approach is an objective way to consistently 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.
    - All individual ELCRs in a given product are added together to obtain a cumulative ELCR ($ELCR_c$) and compared to the $ELCR_c$ for 1R6F Kentucky research cigarettes, which are representative of combusted tobacco products, and to the median $ELCR_c$ of the CTP-authorized ENDS[20] (Memorandum: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications; signed June 3, 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 and as such could add to the cumulative cancer risk.
- Individual constituents of the new products are evaluated and placed into tiers as discussed in Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications (signed June 3, 2024), depending on the information available for the constituent.
    - Tier 1-3 constituents have been evaluated by IARC or 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.
- When the risk assessment is limited to Tier 1-3 constituents, PM0000628.PD1 has an $ELCR_c$ that is 0.17% of the 1R6F $ELCR_c$ and PM0000629.PD1 has an $ELCR_c$ that is 0.12% of the 1R6F $ELCR_c$. The associated $ELCR_c$ of both new products when considering only Tier 1-3 constituents is lower than the median $ELCR_c$ for CTP-authorized ENDS.
    - 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. Thus, it is important to understand and consider the risks represented by 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.

  - The ELCRc based on Tier 1-3 constituents is driven by acrolein, acetaldehyde, and formaldehyde, which are established HPHCs and classified by EPA/IARC into Tiers 1-3.
- When the risk assessment includes Tier 1-4 constituents, PM0000628.PD1 has an $ELCR_c$ that is about 15% of the 1R6F $ELCR_c$ and PM0000629.PD1 has an $ELCR_c$ that is about 14% 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 $ELCR_c$ based on Tier 1-4 constituents is driven by (b) (4) [redacted]
  - The constituents (b) (4) [redacted] 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, signed June 3, 2024), they were not included in the $ELCR_c$ assessments. These unknowns add to the uncertainty of the current risk assessment.
- For 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.
- The 2nd cycle toxicology review assessed nonclinical genotoxicity data based on in vitro exposure with whole smoke (combusted cigarettes) or whole aerosol. However, there is a limitation with genotoxicity assay results based on whole smoke or aerosol. Specifically, both new product aerosols contain ingredients, leachables, and HPHCs that are identifiable as carcinogens and their presence in whole aerosol should result in positivity, whereas the applicant's cited conclusions were negative. Of note, these are the same assays (e.g., Ames, MN assay) that also detected individual constituents as positive. The ELCR approach used in this addendum specifically addresses issues regarding the presence of carcinogens or potential carcinogens in the aerosol of the new products. As such, the individual constituent hazard identifications, exposures, and resultant ELCRs in this addendum are used in aggregate to update the 2nd cycle toxicology review conclusions (Section 3.1.6.1) regarding nonclinical studies that assessed genotoxicity based on whole smoke or whole aerosol as well as qualitative HPHC conclusions.

3.5.1.2 Biomarkers of exposure (BOE)

BCP:

- BOE data submitted from a survey study conducted by the applicant found that participants who had recently used only the new products had lower levels of the measured BOE (i.e., CO, cotinine, CEMA, 3-HPMA, and NNAL) relative to recent users of both the new products and CC (i.e., dual users). These data suggest that exclusive use of the new products may be associated with lower levels of BOE compared to concurrent use with CC.
- The published literature suggests CC smokers will likely experience significant reductions in volatile organic compound (VOC) exposure upon complete switching to ENDS (Goniewicz et al., 2017; Oliveri et al., 2020; Round et al., 2019). The applicant provided yields of some VOC HPHCs (e.g., acrylonitrile, benzene, propylene oxide, toluene) using mainstream smoke (MSS) concentration data derived from peer-reviewed scientific literature to represent the CC category and the levels of these VOCs from the new products. Not all VOCs that were submitted by the applicant are useful as BOE. However, the differences show lower levels of these VOC yields from the new products compared to the CC MSS data. Further details on the comparisons and HPHC yields not derived from the literature can be found in the chemistry and toxicology reviews.
- Heavy metal exposure is likely to stay the same or decrease upon complete switching to ENDS from CC (Goniewicz et al., 2018; Jain, 2019; Prokopowicz et al., 2019). Dual users who do not significantly reduce CC use will likely have comparable tobacco-specific nitrosamine (TSNA) and VOC BOE as CC smokers, or if CC use is reduced, they may experience low to modest reductions in these BOE (Pulvers et al., 2018).

3.5.2 Synthesis

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 tier groups of hazard identification, representing 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 Tier 4 constituents identified in the toxicology addendum have some uncertainty as to their cancer risks In comparative terms, when considering those Tier 1-4 constituents, the estimated $ELCR_C$s indicate that PM0000628.PD1 and PM0000629.PD1 are about 15% (i.e., estimated to carry a risk of 1 case of cancer for every 66 users) and 14% (i.e., estimated to carry a risk of 1 case of cancer for every 73 users), respectively, of the $ELCR_c$ of CC (i.e., estimated to carry a risk of 1 case of

cancer for every 10 users)[21]. While the overall estimated $ELCR_C$ due to exclusive use of the new products is substantially lower than the estimated ELCR due to the use of CC (estimated to be less than 25% of the 1R6F $ELCR_c$), these estimates are based on chemical exposure information, for which a reduction in exposure may not be proportionally associated with a reduction in cancer risk. Thus, there is uncertainty in how much less risk there is for a person who smokes CC and switches completely from CC to one of the new products. Importantly, due to the high cancer risk associated with CC use, even a substantial decrease in cancer risk relative to a CC still results in a significant risk compared to adults who have never used tobacco products or adults who formerly used tobacco products.

It is also important to consider the potential cancer risks associated with switching from a CTP-authorized ENDS to the new products given that adults who currently use ENDS are one of the applicant's intended populations (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 estimated $ELCR_c$ based on Tier 1-4 constituents is higher than the median $ELCR_c$ of CTP-authorized ENDS, which indicates toxicology concerns regarding the cancer risk (both using Tiers 1-4) to users that completely switch from other ENDS. The comparisons to CTP-authorized ENDS must be interpreted while considering the limitations[22] 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.

Regarding the aerosol constituents and HPHCs in the new products, the toxicology review concludes that users of the new products are expected to have similar or less exposure to aerosol HPHCs compared to users of CC, the ENDS comparison product of the same category, and other ENDS products. However, as provided in the toxicology addendum to the 2nd cycle toxicology review, HPHC exposure is not the only concerning genotoxicity risk to users of the new products, which also contain intact ingredients and leachable in the aerosol (see Section 3.5.1.1). As such, and per the toxicology addendum, if assessing risks based on HPHCs, ingredients, and leachables ELCR estimates, the new products' cancer risk is lower than that of continued use of CC. Additionally, per the BCP review, biomarkers of exposure (BOE) data were submitted from a survey study conducted in subjects that recently used only the new products. These subjects had lower levels of the measured BOE (i.e., CO, cotinine, CEMA, 3-HPMA, and NNAL) relative to recent users of both the new

[21] 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.

[22] The limitations of the approach include the limited number of constituents present in the products for which IARC/EPA have provided a complete assessment of inhalation genotoxcity and the limited number of authorized products with which a comparison can be completed.

products and CC (i.e., dual users). Based on the Toxicology and BCP conclusions on aerosol constituents and HPHC exposure and BOE measurements, I note that there may be a potential health benefit for adults who smoke CC and switch completely to the new products or dual use the new products with significant reduction in CC use compared to exclusive use of CC. These data are consistent with the literature on other ENDS and indicate a likely relative health benefit associated with exclusive use of the new products compared 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 of this TPL review 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 discipline reviews.

3.6.1.1 Toxicology

Toxicology:

- Nonclinical studies:
  - Aerosols from the new products and the ENDS comparison product, Leap Go Smooth Tobacco 5%, demonstrated no mutagenic (Ames assay), genotoxic (In Vitro Micronucleus (ivMN) assay), or cytotoxic (neutral red uptake (NRU) assay) potential at the concentrations and under the conditions tested. However, under the conditions tested, the CC comparison product, 1R6F Reference cigarette, showed significant mutagenicity, cytotoxicity, and genotoxicity.

- Toxicant and study integration
  - The applicant provided supporting data from literature reviews of 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) (Appendices B and C). The applicant claims that although data gaps remain on the health effects of ENDS products, the current state of the science supports that "health effects (if observed) from exposure to ENDS are less severe than health effects associated with CC smoke." (Appendix C, pg. 43, m4-5-risk-assess-rpt-app-c.pdf).

3.6.1.2 Bioresearch Monitoring (BIMO) inspection findings

BIMO inspection was not conducted at this time by FDA because the clinical studies were not considered pivotal and reported adverse experiences (AEs) did not raise clinically significant concerns.

3.6.1.3 Addiction as a health endpoint

- BCP:
    - Results from a clinical study provided by the applicant suggest that the new products in PM0000629.PD1 may have lower nicotine exposure than CC. Bridging information provided by the applicant for the untested new product in PM0000628.PD1 suggests that abuse liability for this new product could be as high as, but not higher than, the new product in PM0000629.PD1.
    - Overall, the data suggest that the abuse liability of the new products is likely sufficient to sustain addiction in nicotine-dependent populations.
    - Based on a survey study provided by the applicant and findings in the literature, current adult cigarette smokers (i.e., one intended user population for the new products) may maintain their nicotine addiction via dual use of the new products and CC and are unlikely to quit using tobacco products overall.
    - Overall, the abuse liability of the new products may be somewhat lower than CC, mitigating concern of greater nicotine exposure and addiction potential than CC among non-tobacco users, including youth. However, evidence from the literature suggests the menthol characterizing flavor of the new products may increase the risk of progression to regular use and nicotine dependence among youth, young adults, and non-users.

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

- Epidemiology:
    - 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 provided by NJOY use status and smoking status. However, these results should be interpreted with caution due to the short time period, 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 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 BRFSS studies in

ENDS users who never smoked 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 suggest that dual users may have higher levels of certain biomarkers of exposure including nicotine and its metabolites compared to CC smokers. Dual users have generally not been found to have reduced levels of constituents such as TSNAs and VOCs compared to smokers.
- Switching: One biomarkers study by Goniewicz et al. (2017) found levels of total nicotine and some polycyclic aromatic hydrocarbon metabolites did not change after switching from tobacco 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 do CC smokers (Anic et al., 2022). Nicotine levels among exclusive ENDS users have usually been found to be somewhat lower or comparable to levels among people who smoke cigarettes

- Medical:
  - The applicant's clinical studies provided data to evaluate the short-term-health effects of NJOY DAILY products. These studies were limited due to small sample sizes and relatively short time periods of product exposure, limiting the generalizability of the health effects data to a larger user population and extrapolation to the long-term health effects of the NJOY products. However the identified adverse experiences and health effects of the NJOY products were consistent with other previously authorized ENDS.
  - The applicant's literature review included ENDS as a general category but lacked NJOY specific literature data and bridging of the literature to the new products. However, based on the totality of the data reviewed, including the clinical studies, published literature, and adverse events, medical finds that the health effects identified in the applicant's clinical studies and other submitted data were consistent with those previously described with ENDs as a class of products.
  - The applicant reported non-serious burns in the provided consumer reports.
  - The applicant provided limited data on biomarkers of potential harm, limiting the insight into the health effects of the new products based on the biomarker data alone.
  - Based on the totality of information reviewed by medical, including the clinical studies, published literature, consumer reports, and adverse events, the short-term health effects of the new products are expected and consistent with those reported for this class of products and are thus acceptable from medical's perspective.

3.6.1.5 Likelihood and effects of product misuse

- BCP:
  - The applicant-submitted clinical studies and literature review did not provide data evaluating the likelihood of misusing NJOY DAILY products. Despite the lack of clinical data assessing product misuse, BCP concludes that the likelihood of misuse is low for NJOY DAILY products because they are closed-system ENDS. NJOY DAILY power settings are non-adjustable, and the e-liquid is enclosed in a pod, thereby reducing chances that users may manipulate ENDS product settings and e-liquid constituents, including nicotine levels, which may influence exposure to nicotine and other HPHCs in the aerosol.
  - The design features of the new products make it possible for users to misuse the products by engaging in "stealth vaping." This discreet form of ENDS use may involve inhaling deeply to avoid forming visible aerosol clouds or swallowing of aerosol during exhalation, which has the potential to impact nicotine or toxicant exposure. However, from a BCP perspective, the literature is unclear on whether this behavior influences nicotine and toxicant exposure.
- Medical:
  - The medical review notes that NJOY DAILY is a closed system that minimizes the probability of unintentional ingestion of the e-liquid. The device is powered by battery and although there is a risk for burns or explosions, no SAEs were reported by the applicant and the design of the device mitigates the risk of such adverse experiences.
  - The samples of labeling as provided by the applicant include a warning that the products contain nicotine and that nicotine is addictive. Warning labels on the products state that the new product is not intended for ingestion and could result in poisoning of consumers and that the new product is intended for inhalation by adult consumers only.
  - One concern identified by the applicant is the potential for choking on the silicon protective caps designed to be discarded prior to use; however, no cases of choking have been reported by the applicant and the product label states that the caps should be discarded prior to use. The labeling would mitigate the described potential risk and is thus acceptable from medical's perspective.

3.6.1.6 Adverse experiences

- Engineering:
  - The applicant supplied the consumer complaints (adverse experiences) for these new products for the calendar year 2020. The engineering-related adverse experiences were reviewed and they were not significant or serious per the Engineering perspective.

- Medical:
  - No deaths, serious AEs, or discontinuations of use due to AEs was reported in the applicant-provided clinical studies. Thirteen AEs were reported in the

clinical studies; eleven were described by the applicant as mild and two were moderate. All AEs resolved prior to the end of the studies. Overall, gastrointestinal AEs were the most commonly reported AEs, and were consistent with the AEs reported in the literature related to nicotine intake.

- In the applicant-submitted literature review on ENDS, AEs reported in published studies of ENDS products included cough, dry or irritated mouth or throat, dizziness or light headedness, 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 and were mostly minor in severity.
- Nine AEs were reported with the consumer report data provided by the applicant. One case of chest pain and one incident of difficulty breathing were reported by the applicant but were reported as non-serious experiences. Three reports of non-serious burns related to NJOY DAILY were reported by the applicant.
- The first analysis of the CTP Safety Reporting Portal (SRP) data was performed on 09/20/2020 with search inclusion dates 01/01/2014 to 09/21/2020. This analysis noted four reports of seizures, one pulmonary embolism, and two respiratory issues (coughing and productive cough/sore throat). The provided reports did not specify which NJOY ENDS products were used, the nicotine content, flavors, or whether any other products used in association with the reported AEs. Of the four reported seizures associated with NJOY products, none could be conclusively determined to be caused by the new products due to multiple factors including limited information provided, concomitant substance use, incorrect spelling, etc. No definitive concerns related to NJOY DAILY could be made from the provided information in the SRP.
- The second analysis of the SRP data was performed on 02/07/2023 with search inclusion dates from 09/21/2020 to 02/10/2023. Three new reports of health problems were identified, including one pneumonia, acute kidney injury, and respiratory failure, one burning mouth/throat with hypertension and tachycardia, and one ischemic stroke. The Medical review notes that the identified health effects information is limited and therefore, whether the identified AEs were related to the NJOY DAILY products is unclear.
- The third analysis of the SRP Data was performed on 02/06/2024 with search inclusion dates from 01/01/2014 to 02/01/2024. Two new reports were identified: one reporting product quality and the other reporting leakage and non-functional pods, both involving NJOY ACE pods (not subject to this PMTA review).
- Information in the SRP data is incomplete, which limits the ability to identify potential trends in adverse experiences for the new products to draw conclusions regarding health risks. Because of such limitations in SRP data (e.g., reports are voluntary, TPST reported experiences do not imply causation, reported information is often incomplete, reported information is generally not verifiable, etc.), it is not possible to determine if clinically relevant trends exist for the new products that are the subject of this review based on the SRP reports.

- FDA is aware of several health issues regarding the use of ENDS, specifically lung injury, seizures, and overheating/fire/explosion-related thermal burn injuries (OH/F/Exp).
    - (OH/F/Exp) is a potential risk with all ENDS. There were no reports of OH/F/Exp in the applicant's clinical studies, and consumer reports consisted only of instances of non-serious burns. Additionally, the device UL certification mitigate the risk of such adverse experiences according to Engineering (see Engineering cycle 1 review for details).
    - There were no reports of lung injury in the applicant's clinical studies.
    - 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.
    - 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, lung injury, and OH/F/EXP incidents.

3.6.2 Synthesis

I agree with the BCP review that the abuse liability of the new products is lower than or comparable to CC, yet likely sufficient to sustain addiction in nicotine-dependent populations who do not quit. There is potential that use of the new products, along with significant reduction or quitting cigarette smoking, will result in a reduction in exposure to many HPHCs, and such benefit will likely be greater for smokers who are able to switch completely to the new products. However, the social science review concluded that adults who do not use CC products and adults who formerly used CC products report low curiosity and intent to use the new products, suggesting less such benefit to these populations.

For short- and long-term health effects of ENDS use, there is some epidemiologic evidence suggesting associations between ENDS use and certain adverse health outcomes including cardiovascular disease, respiratory disease, and oral health. However, the Epidemiology and Medical reviews noted that the findings are inconclusive due to the limitation of clinical studies and lack of specific information on the NJOY DAILY products, and, as TPL, I agree with these conclusions. For the identified adverse experiences (AEs), medical review concluded that most reported AEs lacked information to definitely associate them with a specific NJOY DAILY product. For the AEs that were possibly related to NJOY products, the symptoms were mostly mild, and no serious AEs or deaths were reported in any of the applicant-sponsored studies.

BCP notes that the design features of the new products make it possible for users to misuse the products by engaging in "stealth vaping". However, BCP notes that the literature is unclear on whether this behavior influences nicotine and toxicant exposure. As TPL, I agree with BCP's conclusion and also note that no SAEs haven been reported by the applicant or in

the SRP data regarding stealth vaping. For potential risk for burns or explosions due to battery, I agree with Medical conclusions that no serious adverse experiences (SAEs) were reported by the applicant and the design of the device mitigates the risk of such adverse experiences. The Medical review also noted the potential choking risk from the silicon protective caps; however, the product label states that the caps should be discarded prior to use and this issue is being monitored by the applicant (see Section 3.2.2). Overall, as TPL, I agree with the Engineering, BCP, and Medical reviews that, the likelihood of misuse or poisoning is low for the new products due the product design (i.e., closed-system, pre-filled pod).

3.7 POPULATION AND PUBLIC HEALTH

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

Toxicology

- The applicant provided risk assessment analyses for: (1) ingredients in the e-liquids of the new products, (2) HPHCs in the aerosol for the new products, (3) leachables and extractables for the new products, and (4) alternative exposures (secondhand exposure to NJOY DAILY aerosol; oral and intentional ingestion of NJOY DAILY e-liquids; and incidental and accidental dermal exposures to NJOY DAILY products).
    - For ingredients in e-liquids of the new products:
        - A review of the toxicology literature for the identified compounds showed no definitive data on toxicity of these compounds in multiple organs and systems (e.g., developmental and reproductive toxicity, immunotoxicity, respiratory toxicity, and skin sensitization). Toxicology concluded that these ingredients identified by the applicant as possible chronic noncancer hazards are not of toxicological concern.
    - For aerosol HPHCs in the new products:
        - Noncancer outcomes for PG, VG, chromium, and nickel suggest possible adverse health outcomes with use of the new products. Average nickel and chromium aerosol levels are higher than the most conservative reference values (nickel, OEHHA REL; hexavalent chromium, ATSDR MRL) but are below some other reported reference values.
        - For cancer risks, chromium and nickel levels in the new products are higher than respective average CC smoke levels. However, the decreased HPHCs (NNN, NNK, acrylonitrile, cadmium, and lead) likely offset the increase in cancer risk due to chromium and nickel. The applicant submitted average MMS HPHC levels from the literature and FDA50 (Pazo et al., 2016), demonstrating that the

overall cancer risk for the new products is less than the cancer risk posed by the commercially marketed CC comparison products.

- For alternative exposures:
  - Secondhand exposures – secondhand exposures to HPHCs from ENDS aerosol is likely to be less harmful than secondhand CC smoke exposures, and although there is an increased risk of adverse health effects with exposures to e-liquids from alternate sources (i.e., dermal, oral and ingestion), the likelihood of being exposed through these means using these new products is low due to the design of the product (i.e., it is a closed ENDS product).
  - Oral and ingestion exposures – normal use of the NJOY DAILY products would not lead to significant oral exposure to HPHCs. There is a minimal risk from accidental poisoning and misuse of the new products; however, such risk is low due to the design of the new products.
  - Dermal exposures – While e-liquids in general present increased risk should accidental exposure occur, regarding the new product specifically, such exposure is unlikely due to the product design.

- Based on the proposed new products use scenarios, switching completely from CC smoking to the new products will likely result in the greatest reduction in HPHC exposures. Dual use of CC and the new products may offer decreases in HPHC exposures depending on if CC per day is significantly reduced.
- Overall, the risk assessments conclude that with complete switching from use of other tobacco products (i.e., other ENDS and CC) to use of the new products, the potential health risks are likely to be similar to use of other ENDS, and less than CC, when compared to continued exclusive use of these tobacco products. In addition, secondhand exposures to HPHCs from ENDS aerosol is likely to be less harmful than secondhand CC smoke exposures. There is an increased risk of adverse health effects with exposures to NJOY DAILY e-liquids from alternate sources (i.e., dermal, oral and ingestion), however, the likelihood of being exposed through these pathways is low due to the product design.

3.7.1.2 Population health impact (PHI) model

Epidemiology:

- The data inputs used in the applicant's population health modeling scenarios for ENDS generally and NJOY DAILY specifically both 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 Toxicology conclusions that switching completely from CC smoking to the new products may result in significant reduction in HPHC exposures in current CC smoking populations. I agree that the adverse health risks from secondhand exposures are lower than CC, and the closed-system design likely minimizes accidental exposures through the oral and dermal routes, which is consistent with the Child Nicotine Poisoning Prevention Act of 2015 as noted by Engineering review (Section 3.2.1.1). I also agree that the new products are most likely to result in dual use with CC, and dual use of CC and the new products may offer decreases in HPHC exposures depending on if CC per day is significantly reduced; however, reductions in exposure to HPHCs may not be as great in the dual user population compared to those who completely switch to use of the new products.

The applicant developed a population health impact model for specific NJOY DAILY use scenarios and also for all ENDS use in general. As TPL, I agree with Epidemiology conclusions that the applicant's modeling may overestimate actual switching rate from CC smoking to exclusive ENDS use, therefore overestimate whole population health benefits of the new products if marketed. Additionally, the modeling scenarios did not consider ENDS use among youth populations, an important aspect of public health consideration. The population health model is not particularly informative in the evaluation of whether marketing the new products is appropriate for the protection of public health. Given these limitations in the applicant's modeling methodology, the modeling projections are not particularly informative in the evaluation of whether the new products are appropriate for the protection of the public health. The determination of APPH will be made based on overall information evaluated.

3.8 STATUTORY REQUIREMENTS

3.8.1 Public health conclusion

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

3.8.2 Tobacco product manufacturing practices[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.

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

3.8.4 Product standards

There are no applicable product standards for the new products in 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 the conclusion.

4.2 ENVIRONMENTAL CONCLUSION

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

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 adult users who completely switch to less harmful tobacco products).

Based on the information provided in the application 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 when finished. 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). These same data show that, among youth, NJOY products are the 10th most-reported brand used in the past 30 days (Birdsey et al., 2023). According to the applicant's 2019 Youth Perceptions Study, more youth reported starting with menthol-flavored NJOY DAILY products than tobacco-flavored NJOY DAILY products (not subject to this PMTA review), demonstrating the new products' risk to youth.

Thus, the new products could be APPH only if the PMTAs present sufficient reliable and robust evidence of a potential benefit to adults who smoke CC and completely switch from, or significantly reduce, CC that outweighs the risk of appeal, initiation, and continued use to youth. The applicant submitted data and analyses from an online, observational LCS that assessed the rates of complete switching from CC (i.e., cessation of CC with continued ENDS use, as well as cessation of both CC and ENDS) when adults were using the new products (PM0000628.PD1, NJOY DAILY Menthol 4.5%; PM0000629.PD1, NJOY DAILY EXTRA Menthol 6%) and tobacco-flavored NJOY DAILY products (not subject to this PMTA review) over six months. The results suggest the new products' robust absolute switching rates (ranging 21-32%) comparing to the estimates for ENDS in general in the literature. Additionally, the results provide consistent and robust evidence that the menthol-flavored new products are associated with statistically significant and substantially higher rates (32-43%) of complete switching than the tobacco-flavored NJOY DAILY ENDS (21-37%; not subject to this PMTA review) at 3 or 6 months. Therefore, both of the new products provide a substantial added behavioral benefit (i.e., OR range 1.24-1.50) compared to tobacco-flavored NJOY DAILY ENDS (not subject to this PMTA review) among adults who quit smoking CC. As TPL, I believe this added benefit outweighs the menthol-flavored new products' risk to youth.

Furthermore, applicant-submitted clinical studies demonstrate that the new products' abuse liability is similar to CC among adults who are experienced with ENDS use, suggesting that the new products 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. Indeed, chemical evaluation of the new products' aerosols suggests that the new products have fewer, and lower levels of, many HPHCs compared to CC. Furthermore, a toxicology evaluation of the new products' estimated lifetime cancer risk (ELCR) predicts that adults who exclusively use the new products will have significantly lower concern of cancer risks than adults who use 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.

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 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 DAILY ENDS on third-party websites.

Together, the available evidence suggests that although the menthol-flavored new products pose risks to youth, the potential of the new products for adult who smoke CC 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, as TPL, I find that permitting the marketing of the new products, as described in the applications and specified in 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.

FDA has examined the environmental effects of issuing MGO 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.

6. REFERENCES

Anic, G. M., Rostron, B. L., Hammad, H. T., van Bemmel, D. M., Valle-Pinero, D., Arseima, Y., Christensen, C. H., Erives, G., Faulcon, L. M., & Blount, B. C. (2022). Changes in biomarkers of tobacco exposure among cigarette smokers transitioning to ENDS use: the population assessment of tobacco and health study, 2013–2015. *International journal of environmental research and public health*, *19*(3), 1462.

Apelberg, B. J., Corey, C. G., Hoffman, A. C., Schroeder, M. J., Husten, C. G., Caraballo, R. S., & Backinger, C. L. (2014). Symptoms of tobacco dependence among middle and high school tobacco users: results from the 2012 National Youth Tobacco Survey. *Am J Prev Med*, *47*(2 Suppl 1), S4-14. https://doi.org/10.1016/j.amepre.2014.04.013

Arnold, M. J., Nollen, N. L., Mayo, M. S., Ahluwalia, J. S., Leavens, E. L., Zhang, G., Rice, M., & Pulvers, K. (2021). Harm Reduction Associated with Dual Use of Cigarettes and e-Cigarettes in Black and Latino Smokers: Secondary Analyses from a Randomized Controlled e-Cigarette Switching Trial. *Nicotine Tob Res*, *23*(11), 1972-1976. https://doi.org/10.1093/ntr/ntab069

Audrain-McGovern, J., Rodriguez, D., Pianin, S., & Alexander, E. (2019). Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents. *Drug Alcohol Depend*, *202*, 149-155. https://doi.org/10.1016/j.drugalcdep.2019.04.037

Azagba, S., Latham, K., & Shan, L. (2019). Cigarette smoking, e-cigarette use, and sexual identity among high school students in the USA. *European Journal of Pediatrics*, *178*, 1343-1351.

Birdsey, J., Cornelius, M., Jamal, A., Park-Lee, E., Cooper, M. R., Wang, J., Sawdey, M. D., Cullen, K. A., & Neff, L. (2023). Tobacco product use among US middle and high school students—National Youth Tobacco Survey, 2023. *Morbidity and Mortality Weekly Report*, *72*(44), 1173.

Boykan, R., Messina, C. R., Chateau, G., Eliscu, A., Tolentino, J., & Goniewicz, M. L. (2019). Self-Reported Use of Tobacco, E-cigarettes, and Marijuana Versus Urinary Biomarkers. *Pediatrics*, *143*(5). https://doi.org/10.1542/peds.2018-3531

Carpenter, M. J., Wahlquist, A. E., Dahne, J., Gray, K. M., Cummings, K. M., Warren, G., Wagener, T. L., Goniewicz, M. L., & Smith, T. T. (2023). Effect of unguided e-cigarette provision on uptake, use, and smoking cessation among adults who smoke in the USA: a naturalistic, randomised, controlled clinical trial. *EClinicalMedicine*, *63*, 102142. https://doi.org/10.1016/j.eclinm.2023.102142

Cho, J., Goldenson, N. I., Stone, M. D., McConnell, R., Barrington-Trimis, J. L., Chou, C.-P., Sussman, S. Y., Riggs, N. R., & Leventhal, A. M. (2018). Characterizing polytobacco use trajectories and their associations with substance use and mental health across mid-adolescence. *Nicotine and Tobacco Research*, *20*(suppl_1), S31-S38.

Chopyk, J., Chattopadhyay, S., Kulkarni, P., Smyth, E. M., Hittle, L. E., Paulson, J. N., Pop, M., Buehler, S. S., Clark, P. I., Mongodin, E. F., & Sapkota, A. R. (2017). Temporal Variations in Cigarette Tobacco Bacterial Community Composition and Tobacco-Specific Nitrosamine Content Are Influenced by Brand and Storage Conditions. *Front Microbiol*, *8*, 358. https://doi.org/10.3389/fmicb.2017.00358

Cohen, G., Goldenson, N. I., Bailey, P. C., Chan, S., & Shiffman, S. (2021). Changes in Biomarkers of Cigarette Smoke Exposure After 6 Days of Switching Exclusively or Partially to Use of the JUUL System with Two Nicotine Concentrations: A Randomized Controlled Confinement Study in Adult Smokers. *Nicotine Tob Res*, *23*(12), 2153-2161. https://doi.org/10.1093/ntr/ntab134

Coleman, B., Rostron, B., Johnson, S. E., Persoskie, A., Pearson, J., Stanton, C., Choi, K., Anic, G., Goniewicz, M. L., Cummings, K. M., Kasza, K. A., Silveira, M. L., Delnevo, C., Niaura, R., Abrams, D. B., Kimmel, H. L., Borek, N., Compton, W. M., & Hyland, A. (2019). Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study,

Waves 1 and 2 (2013-2015). *Tob Control*, *28*(1), 50-59. https://doi.org/10.1136/tobaccocontrol-2017-054174

Conway, K. P., Green, V. R., Kasza, K. A., Silveira, M. L., Borek, N., Kimmel, H. L., Sargent, J. D., Stanton, C. A., Lambert, E., & Hilmi, N. (2018). Co-occurrence of tobacco product use, substance use, and mental health problems among youth: Findings from wave 1 (2013–2014) of the population assessment of tobacco and health (PATH) study. *Addictive Behaviors*, *76*, 208-217.

Cook, S., Hirschtick, J. L., Patel, A., Brouwer, A., Jeon, J., Levy, D. T., Meza, R., & Fleischer, N. L. (2022). A longitudinal study of menthol cigarette use and smoking cessation among adult smokers in the US: Assessing the roles of racial disparities and E-cigarette use. *Preventive Medicine*, *154*, 106882. https://doi.org/https://doi.org/10.1016/j.ypmed.2021.106882

Cooper, M., Park-Lee, E., Ren, C., Cornelius, M., Jamal, A., & Cullen, K. A. (2022). Notes from the Field: E-cigarette Use Among Middle and High School Students-United States, 2022. *MMWR Morb Mortal Wkly Rep*, *71*(40), 1283-1285. https://doi.org/10.15585/mmwr.mm7140a3

Corey, C. G., Ambrose, B. K., Apelberg, B. J., & King, B. A. (2015). Flavored tobacco product use among middle and high school students—United States, 2014. *MMWR Morb Mortal Wkly Rep*, *64*(38), 1066-1070. https://doi.org/10.15585/mmwr.mm6438a2

Cullen, K. A., Liu, S. T., Bernat, J. K., Slavit, W. I., Tynan, M. A., King, B. A., & Neff, L. J. (2019). Flavored Tobacco Product Use Among Middle and High School Students - United States, 2014-2018. *MMWR Morb Mortal Wkly Rep*, *68*(39), 839-844. https://doi.org/10.15585/mmwr.mm6839a2

Czoli, C. D., Fong, G. T., Goniewicz, M. L., & Hammond, D. (2019). Biomarkers of Exposure Among "Dual Users" of Tobacco Cigarettes and Electronic Cigarettes in Canada. *Nicotine Tob Res*, *21*(9), 1259-1266. https://doi.org/10.1093/ntr/nty174

D'Ruiz, C. D., Graff, D. W., & Robinson, E. (2016). Reductions in biomarkers of exposure, impacts on smoking urge and assessment of product use and tolerability in adult smokers following partial or complete substitution of cigarettes with electronic cigarettes. *BMC Public Health*, *16*, 543. https://doi.org/10.1186/s12889-016-3236-1

Denlinger-Apte, R. L., Cassidy, R. N., Carey, K. B., Kahler, C. W., Bickel, W. K., O'Connor, R. J., Thussu, S., & Tidey, J. W. (2021). The impact of menthol flavoring in combusted tobacco on alternative product purchasing: A pilot study using the Experimental Tobacco Marketplace. *Drug Alcohol Depend*, *218*, 108390. https://doi.org/10.1016/j.drugalcdep.2020.108390

DeVito, E. E., Jensen, K. P., O'Malley, S. S., Gueorguieva, R., Krishnan-Sarin, S., Valentine, G., Jatlow, P. I., & Sofuoglu, M. (2020). Modulation of "Protective" Nicotine Perception and Use Profile by Flavorants: Preliminary Findings in E-cigarettes. *Nicotine Tob Res*, *22*(5), 771-781. https://doi.org/10.1093/ntr/ntz057

Djordjevic, M. V., Fan, J., Bush, L. P., Brunnemann, K. D., & Hoffann, D. (1993). Effects of storage conditions on levels of tobacco-specific N-nitrosamines and N-nitrosamino acids in U.S. moist snuff. *Journal of Agricultural and Food Chemistry*, *41*(10), 1790-1794. https://doi.org/10.1021/jf00034a051

Evans-Polce, R. J., Patrick, M. E., Lanza, S. T., Miech, R. A., O'Malley, P. M., & Johnston, L. D. (2018). Reasons for Vaping Among U.S. 12th Graders. *Journal of Adolescent Health*, *62*(4), 457-462. https://doi.org/https://doi.org/10.1016/j.jadohealth.2017.10.009

Gentzke, A. S., Wang, T. W., Cornelius, M., Park-Lee, E., Ren, C., Sawdey, M. D., Cullen, K. A., Loretan, C., Jamal, A., & Homa, D. M. (2022). Tobacco Product Use and Associated Factors Among Middle and High School Students - National Youth Tobacco Survey, United States, 2021. *MMWR Surveill Summ*, *71*(5), 1-29. https://doi.org/10.15585/mmwr.ss7105a1

Goldenson, N. I., Augustson, E. M., & Shiffman, S. (2022). Differences in switching away from cigarettes and JUUL use characteristics among adult menthol and nonmenthol smokers who purchased the JUUL System. *Drug Alcohol Depend*, *231*, 109238. https://doi.org/10.1016/j.drugalcdep.2021.109238

Goldenson, N. I., Buchhalter, A. R., Augustson, E. M., Rubinstein, M. L., & Henningfield, J. E. (2020). Abuse liability assessment of the JUUL system in four flavors relative to combustible cigarette, nicotine gum and a comparator electronic nicotine delivery system among adult smokers. *Drug Alcohol Depend*, *217*, 108395. https://doi.org/10.1016/j.drugalcdep.2020.108395

Goldenson, N. I., Shiffman, S., Hatcher, C., Lamichhane, D., Gaggar, A., Le, G. M., Prakash, S., & Augustson, E. M. (2021). Switching away from Cigarettes across 12 Months among Adult Smokers Purchasing the JUUL System. *Am J Health Behav*, *45*(3), 443-463. https://doi.org/10.5993/AJHB.45.3.4

Goniewicz, M. L., Boykan, R., Messina, C. R., Eliscu, A., & Tolentino, J. (2019). High exposure to nicotine among adolescents who use Juul and other vape pod systems ('pods'). *Tob Control*, *28*(6), 676-677. https://doi.org/10.1136/tobaccocontrol-2018-054565

Goniewicz, M. L., Gawron, M., Smith, D. M., Peng, M., Jacob, P., 3rd, & Benowitz, N. L. (2017). Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study. *Nicotine Tob Res*, *19*(2), 160-167. https://doi.org/10.1093/ntr/ntw160

Goniewicz, M. L., Smith, D. M., Edwards, K. C., Blount, B. C., Caldwell, K. L., Feng, J., Wang, L., Christensen, C., Ambrose, B., Borek, N., van Bemmel, D., Konkel, K., Erives, G., Stanton, C. A., Lambert, E., Kimmel, H. L., Hatsukami, D., Hecht, S. S., Niaura, R. S., . . . Hyland, A. J. (2018). Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. *JAMA Netw Open*, *1*(8), e185937. https://doi.org/10.1001/jamanetworkopen.2018.5937

Hajek, P., Pittaccio, K., Pesola, F., Myers Smith, K., Phillips-Waller, A., & Przulj, D. (2020). Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction*, *115*(6), 1141-1148. https://doi.org/10.1111/add.14936

Han, G., & Son, H. (2022). A systematic review of socio-ecological factors influencing current e-cigarette use among adolescents and young adults. *Addictive Behaviors*, *135*, 107425. https://doi.org/https://doi.org/10.1016/j.addbeh.2022.107425

Hawkins, S. S., Wylie, B. J., & Hacker, M. R. (2020). Use of ENDS and cigarettes during pregnancy. *American Journal of Preventive Medicine*, *58*(1), 122-128.

Jackson, A., Green, B., Erythropel, H. C., Kong, G., Cavallo, D. A., Eid, T., Gueorguieva, R., Buta, E., O'Malley, S. S., & Krishnan-Sarin, S. (2020). Influence of menthol and green apple e-liquids containing different nicotine concentrations among youth e-cigarette users. *Exp Clin Psychopharmacol*. https://doi.org/10.1037/pha0000368

Jain, R. B. (2019). Concentrations of cadmium, lead, and mercury in blood among US cigarettes, cigars, electronic cigarettes, and dual cigarette-e-cigarette users. *Environ Pollut*, *251*, 970-974. https://doi.org/10.1016/j.envpol.2019.05.041

Jay, J., Pfaunmiller, E., Huang, N. J., Cohen, G., & Graff, D. W. (2020). Five-Day Changes in Biomarkers of Exposure Among Adult Smokers After Completely Switching From Combustible Cigarettes to a Nicotine-Salt Pod System. *Nicotine & Tobacco Research*, *22*, 1285 - 1293.

Leventhal, A. M., Cho, J., Barrington-Trimis, J., Pang, R., Schiff, S., & Kirkpatrick, M. (2019). Sensory attributes of e-cigarette flavours and nicotine as mediators of interproduct differences in appeal among young adults. *Tob Control*. https://doi.org/10.1136/tobaccocontrol-2019-055172

Leventhal, A. M., Goldenson, N. I., Barrington-Trimis, J. L., Pang, R. D., & Kirkpatrick, M. G. (2019). Effects of non-tobacco flavors and nicotine on e-cigarette product appeal among young adult never, former, and current smokers. *Drug Alcohol Depend*, *203*, 99-106. https://doi.org/10.1016/j.drugalcdep.2019.05.020

Leventhal, A. M., Goldenson, N. I., Cho, J., Kirkpatrick, M. G., McConnell, R. S., Stone, M. D., Pang, R. D., Audrain-McGovern, J., & Barrington-Trimis, J. L. (2019). Flavored E-cigarette Use and Progression of Vaping in Adolescents. *Pediatrics*, *144*(5). https://doi.org/10.1542/peds.2019-0789

Leventhal, A. M., Madden, D. R., Peraza, N., Schiff, S. J., Lebovitz, L., Whitted, L., Barrington-Trimis, J., Mason, T. B., Anderson, M. K., & Tackett, A. P. (2021). Effect of Exposure to e-Cigarettes With Salt vs Free-Base Nicotine on the Appeal and Sensory Experience of Vaping: A Randomized Clinical Trial. *JAMA Netw Open*, *4*(1), e2032757. https://doi.org/10.1001/jamanetworkopen.2020.32757

Lindson, N., Butler, A. R., McRobbie, H., Bullen, C., Hajek, P., Begh, R., Theodoulou, A., Notley, C., Rigotti, N. A., Turner, T., Livingstone-Banks, J., Morris, T., & Hartmann-Boyce, J. (2024). Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*, *1*(1), Cd010216. https://doi.org/10.1002/14651858.CD010216.pub8

Lindson, N., Theodoulou, A., Ordóñez-Mena, J. M., Fanshawe, T. R., Sutton, A. J., Livingstone-Banks, J., Hajizadeh, A., Zhu, S., Aveyard, P., Freeman, S. C., Agrawal, S., & Hartmann-Boyce, J. (2023). Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. *Cochrane Database Syst Rev*, *9*(9), Cd015226. https://doi.org/10.1002/14651858.CD015226.pub2

Liu, S. T., Snyder, K., Tynan, M. A., & Wang, T. W. (2019). Youth Access to Tobacco Products in the United States, 2016-2018. *Tob Regul Sci*, *5*(6), 491-501. https://doi.org/10.18001/TRS.5.6.2

Meyers, M. J., Delucchi, K., & Halpern-Felsher, B. (2017). Access to Tobacco Among California High School Students: The Role of Family Members, Peers, and Retail Venues. *J Adolesc Health*, *61*(3), 385-388. https://doi.org/10.1016/j.jadohealth.2017.04.012

Miech, R., Leventhal, A., Johnston, L., O'Malley, P. M., Patrick, M. E., & Barrington-Trimis, J. (2021). Trends in Use and Perceptions of Nicotine Vaping Among US Youth From 2017 to 2020. *JAMA Pediatr*, *175*(2), 185-190. https://doi.org/10.1001/jamapediatrics.2020.5667

Morean, M. E., Butler, E. R., Bold, K. W., Kong, G., Camenga, D. R., Cavallo, D. A., Simon, P., O'Malley, S. S., & Krishnan-Sarin, S. (2018). Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PloS one*, *13*(1), e0189015. https://doi.org/10.1371/journal.pone.0189015

Morris, P., McDermott, S., Chapman, F., Verron, T., Cahours, X., Stevenson, M., Thompson, J., Chaudhary, N., & O'Connell, G. (2022). Reductions in biomarkers of exposure to selected harmful and potentially harmful constituents following exclusive and partial switching from combustible cigarettes to myblu() electronic nicotine delivery systems (ENDS). *Intern Emerg Med*, *17*(2), 397-410. https://doi.org/10.1007/s11739-021-02813-w

Nollen, N. L., Leavens, E. L. S., Ahluwalia, J. S., Rice, M., Mayo, M. S., & Pulvers, K. (2022). Menthol versus non-menthol flavouring and switching to e-cigarettes in black and Latinx adult menthol combustible cigarette smokers: secondary analyses from a randomised clinical trial. *Tob Control*. https://doi.org/10.1136/tobaccocontrol-2021-057180

O'Connell, G., Graff, D. W., & D'Ruiz, C. D. (2016). Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents (HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Toxicol Mech Methods*, *26*(6), 443-454. https://doi.org/10.1080/15376516.2016.1196282

O'Connell, G., Pritchard, J. D., Prue, C., Thompson, J., Verron, T., Graff, D., & Walele, T. (2019). A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med*, *14*(6), 853-861. https://doi.org/10.1007/s11739-019-02025-3

Obisesan, O. H., Osei, A. D., Uddin, S. I., Dzaye, O., Cainzos-Achirica, M., Mirbolouk, M., Orimoloye, O. A., Sharma, G., Al Rifai, M., & Stokes, A. (2020). E-cigarette use patterns and high-risk behaviors in pregnancy: Behavioral risk factor surveillance system, 2016–2018. *American Journal of Preventive Medicine*, *59*(2), 187-195.

Oliveri, D., Liang, Q., & Sarkar, M. (2020). Real-World Evidence of Differences in Biomarkers of Exposure to Select Harmful and Potentially Harmful Constituents and Biomarkers of Potential Harm

Between Adult E-Vapor Users and Adult Cigarette Smokers. *Nicotine Tob Res*, *22*(7), 1114-1122. https://doi.org/10.1093/ntr/ntz185

Osibogun, O., Bursac, Z., McKee, M., Li, T., & Maziak, W. (2020). Cessation outcomes in adult dual users of e-cigarettes and cigarettes: the Population Assessment of Tobacco and Health cohort study, USA, 2013-2016. *Int J Public Health*, *65*(6), 923-936. https://doi.org/10.1007/s00038-020-01436-w

Patskan, G. J., Podraza, K. F., Meurrens, K., Coggins, C. R., Friedrichs, B., Gerstenberg, B., Gomm, W., Schnell, P., Stabbert, R., Veltel, D., Weber, S., & Terpstra, P. (2008). Toxicological comparisons of three styles of a commercial U.S. cigarette (Marlboro with the 1R4F reference cigarette. *Inhal Toxicol*, *20*(7), 695-721. https://doi.org/10.1080/08958370801935174

Pazo, D. Y., Moliere, F., Sampson, M. M., Reese, C. M., Agnew-Heard, K. A., Walters, M. J., Holman, M. R., Blount, B. C., Watson, C. H., & Chambers, D. M. (2016). Mainstream Smoke Levels of Volatile Organic Compounds in 50 U.S. Domestic Cigarette Brands Smoked With the ISO and Canadian Intense Protocols. *Nicotine Tob Res*. https://doi.org/10.1093/ntr/ntw118

Pepper, J., Ribisl, K., & Brewer, N. (2016). Adolescents' interest in trying flavoured e-cigarettes. *Tobacco control*, *25*(Suppl 2), ii62-ii66.

Pierce, J. P., Distefan, J. M., Kaplan, R. M., & Gilpin, E. A. (2005). The role of curiosity in smoking initiation. *Addictive Behaviors*, *30*(4), 685-696. https://doi.org/https://doi.org/10.1016/j.addbeh.2004.08.014

Piper, M. E., Baker, T. B., Benowitz, N. L., & Jorenby, D. E. (2020). Changes in Use Patterns Over 1 Year Among Smokers and Dual Users of Combustible and Electronic Cigarettes. *Nicotine Tob Res*, *22*(5), 672-680. https://doi.org/10.1093/ntr/ntz065

Polosa, R., Morjaria, J. B., Caponnetto, P., Campagna, D., Russo, C., Alamo, A., Amaradio, M., & Fisichella, A. (2014). Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Intern Emerg Med*, *9*(5), 537-546. https://doi.org/10.1007/s11739-013-0977-z

Prokopowicz, A., Sobczak, A., Szula-Chraplewska, M., Ochota, P., & Kosmider, L. (2019). Exposure to Cadmium and Lead in Cigarette Smokers Who Switched to Electronic Cigarettes. *Nicotine Tob Res*, *21*(9), 1198-1205. https://doi.org/10.1093/ntr/nty161

Pulvers, K., Emami, A. S., Nollen, N. L., Romero, D. R., Strong, D. R., Benowitz, N. L., & Ahluwalia, J. S. (2018). Tobacco Consumption and Toxicant Exposure of Cigarette Smokers Using Electronic Cigarettes [Article]. *Nicotine Tob Res*, *20*(2), 206-214. https://doi.org/10.1093/ntr/ntw333

Pulvers, K., Nollen, N. L., Rice, M., Schmid, C. H., Qu, K., Benowitz, N. L., & Ahluwalia, J. S. (2020). Effect of Pod e-Cigarettes vs Cigarettes on Carcinogen Exposure Among African American and Latinx Smokers: A Randomized Clinical Trial. *JAMA Netw Open*, *3*(11), e2026324. https://doi.org/10.1001/jamanetworkopen.2020.26324

Riehm, K. E., Young, A. S., Feder, K. A., Krawczyk, N., Tormohlen, K. N., Pacek, L. R., Mojtabai, R., & Crum, R. M. (2019). Mental health problems and initiation of e-cigarette and combustible cigarette use. *Pediatrics*, *144*(1).

Roemer, E., Stabbert, R., Rustemeier, K., Veltel, D. J., Meisgen, T. J., Reininghaus, W., Carchman, R. A., Gaworski, C. L., & Podraza, K. F. (2004). Chemical composition, cytotoxicity and mutagenicity of smoke from US commercial and reference cigarettes smoked under two sets of machine smoking conditions. *Toxicology*, *195*(1), 31-52. https://doi.org/10.1016/j.tox.2003.08.006

Romberg, A. R., Miller Lo, E. J., Cuccia, A. F., Willett, J. G., Xiao, H., Hair, E. C., Vallone, D. M., Marynak, K., & King, B. A. (2019). Patterns of nicotine concentrations in electronic cigarettes sold in the United States, 2013-2018. *Drug Alcohol Depend*, *203*, 1-7. https://doi.org/10.1016/j.drugalcdep.2019.05.029

Rosbrook, K., & Green, B. G. (2016). Sensory Effects of Menthol and Nicotine in an E-Cigarette. *Nicotine Tob Res*, *18*(7), 1588-1595. https://doi.org/10.1093/ntr/ntw019

Rose, S. W., Johnson, A. L., Glasser, A. M., Villanti, A. C., Ambrose, B. K., Conway, K., Cummings, K. M., Stanton, C. A., Delnevo, C., Wackowski, O. A., Edwards, K. C., Feirman, S. P., Bansal-Travers, M., Bernat, J., Holder-Hayes, E., Green, V., Silveira, M. L., Zhou, Y., Abudayyeh, H., & Hyland, A. (2020). Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2014-2015. *Tob Control*, *29*(4), 432-446. https://doi.org/10.1136/tobaccocontrol-2018-054852

Rostron, B. L., Chang, J. T., Chang, C. M., Jackson, R. A., & Ambrose, B. K. (2020). ENDS Flavor Preference by Menthol Cigarette Smoking Status among US Adults, 2018-2019. *Int J Environ Res Public Health*, *18*(1). https://doi.org/10.3390/ijerph18010240

Rostron, B. L., Cheng, Y. C., Gardner, L. D., & Ambrose, B. K. (2020). Prevalence and Reasons for Use of Flavored Cigars and ENDS among US Youth and Adults: Estimates from Wave 4 of the PATH Study, 2016-2017. *Am J Health Behav*, *44*(1), 76-81. https://doi.org/10.5993/AJHB.44.1.8

Round, E. K., Chen, P., Taylor, A. K., & Schmidt, E. (2019). Biomarkers of Tobacco Exposure Decrease After Smokers Switch to an E-Cigarette or Nicotine Gum. *Nicotine Tob Res*, *21*(9), 1239-1247. https://doi.org/10.1093/ntr/nty140

Schneller, L. M., Bansal-Travers, M., Goniewicz, M. L., McIntosh, S., Ossip, D., & O'Connor, R. J. (2019). Use of Flavored E-Cigarettes and the Type of E-Cigarette Devices Used among Adults and Youth in the US-Results from Wave 3 of the Population Assessment of Tobacco and Health Study (2015-2016). *Int J Environ Res Public Health*, *16*(16). https://doi.org/10.3390/ijerph16162991

Shang, C., Weaver, S. R., White, J. S., Huang, J., Nonnemaker, J., Cheng, K.-W., & Chaloupka, F. J. (2020). E-Cigarette product preferences among adult smokers: a discrete choice experiment. *Tob Regul Sci*, *6*(1), 66-80. https://doi.org/10.18001/trs.6.1.7

St Helen, G., Dempsey, D. A., Havel, C. M., Jacob, P., 3rd, & Benowitz, N. L. (2017). Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug Alcohol Depend*, *178*, 391-398. https://doi.org/10.1016/j.drugalcdep.2017.05.042

Stanton, C. A., Sharma, E., Edwards, K. C., Halenar, M. J., Taylor, K. A., Kasza, K. A., Day, H., Anic, G., Gardner, L. D., Hammad, H. T., Bansal-Travers, M., Limpert, J., Borek, N., Kimmel, H. L., Compton, W. M., & Hyland, A. (2020). Longitudinal transitions of exclusive and polytobacco electronic nicotine delivery systems (ENDS) use among youth, young adults and adults in the USA: findings from the PATH Study Waves 1-3 (2013-2016). *Tob Control*, *29*(Suppl 3), s147-s154. https://doi.org/10.1136/tobaccocontrol-2019-055574

Tanski, S., Emond, J., Stanton, C., Kirchner, T., Choi, K., Yang, L., Ryant, C., Robinson, J., & Hyland, A. (2019). Youth Access to Tobacco Products in the United States: Findings From Wave 1 (2013-2014) of the Population Assessment of Tobacco and Health Study. *Nicotine Tob Res*, *21*(12), 1695-1699. https://doi.org/10.1093/ntr/nty238

U.S. Department of Health and Human Services. (2012). *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta, GA: U.S. Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health

U.S. Department of Health and Human Services. (2014). *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health

U.S. Food and Drug Administration. (2020). *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised)* (Guidance for Industry)*. Center for Tobacco Products, Food and Drug Administration, U.S. Department of Health and Human Services Retrieved from https://www.fda.gov/media/133880/download (accessed April 2024)

Villanti, A. C., Johnson, A. L., Glasser, A. M., Rose, S. W., Ambrose, B. K., Conway, K. P., Cummings, K. M., Stanton, C. A., Edwards, K. C., Delnevo, C. D., Wackowski, O. A., Feirman, S. P., Bansal-Travers,

M., Bernat, J. K., Holder-Hayes, E., Green, V. R., Silveira, M. L., & Hyland, A. (2019). Association of Flavored Tobacco Use With Tobacco Initiation and Subsequent Use Among US Youth and Adults, 2013-2015. *JAMA Network Open*, *2*(10), e1913804-e1913804. https://doi.org/10.1001/jamanetworkopen.2019.13804

Voos, N., Smith, D., Kaiser, L., Mahoney, M. C., Bradizza, C. M., Kozlowski, L. T., Benowitz, N. L., O'Connor, R. J., & Goniewicz, M. L. (2020). Effect of e-cigarette flavors on nicotine delivery and puffing topography: results from a randomized clinical trial of daily smokers. *Psychopharmacology (Berl)*, *237*(2), 491-502. https://doi.org/10.1007/s00213-019-05386-x

Vu, A. T., Taylor, K. M., Holman, M. R., Ding, Y. S., Hearn, B., & Watson, C. H. (2015). Polycyclic Aromatic Hydrocarbons in the Mainstream Smoke of Popular U.S. Cigarettes. *Chem Res Toxicol*, *28*(8), 1616-1626. https://doi.org/10.1021/acs.chemrestox.5b00190

Wang, T. W., Neff, L. J., Park-Lee, E., Ren, C., Cullen, K. A., & King, B. A. (2020). E-cigarette Use Among Middle and High School Students - United States, 2020. *Morbidity and mortality weekly report : MMWR /*, *69*(37), 1310-1312. https://doi.org/10.15585/mmwr.mm6937e1

Wheldon, C. W., & Wiseman, K. P. (2019). Tobacco use among transgender and gender non-conforming adults in the United States. *Tobacco use insights*, *12*, 1179173X19849419.

Yingst, J. M., Hrabovsky, S., Hobkirk, A., Trushin, N., Richie, J. P., Jr., & Foulds, J. (2019). Nicotine Absorption Profile Among Regular Users of a Pod-Based Electronic Nicotine Delivery System. *JAMA Netw Open*, *2*(11), e1915494. https://doi.org/10.1001/jamanetworkopen.2019.15494

Zulfiqar, H., Sankari, A., & Rahman, O. (2024). Vaping-Associated Pulmonary Injury. In *StatPearls*. https://www.ncbi.nlm.nih.gov/pubmed/32809491

7. APPENDIX

Appendix A. New products

Table 4. New tobacco products subject to Granted Orders [24,25,26]

Common Attributes	
Submit date	March 30, 2020
Receipt date	March 30, 2020
Applicant	NJOY LLC
Product manufacturer	NJOY LLC
Product category	ENDS (VAPES)
Product subcategory	Closed E-Cigarette
Attributes	**New Tobacco Product**
STN	**PM0000628.PD1**
Product name	NJOY DAILY Menthol 4.5%
Package type	Box
Package quantity	1 E-Cigarette
Characterizing flavor	Menthol
Battery capacity	200 milliampere hours (mAh) (lithium ion; non-rechargeable)
Diameter	8.4 millimeters (mm)
E-liquid volume	0.9 milliliters (mL)
Length	106.9 mm
Nicotine concentration	4.5% weight per weight (w/w)
PG/VG ratio	47.27/43.50
Wattage	4 Watts (W)
Nicotine Source	Tobacco
Additional property	Disposable E- Liquid Reservoir
STN	**PM0000629.PD1**
Product name	NJOY DAILY EXTRA Menthol 6%
Package type	Box
Package quantity	1 E-Cigarette
Characterizing flavor	Menthol
Battery capacity	200 mAh (lithium ion; non-rechargeable)
Diameter	8.4 mm
E-liquid volume	0.9 mL
Length	106.9 mm
Nicotine concentration	6% w/w
PG/VG ratio	45.92/42.00
Wattage	4 W
Nicotine Source	Tobacco
Additional property	Disposable E- Liquid Reservoir

[24] Product name is brand/sub-brand or other commercial name used in commercial distribution.
[25] 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.
[26] PD numbers have been assigned to each STN since the issuance of previous letters for the products listed in Appendix A.

Appendix B. Amendments and additional submissions received

Table 5. Amendments received

Submit Date	Receipt Date	Applications being amended	Reviewed	Brief Description
June 16, 2020	June 16, 2020	All	Yes	Correction or clarification to update report: Adverse Events - NJOY Report DAILY - Qtr. 1 2020 Update: Adverse Experience (Module 5.5)
July 13, 2020	July 14, 2020	All	Yes	Correction or clarification to Study Reports: NJOY User Survey (Module 6.2.4) & Population Module (Module 6.6)
November 25, 2020	November 25, 2020	All	Yes	Response to November 12, 2020 FDA Information Request
March 04, 2021	March 04, 2021	All	Yes	Response to December 17, 2020 Deficiency Letter
December 21, 2022	December 21, 2022	All	Yes	Correction or clarification to original submission

Table 6. 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, LLCv. FDA decision
January 11, 2024	January 11, 2024	Yes	Form 4057a and response to Wages and White Lion Investments, LLCv. FDA decision
February 6, 2024	February 6, 2024	Yes	Letter of Authorization for TPMF
April 29, 2024	April 29, 2024	Yes	Address update