U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review[1]	
Submission tracking numbers (STNs)	PM0000613.PD1 - PM0000615.PD1, and PM0000622.PD1
Common Attributes of PMTAs	
Submission date	March 10, 2020
Receipt date	March 10, 2020
Applicant	NJOY LLC
Product manufacturer	NJOY LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	Closed E-Cigarette, Closed E-Liquid
Cross-Referenced Submissions	
All STNs	(b)(4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	• OHCE Consultation finalized on 3/14/2022 • TPST Search for AE Reports involving NJOY LLC ACE ENDS products finalized on 2/15/2022
Recommendation	
Issue marketing granted order letter for PM0000613.PD1 - PM0000615.PD1, and PM0000622.PD1	

Technical Project Lead (TPL):

Digitally signed by Zheng Tu -S
Date: 2022.04.25 13:31:56 -04'00'

Zheng (Alex) Tu, Ph.D.
Supervisory Pharmacologist
Division of Nonclinical Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2022.04.25 13:57:22 -04'00'

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

[1] Tobacco product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application(s).

TABLE OF CONTENTS

LIST OF TABLES

1. EXECUTIVE SUMMARY

Based on the information provided in the application and other scientific data, as described in this Technical Project Lead 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 be issued for the new products, subject to the marketing restrictions and post-market requirements.

1.1. APPH STANDARD

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

In making the APPH assessment for a noncombustible tobacco product such as an electronic nicotine delivery system (ENDS), FDA weighs, among other things, the negative public health impact stemming from youth initiation and use of the product against the potential positive public health impact stemming from adult cigarette smokers transitioning away from combustible cigarettes to the ENDS product. In order to show that an ENDS is APPH, an applicant must show that the benefits, including those to adult smokers, outweigh the risks, including those to youth, resulting in a net benefit to the public health. As the known risks of the product increases or decreases, the burden of demonstrating a substantial enough benefit likewise increases or decreases. For flavored ENDS[2] (i.e., ENDS with e-liquid flavors other than tobacco or menthol, such as fruit), there is a known and substantial risk of youth initiation and use; accordingly, an applicant has a higher burden to establish that the likely benefits to adult smokers outweigh that risk. For tobacco-flavored ENDS the risk to youth is lower; accordingly, a lesser showing of benefit may suffice. Assessments for menthol-flavored ENDS will be addressed separately. When it comes to evaluating the risks and benefits of a marketing authorization, the assessment for menthol ENDS, as compared to other flavored ENDS, raises unique considerations.

In making the APPH assessment for a flavored ENDS, FDA has determined that it is appropriate to compare flavored ENDS with tobacco-flavored ENDS. Tobacco-flavored ENDS may offer the same type

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

of public health benefit as flavored ENDS, i.e., increased 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 adult smokers comparable options for switching or cigarette reduction bears on the extent of the public health benefit that the subject ENDS arguably provide to that population. Therefore, in making the APPH determination for a flavored ENDS, FDA considers whether the applicant has provided acceptably strong evidence of an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers 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 impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and tobacco use. Such mitigation efforts include advertising and promotion restrictions (e.g., measures such as limiting advertising to platforms that are predominantly used by adults and using advertising content and methods that are not known to resonate with youth); sales access restrictions (e.g., measures such as selling products only in face to face interactions, in adult-only facilities, or via websites that require robust age verification); and device access restrictions (e.g., technologies that require adult user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product). FDA evaluates these measures in the context of the overall public health evaluation of the product, weighing the known risks to youth against the benefit to adults. In the case of flavored ENDS, the risk of youth initiation and use is well documented and substantial. Experience shows that advertising and promotion restrictions and sales access restrictions cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH.[3] Rather, for flavored ENDS, only the most stringent mitigation measures – specifically device access restrictions – have such mitigation potential.[4] In contrast, the risk of youth initiation and use with tobacco-flavored ENDS is lower. Restrictions on advertising and promotion and sales access for tobacco-flavored ENDS could mitigate that more limited risk and impact the overall net benefit assessment. In addition, restrictions on advertising and promotion and sales access are important to include in marketing granted orders (MGOs) because they can help ensure that the marketing of a new tobacco product remains APPH after authorization. FDA has included such restrictions in MGOs issued to date.

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

1.2. SUBJECT APPLICATIONS

[3] *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").

[4] Device access restrictions are novel and rare. To the extent flavored ENDS applicants purport to have device access restrictions (which, as components or parts of the product, would be discussed in the product formulation and engineering sections of a PMTA, rather than solely in the marketing plan), FDA's approach is to engage in further scientific review of those applications.

Based on its evaluation of these PMTAs, FDA determined that these PMTAs contain sufficient information to characterize the product design and that there are adequate process controls and quality assurance procedures to help ensure both the device and e-liquids are manufactured consistently. Chemical testing submitted in the PMTAs was sufficient to determine that overall harmful and potentially harmful constituent (HPHC) levels in the aerosol of these products are lower than in combusted cigarette smoke. The overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in aerosol HPHCs of the new products compared to cigarettes. Further, biomarker data provided by the applicant demonstrated that participants who had used only the NJOY ACE products had lower levels of biomarkers of exposure to HPHCs (e.g., CO, cotinine, CEMA, 3-HPMA, and NNAL) compared to the dual users of the new products and combusted cigarettes. Based on the information provided in the PMTAs, the new products' abuse liability—i.e., ability to promote continued use, addiction, or dependence—is comparable to that of combusted cigarettes and other ENDS tested. Therefore, these products have the potential to benefit adult smokers who switch completely or significantly reduce their cigarette consumption. In the applicant's Prevalence and Perception Study, current adult smokers had the most interest in the Classic Tobacco 5% nicotine product. Further, the NJOY User Study demonstrated that switching from combusted cigarettes to the new ENDS products does occur among current adult smokers. The applicant has therefore demonstrated the potential for these products to benefit adult smokers as compared to continued exclusive cigarette use.

In terms of the risks to non-users, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. Existing evidence consistently indicates that use of tobacco-flavored ENDS is less common compared to flavored ENDS among youth. Consistent with these findings, in the applicant's youth Prevalence and Perception studies, curiosity to use the tobacco-flavored products (b)(4) (b)(4). The same studies also showed that the percentage of youth reporting ever using ENDS and started with tobacco-flavored ENDS was much lower than that of (b)(4). Nonetheless, given the strong evidence regarding the impact of youth exposure to marketing on youth appeal and initiation of tobacco use, any marketing authorization should include marketing restrictions and postmarket requirements to help ensure that youth exposure to tobacco marketing is limited.

Regarding product stability, the applicant stated that the shelf life of the new products is (b)(4). However, the applicant only provided chemistry data to support that the new products are chemically stable over (b)(4). In addition, the applicant provided data that only supports microbial stability over (b)(4) for NJOY ACE POD 5% Rich Tobacco (PM0000622.PD1). The chemical and microbial stability data in the PMTAs is acceptable and indicates that the products are low-risk for chemical instability and microbial growth over the period tested. There are no other stability concerns, and therefore the lack of stability data for (b)(4) does not preclude an APPH finding for the products.

Together, based on the information provided in the PMTAs and the available evidence, I find that permitting the marketing of the new products, subject to certain marketing restrictions, would be APPH. The potential of the new products to benefit smokers who significantly reduce their combusted cigarette use (or switch completely to the new products) outweighs the risk to youth, provided that the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to marketing of the new products and youth access to the new products.

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

2. BACKGROUND

2.1. NEW TOBACCO PRODUCTS

The applicant, NJOY LLC, submitted information for the four new tobacco products listed on the cover page and with more detail in the Appendix (Table 3), sold under the brand names NJOY and NJOY ACE. Briefly, a complete NJOY ACE ENDS is composed of a rechargeable Power Unit (closed device, PM0000613.PD1), a prefilled pod containing thete-liquids, and an accessory USB charger for the power unit. The power unit and cartridge settings are not adjustable by the user. The pods contain e-liquids identified by the applicant as containing the following flavors: Classic Tobacco flavor with 2.4% nicotine (PM0000614.PD1), Classic Tobacco flavor with 5% nicotine (PM0000615.PD1), and Rich Tobacco flavor with 5% nicotine (PM0000622.PD1).

2.2. REGULATORY ACTIVITY

On March 10, 2020, FDA received four PMTAs from NJOY LLC. FDA issued an Acceptance letter to the applicant on March 17, 2020. FDA issued a Filing letter to the applicant on March 26, 2020. FDA issued a Deficiency letter to the applicant on July 29, 2020.

Refer to the Appendix (Table 4) for a complete list of amendments received by FDA.

2.3. SCOPE OF REVIEW

This review captures all compliance and scientific reviews completed for the new products subject to this review, as well as cross-referenced tobacco product master files (TPMFs) (b)(4)

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Regulatory	Kristopher Van Amburg	3/17/2020	Dyamond Govan	N/A
Engineering	Nashaat Rasheed	7/27/2020	Pritesh Darji	4/21/2022
Chemistry	Selena Russell	7/27/2020	Yougbang Liu	4/22/2022
Microbiology	David Craft	7/27/2020	Prashanthi Mulinti	4/25/2022
Toxicology	Kamau Peters	7/28/2020	Kamau Peters	4/25/2022
Behavioral and Clinical Pharmacology	Babita Das/ Marzena Spindle	7/27/2020	Arit Harvanko	4/21/2022
Medical	Edna Termilus	7/27/2020	Not assigned	N/A
Epidemiology	Rebecca Jackson	7/27/2020	Maria Cooper	4/22/2022
Social science	Elisabeth Donaldson	7/27/2020	Lisa Lagasse	4/22/2022
Environmental Science	Rudaina Alrefai-Kirkpatrick	7/27/2020	Ron Edwards	4/22/2022

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
OCEt– BIMO[5]	Carlos Carmona	4/13/2020	Not assigned	N/A
OCE– Manufacturing/Lab	Jiali He	4/8/2020	Not assigned	N/A

Table 2. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Statistics	Not assigned	N/A	Christopher Ellison	1/25/2021
OCE – DPAL	*Rohit Mathew*	7/2/2020	Not assigned	N/A
OHCE	Emily Talbert	4/29/2020	Allison ODonnell	3/14/2022
TPST	Susan Rudy	4/7/2020	Susan Rudy	2/15/2022

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

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

- Comparison products used in specific studies or evaluations
  - Engineering: The applicant compared NJOY ACE products with JUUL and Vuse Alto. NJOY ACE and Vuse Alto have comparable design parameters such as e-liquid volume (mL), e-liquid pH, battery cell capacity (mAh), atomizer resistance (Ω), and the same atomizer type. Although not all design parameters are comparable with comparison products, the applicant's rationale for selection of these comparison products is acceptable from an engineering perspective.
  - Chemistry: The applicant measured aerosol constituent concentrations of the comparison product Vuse Alto Original 5%. It is a tobacco product in the same product category and subcategory and with similar e-liquid flavors that contain nicotine salts as the new products. The Chemistry review also compared constituent yields from the new product aerosols to the cigarette mainstream smoke yields from 50 commercially available combusted cigarettes (FDASO). The applicant's rationale for selection of the comparison product and data from the additional comparison with combustible cigarettes is acceptable from a Chemistry perspective.
  - Toxicology:
    - The applicant provided comparisons between the new products and combusted cigarettes. The applicant used the average combusted cigarette mainstream smoke (MSS) concentration data from peer-reviewed scientific literature to represent the combusted cigarette

[5] Second cycle review was not necessary as there was no additional data that required review by Office of Compliance and Enforcement (OCE).

category. The applicant's rationale for this comparison is based on the premise of reduction of risk of overall adverse health effects for combusted cigarette smokers switching completely to the new products. The rationale and selection of average combusted cigarette data is an appropriate representative of the combusted cigarettes because the studies were peer-reviewed and selected studies that were recently published measured many of the same harmful and potentially harmful constituents (HPHCs), included cigarettes that are currently on the market, and tested the cigarettes using common puffing protocols (e.g., ISO and HCI) across the studies. An additional analysis by Chemistry compared HPHC yields from aerosol from the new products to MSS concentration data from FDA50. Chemistry's analysis using FDA50 showed similar HPHC profiles (i.e., the same HPHCs, with similar concentrations) to HPHCs concentrations from the applicant's comparison products, average combusted cigarette MSS. Therefore, from a toxicological perspective the applicant's rationale for using combusted cigarettes as a comparison product is acceptable, and the use of average combusted cigarette data from the published toxicology literature is an acceptable representative of the combusted cigarette category.

- The applicant provided in vitro mutagenicity, cytotoxicity and genotoxicity studies that used the Kentucky Reference 1R6F cigarette as a comparison product. 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 (Vu et al., 2015; Roemer et al., 2004; Patskan et al., 2007). 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 the ENDS comparison product, Vuse Alto Original with 5% nicotine. The rationale for this comparison was that Vuse Alto is also a closed-system ENDS with a rechargeable battery and single-use pod that is filled by the manufacturer with nicotine salt-containing e-liquid. The applicant also states that Vuse Alto flavors (Original, Menthol, Mixed Berry, and Rich Tobacco) and nicotine content (5% nicotine) are similar to the new products with selected flavors (Classic Tobacco, Rich Tobacco, (b)(4) (b)(4) at 2.4% and 5% nicotine). From a toxicological perspective, the applicant's rationale for using Vuse Alto Original 5% as a comparison product is acceptable and the product similarities make it a useful ENDS comparison product.
- 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 category. The applicant states that the rationale for using this comparison was to give insight into HPHC comparison between the new products to other ENDS products, and to allow for the consideration of possible HPHC exposures for 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 the comparison represents a variety of ENDS products, which may be considered as alternatives to the new products or may be used in conjunction with the new products.

- Epidemiology: The applicant's observational studies included both combusted cigarette smokers and never smokers as comparison groups. Based on the information provided in the application, current combusted cigarette smokers are among the intended user population for these new products. Therefore, comparisons between the new products and combusted cigarettes may assist FDA's determination of whether permitting the marketing of the new products is appropriate for the protection of public health (APPH) because combusted cigarette smokers are a likely user population.
- Medical: The applicant used NJOY DAILY Rich Tobacco 4.5%, NJOY DAILY Rich Tobacco 6%, NJOY Loop Rich Tobacco 4.5%, JUUL Virginia Tobacco 5% and subject's usual combusted cigarettes as comparison products in the clinical studies to collect data on adverse experiences (AE) and health effects. All products used were of the same product category as the new products and contained generally similar amounts of nicotine except for combusted cigarettes. It is acceptable to compare ENDS to combusted cigarettes in this analysis because combusted cigarettes provide AE and health effects data on products that represent the current tobacco market.
- Microbiology: ENDS comparator product (VUSE Alto) stability information was not provided for the PMTAs. Therefore, a comparison of how product characteristics affect stability, when compared to similar ENDS tobacco products, could not be completed. However, based on the stability data (pH, moisture contentment, total aerobic microbial counts (TAMC), total yeast and mold counts (TYMC) and Bacterial Endotoxin (BET) over shelf life of the new products, the lack of stability data for the ENDS comparison products is acceptable from a microbiology perspective. A literature review was provided to establish acceptable levels of microbial content in non-sterile inhalation solutions and endotoxin levels in sterile inhalation water solutions. The new products have microbial content and endotoxin content below FDA and USP guidelines.
- Social Science: The applicant-submitted studies included comparisons of the new products to combusted cigarettes, as well as to other ENDS and nicotine replacement therapies. Based upon available data on perceptions and curiosity about and intentions to try the new products, the likely users of the new products will include current adult smokers. Detailed discussion

about the impact of the new products on current adult smokers and youth is provided below in Section 3.4.

- Behavioral & Clinical Pharmacology (BCP):
  - The applicant used Usual Brand (UB) cigarettes as the comparison product in one key clinical study that provided data on abuse liability, nicotine exposure, subjective effects, and puff topography. BCP determined that the data and rationale to support the applicant's chosen comparison product (UB cigarettes) was appropriate for comparison to the new products because cigarette smokers are the applicant's stated intended users of the new products and applicant-submitted survey data shows that cigarette smokers and dual users (of cigarettes and ENDS) are likely to use the new products.
  - The applicant used closed system ENDS containing nicotine salt formulations (i.e., NJOY Daily, Rich Tobacco; NJOY Extra, Rich Tobacco; NJOY Loop, Rich Tobacco; JUUL, Virginia Tobacco) as the comparison products in one key clinical study that provided data on abuse liability, nicotine exposure, subjective effects, and puff topography of one new product (PM0000615.PD1). BCP determined that these comparison products were appropriate as ENDS users are also the applicant's stated intended users, and likely to use the new products in this application.

3.1.2. Synthesis

The applicant provided comparisons between the new products and combusted cigarettes, as well as other ENDS products, in various studies and literature reviews.

The applicant compared the new products with Vuse Alto and JUUL for engineering parameters. The applicant also provided comparison data for aerosol constituent concentrations between the new products and Vuse Alto Original with 5% nicotine, which is an ENDS product in the same product category and subcategory and with similar flavors and nicotine salts. For in vitro mutagenicity, cytotoxicity and genotoxicity studies, the applicant used the Kentucky Reference 1R6F cigarette as a comparison product.

In their clinical studies, the applicant used subject's UB combusted cigarettes and NJOY DAILY Rich Tobacco 4.5%, NJOY DAILY Rich Tobacco 6%, NJOY Loop Rich Tobacco 4.5%, JUUL Virginia Tobacco 5%, as comparison products to collect data on AE, health effects, abuse liability, nicotine exposure, subjective effects, and puff topography. In their online survey studies, the applicant compared the new products to combusted cigarettes, as well as to other ENDS products and nicotine replacement therapies on product perceptions, appeal, and behavioral intentions.

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

As TPL, I agree with Chemistry, Toxicology, Epidemiology, Social Science, Medical and BCP conclusions that the applicant's rationale for the selection of combusted cigarettes and other ENDS as comparison products of the new products is appropriate because the applicant's stated intention is to market the new products to current adult tobacco users, including current cigarette smokers and current ENDS users. I further agree that the applicant provided adequate data to support the comparison between the new products and the chosen comparison products.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

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

3.2.1.1. Product design and composition

- Engineering: The applicant submitted the design parameters of the new products. The applicant provided the target specifications and upper and lower range limits for all of the design parameters for the new products.
- Chemistry: The applicant provided sufficient details of the single chemical ingredients for all thete-liquids and structure materials to characterize the product composition. The information submitted regarding product composition is acceptable from a chemistry perspective.
- Microbiology: The new products contain humectants (b)(4), and (b)(4) that may impact microbial activity during the applicant's proposed product shelf life. Microbiology stability data is discussed in detail in Section 3.2.1.3.

3.2.1.2. Manufacturing

- Engineering: The applicant submitted the manufacturing process for the new products, including nicotine manufacturing, (b)(4) manufacturing, bulk e-liquid manufacturing, and finished product (device and e-liquids) manufacturing and packaging. The information submitted regarding the manufacturing process is acceptable from an engineering perspective.
- Chemistry: The applicant provided manufacturing procedures and quality control measures for all e-liquid products to ensure products are manufactured in a consistent manner that minimizes variability in product quality. The applicant also provided representative ingredient Certificate of Analysis (COAs), raw ingredient quality control test results, batch verification, liquid properties, pH, and constituent measurements. All the provided data are within the acceptance criteria indicating product batch consistency. Therefore, the information submitted regarding product manufacturing is acceptable from a chemistry perspective.
- Microbiology: Bulk e-liquid manufacturers conduct e-liquid blending and filling operations in an International Organization for Standardization (ISO)t(b)(4) clean room. (b)(4) is an A2LA ISO 17025:2005 certified laboratory that performs release testing on the bulk e-liquids. The information submitted regarding the manufacturing of the new products is acceptable from a microbiology perspective.

3.2.1.3. Product stability

- Chemistry:
  - The applicant proposes a (b)(4) shelf life for the finished e-liquids. In order to support a (b)(4) product shelf life, the applicant is required to provide full (b)(4) finished product chemical stability data under ambient conditions (b)(4) RH) demonstrating that the finished e-liquids are chemically stable during a (b)(4) storage. Without full (b)(4) ambient stability data, the applicant is required to provide an additional (b)(4) of chemical stability data under accelerated conditions (b)(4) RH) with statistical analysis to extrapolate to ambient storage time of at least (b)(4) However, the applicant provided only (b)(4) of finished product chemical stability data under ambient conditions (b)(4) RH) and (b)(4) of chemical stability data under accelerated conditions (b)(4) RH) without extrapolation statistical analysis. The applicant would need to provide stability data for the last (b)(4) at ambient conditions to ensure the new products are chemically stable fort (b)(4) or statistical analysis of the (b)(4) of chemical stability data under accelerated conditions to extrapolate to ambient storage time of at least (b)(4) The data provided supports a (b)(4) product stability from a chemistry perspective.
- Microbiology:
  - The microbial stability data is necessary for the proposed shelf life as bacterial communities change as a function of storage time (Chopyk et al., 2017; Djordjevic et al., 1993). Increased microbial growth over time can impact stability of the product and may result in an increased risk to public health as the product sits in storage. Stability data (TAMC and TYMC) that spans (b)(4) for the finished e-liquids, and endotoxin data measured at the beginning of the (b)(4) period was provided for PM0000614.PD1-PM0000615.PD1.[6] Over that period, the TAMC and TYMC were not detected or (b)(4) cfu /ml. The stability data for TAMC and TYMC support (b)(4) stability from a microbiology perspective.
  - PM0000622.PD1 provided stability data (pH, water content, TAMC and TYMC) over (b)(4) and endotoxin data measured at the beginning of that time period for the finished new product. The provided stability data is acceptable from a microbiology perspective. However, stability data provided only supports microbial stability for (b)(4) The applicant stated that shelf life data from other tested products can be bridged to support a shelf life of (b)(4) for PM0000622.PD1 because the products are expected to have similar water content based on composition and due to the antimicrobial properties of 5% nicotine. However, the flavor profile of these products are different and literature shows that flavor ingredients influence the antimicrobial activity of e-liquids (Fuochi et al., 2020). Therefore, FDA would not be able to bridge the data from other products to PM0000622.PD1. In conclusion, for PM0000622.PD1, although the applicant

[6] The new products contain endotoxin levels below (b)(4) EU/mL. Based on the TAMC and TYMC data, further increase in endotoxin beyond time zero is unlikely. Therefore, the lack of endotoxin data beyond time zero of shelf life is not of concern for all new products.

proposed that the product is stable for (b)(4), the data only supports that the product remains stable for (b)(4) from a microbiology perspective.

3.2.1.4. Product test data

- Engineering: The power unit (PM0000613.PD1) contains a rechargeable 400 mAh lithium battery and printed circuit board assembly (PCBA) and is packaged with a universal serial bus (USB) charger. The NJOY ACE device does not include software. Charging and output power is controlled by the PCBA. The battery protection integrated circuit provides overcharging protection, over-discharging protection, overcurrent protection, short circuit protection, over-temperature protection, reverse charging protection, and reverse battery connection protection. The new products do not have user settings and cannot be modified by the user. The applicant submitted test data for all the required design parameters and the test data adequately demonstrate product consistency.
- Chemistry:
  - Most analytical methods and method validation are sufficient to support this review. There were method validation issues for four analytes tested, (b)(4) and (b)(4). However, the effect of the method validation issues is minimal because the concentrations of these four analytes are very low in thete-liquids.
  - Most constituents' aerosol yields are decreased in the products compared to the combusted cigarette and VUSE Alto Original 5% nicotine comparison products. The constituents with increased yields in the products are discussed in Toxicology Section 3.5.1.
  - The applicant also provided HPHC data for the product puff lifecycle for the 5% nicotine e-liquids (PM0000615.PD1 and PM0000622.PD1). Although there is some observed HPHC variability between puff blocks, the results show no significant trends of increasing aerosol HPHC concentrations over the product puff lifecycle. Moreover, due to similarity in e-liquid formulations and similar HPHC exposures between the 2.4% and 5% nicotine e-liquids, the risk of aerosol HPHC increases during product puff lifecycle of the 2.4% NJOY ACE PODs is unlikely to be meaningfully different from the data for the 5% nicotine e-liquids and is therefore acceptable from a chemistry perspective.

3.2.2. Synthesis

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

As TPL, I agree with the chemistry conclusions that these PMTAs contain sufficient ingredient information to characterize the product composition. In addition, the applicant implemented manufacturing procedures and quality control measures for all e-liquids to

ensure products are manufactured in a consistent manner. NJOY ACE device (PM0000613.PD1) is a closed ENDS with no adjustable parameters. PM0000613.PD1 uses NJOY ACE pods (PM0000614.PD1, PM0000615.PD1 and PM0000622.PD1) which are sealed, pre-filled, and non-refillable. The aerosol HPHC measurement provided by the applicant reflects the combined effects of both the device and e-liquids. The HPHC data showed, when comparing to combusted cigarette mainstream smoke, the aerosols of the new products have a lower number of HPHCs and many of the HPHCs present in the aerosols have comparatively lower potencies (i.e., lower magnitude or severity of toxicological effect, at a given dose or exposure level) than HPHCs present in combusted cigarette smoke (discussed in details in Section 3.5).

The applicant proposed a (b)(4) shelf life for the e-liquids, but only provided (b)(4) of finished product chemical stability data under ambient conditions. In addition, the applicant provided (b)(4) of microbial stability data for thete-liquids in PM0000614.PD1-PM0000615.PD1 and (b)(4) of microbial stability data for thete-liquid in PM0000622.PD1. Because the stability data provided by the applicant is acceptable and indicates that the products are low-risk for microbial growth over the period tested and because there are no other stability concerns, the lack of stability data for (b)(4) does not preclude an APPH finding for the new products. Therefore, although the applicant proposed a b)(4) shelf life, an authorization for PM0000614.PD1-0000615 should note that stability data submitted by the applicant supported that the product would remain stable for (b)(4) and for PM0000622.PD1, stability data submitted by the applicant supported that the product would remain stable for (b)(4).

3.3. ABUSE LIABILITY

3.3.1. Discipline key findings

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

3.3.1.1. Current tobacco users (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 product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted.
- Based on evidence from the applicant-submitted studies on the new products and published literature on ENDS similar to the new products, BCP concludes that the abuse liability of the new products is lower than or comparable to combusted cigarettes for inexperienced ENDS users, and comparable to combusted cigarettes for experienced ENDS users.
- Published literature shows that e-liquids with nicotine salts, like the new products in PM0000614.PD1, PM0000615.PD1, and PM0000622.PD1, can reach or exceed nicotine exposures associated with cigarettes (Goniewicz et al., 2019; Hajek et al., 2020) and other ENDS with free-base nicotine formulations (Boykan, Goniewicz, et

al., 2019; O'Connell et al., 2019; Yingst, Hrabovsky, et al., 2019). However, based on data from the applicant submitted clinical studies, BCP concluded that the abuse liability of NJOY ACE products is somewhat lower than or comparable to combusted cigarettes, mitigating concern of greater nicotine exposure (addiction potential) than combusted cigarettes.

- Smokers who are inexperienced with ENDS took similar individual puff durations and puff volumes of NJOY ACE products and their Usual Brand (UB) cigarettes; smokers took longer total puff durations when using the tested NJOY ACE products compared to smoking cigarettes. Compared with ENDS-inexperienced cigarette smokers, experienced ENDS users may take significantly larger/longer puffs and thereby obtain more nicotine from the same ENDS than ENDS-inexperienced cigarette smokers (Farsalinos et al., 2015; Hiler et al., 2017).

3.3.2. Synthesis

The applicant provided two clinical studies to examine the pharmacokinetics (PK), pharmacodynamics, subjective effects, and puffing behavior of the new products in this application. The submitted data demonstrated that, for inexperienced ENDS users, the new products are associated with a lower maximum nicotine concentration (Cmax) and area-under-the-concentration-time-curve (AUC), and a greater time to maximum nicotine concentration (T_{max}) compared to combusted cigarettes, indicating a lower abuse liability of the new products. Therefore, it is possible that an inexperienced ENDS user or non-user may not be able to achieve nicotine levels that would sustain ongoing use and the development of dependence. However, for experienced ENDS users, the study data and published literature showed that the new products have a Cmax and Tmax comparable to regular smokers of combusted cigarettes. The difference is likely due to experienced ENDS users taking significantly larger and longer puffs, thus attaining higher plasma nicotine concentrations compared to inexperienced ENDS users.

Although the abuse liability of long-term use was not examined in the studies, I agree with BCP review that having comparable abuse liability to combusted cigarettes potentially helps reduce smokers' urge to smoke, and therefore may facilitate smokers switching. With experience, users might reach higher nicotine levels to satisfy the withdrawal and craving symptoms. 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, while being exposed to lower levels of HPHCs.

3.4. USER POPULATIONS

3.4.1. Discipline key findings

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

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

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

- The applicant submitted two clinical studies that were conducted in current adult cigarette smokers and current adult ENDS users.

3.4.1.2. Current tobacco users

- Social Science:
  - Report of being "somewhat" or "very" curious about using the new products was low among current adult smokers (b)(4) but was greater than curiosity among former smokers (b)(4) and never smokers (b)(4). A similar proportion of current adult smokers were curious about the Rich Tobacco and Classic Tobacco flavors[7] (b)(4) respectively). (b)(4) (b)(4) (b)(4).
  - The proportion of adults who responded "definitely yes" to whether they intend to try the new products in the next year was low among adult current smokers (b)(4) but was greater than intention to try among former smokers (b)(4) and never smokers (b)(4). (b)(4) (b)(4) (b)(4) (b)(4). A similar proportion of current adult smokers intended to try Rich and Classic Tobacco flavors (b)(4) and (b)(4) respectively).
  - In summary, based on ratings of curiosity and intentions to use, the applicant's data suggest that (b)(4) (b)(4) compared to the Classic and Rich Tobacco products.
- Epidemiology:
  - The prevalence of the NJOY ACE products use was approximately (b)(4) among adults in the Adult Prevalence Study. The proportion of adult combusted cigarette users who reported use of the NJOY ACE products was (b)(4) Overall, (b)(4) of respondents reported using any ENDS product, slightly higher than but similar to estimated national prevalence of adult ENDS use in the 2018 NHIS (3.2%) (Bao et al., 2019). Similar to the published literature, more current and former smokers used ENDS generally and the new products specifically. The applicant reported that most ENDS initiation in adults occurred after combusted cigarette initiation, and current or former combusted cigarette smokers were more likely to initiate than never tobacco users. However, some of these outcomes could be due to cohort effects or generational differences in the marketplace when most adults initiated tobacco use.
  - In the applicant's NJOY User Study, the estimates of complete switching from combusted cigarettes to ENDS at three months was 32%, which is higher than what is typically seen in the literature for estimates of complete switching from combusted cigarettes to ENDS (3.4% - 5.9%) (Coleman et al., 2019; Stanton et al., 2020; Piper et al., 2020).

[7] "Classic tobacco" and "Rich tobacco" refer to the applicant-provided characterizing flavor for PM0000614.PD1615 and PM0000622.PD1, respectively. FDA determined that no additional information regarding characterizing flavor was necessary.

Furthermore, the applicant's data suggests there was a decrease in complete switching (measured by 30-day point prevalence abstinence (PPA)) between two months and three months. These high estimates of complete switching in the applicant's NJOY User Study are possibly inflated due to use of a convenience sample with a low enrollment rate and considerable loss to follow-up.

- Based on the applicant's data, a large number of new product users (likely >40%) could become dual users with combusted cigarettes, similar to patterns of dual use reported in the literature (43.5% - 54.1%) (Coleman et al., 2019; Stanton et al., 2020; Piper et al., 2020). While the NJOY User Study suggests there may be a reduction in combusted cigarette smoking among smokers who also use the new products, data from the literature is mixed. Estimates from the published literature suggest that, among adult dual users, 43.5% - 54.1% will discontinue ENDS use over time, 3.4% - 5.9% will transition to ENDS only use, and 1.4% - 11.0% will discontinue use of both products (Coleman et al., 2019; Stanton et al., 2020; Piper et al., 2020).

- BCP:
  - Among inexperienced ENDS users, abuse liability and nicotine exposures of the new products are somewhat lower than or comparable to combusted cigarettes.
  - Among experienced ENDS users, the abuse liability and nicotine exposures of the new tobacco products may be comparable to combusted cigarettes.
  - Cigarette smokers who initiate use of NJOY ACE likely will become either dual users of NJOY ACE and combusted cigarettes, or they will switch to NJOY ACE use completely. However, some cigarette smokers may temporarily adopt the new products before switching back to combusted cigarettes, which are rated higher in terms of liking and satisfaction compared with ENDS (e.g., Adriaens et al., 2018; Hajek et al., 2019; Stein et al., 2018; Stiles et al., 2017; Stiles et al., 2018).
  - Survey data provided by the applicant following dual-users of combusted cigarettes or exclusive users of the new products over a period of 3-months demonstrated that only 1% of users became completely abstinent from nicotine during this time period. This suggests that the vast majority of users of the applicant's product will not become completely abstinent from tobacco products.

3.4.1.3. Tobacco non-users (including youth)

- Social Science:
  - Overall, reported curiosity and intention to try the new product was low (<2%) among adult never and former smokers. These data suggest that former and never smoking adults are not interested in trying the new products.
  - (b)(4)
    (b)(4)
    (b)(4)
    (b)(4)

(b)(4)

b)(4)

b)(4)

- In 2021, 11.3% of high school students and 2.8% of middle school students reported current e-cigarette use (Park-Lee et al. 2021). It is possible that the number of youth who were current ENDS users was higher than reported in 2021; approximately half of the students took the survey at home, which may have resulted in an under-reporting of tobacco use behaviors (Biglan et al. 2004; HHS 2012). Additionally, longitudinal research using 2013-2015 PATH data indicated that 42.2% of past 30-day youth ENDS users remained past 30-day ENDS users one year later (Stanton et al., 2019). These published findings indicate risk of ENDS use among youth. However, youth are less likely to initiate with tobacco-flavored ENDS and subsequently progress to regular use than with non-tobacco flavored ENDS. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first ENDS that they used was non-tobacco flavored. In another PATH study, more youth, young adults and adults who initiated ENDS use between Wave 1 and Wave 2 reported use of a non-tobacco flavored product than a tobacco-flavored product. Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older (Rostron et al. 2020). Additionally, existing literature on non-tobacco flavored product use suggests that non-tobacco flavors not only facilitate initiation, but also promote established regular ENDS use. For example, regional studies have found that the use of non-tobacco flavored ENDS was associated with a greater frequency of ENDS used per day among a sample of adolescents in Connecticut in 2014 (Morean et al., 2018) and continuation of ENDS use in a sample of adolescents in California from 2014-2017 (Leventhal et al., 2019). Use of non-traditional flavors (vs. tobacco, mint/menthol, flavorless) was associated with increased likelihood of continued use and taking more puffs per episode (Leventhal et al., 2019). Data from a regional survey in Philadelphia, PA found initial use of a non-tobacco flavored vs. tobacco flavored ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months. Finally, similar effects have been found in the PATH study among young adults (18-24 years), where "ever use" of non-tobacco flavored ENDS at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2. Collectively, these findings indicate that while all ENDS pose risks to youth, youth are less likely to initiate with tobacco-flavored ENDS and subsequently progress to regular use, than with non-tobacco flavored ENDS.
- The interest in tobacco flavor is low among youth. The available evidence (NYTS 2021) indicates that a higher proportion of middle and high school current users reported using flavored ENDS than unflavored ENDS (including tobacco flavor) (Park-Lee, et al., 2021).

- According to National Youth Tobacco Survey (NYTS) 2021 data, 28.7% of middle and high school users reported prefilled or refillable pods or cartridges as the ENDS device types they used most often (Park-Lee, et al., 2021). Sleek design, ability to use products discreetly, and user-friendly nature make pod mod (rechargeable cartridge-based ENDS) products appealing among youth. Although there is some risk of youth uptake of the new products, in general, tobacco-flavored ENDS are less appealing to youth compared to non-tobacco flavored ENDS, making the risk of youth initiation low for these products. Findings from a discrete choice experiment showed that non-tobacco flavors were associated with more curiosity, less perceived danger, and greater perceived ease-of-use among high school students, compared to tobacco flavor (Chaffee et al. 2020). Additionally, the published literature indicates that youth report significantly higher preference for non-tobacco flavored ENDS compared to tobacco flavored ENDS (Harrell et al. 2016; Groom et al. 2020). Moreover, the evidence indicates that tobacco flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors. The findings from the 2020 Monitoring the Future (MTF) survey provide evidence that youth use of tobacco flavored ENDS is less common compared to other flavored ENDS including mint (Miech et al. 2021). According to the 2020 MTF data, the prevalence of tobacco flavor use was 2.9% among 10th and 12th graders while mint was the second most often used flavor (26.9%) after fruit (59.3%) (Miech et al. 2021).
- In addition, the digital marketing and TV and radio restrictions recommended by OHCE will help to mitigate the risk of youth initiation.

- BCP:
  - BCP's review of ENDS use in nonusers and youth is based solely on published literature.
  - ENDS use is highly prevalent among youth (Cullen et al., 2018), and the majority of youth use pod-style ENDS (Hammond et al., 2020; Lin et al., 2020; Wang et al., 2020). Youth who use pod-style ENDS (i.e., Juul, Sourin, Phix, Bo) have nicotine exposures that are comparable to or higher than that of youth cigarette smokers (Goniewicz et al., 2019) and non-pod-ENDS users (Boykan, Messina, et al., 2019). The new products contain high nicotine concentrations (i.e., 2.4-5%), similar to the pod-style ENDS tested in the literature (approximate range= 2-5% based on product labeling (Goniewicz et al., 2019)); therefore, nicotine exposures across these products may be comparable. High nicotine exposure may facilitate continued nicotine use and development of nicotine dependence.
  - The new product e-liquids contain nicotine salt formulations, which may be easier (i.e., less irritating) to inhale at high nicotine concentrations (Caldwell et al., 2012; Omaiye et al., 2019; Prochaska & Benowitz, 2019; Talih et al., 2019), thereby facilitating initiation and use of ENDS with high amounts of nicotine. However, based on data from the applicant submitted clinical studies, BCP concluded that the abuse liability of NJOY ACE products is somewhat lower than or comparable to

combusted cigarettes, mitigating concern of greater nicotine exposure (addiction potential) than combusted cigarettes.

- Youth users of pod-style ENDS report more symptoms of nicotine dependence than non-pod-ENDs users (Martinez et al., 2020; Morean et al., 2019).

- Epidemiology:
  - The applicant reports a low prevalence of new product use among adolescents in the Youth Prevalence Studies 1 and 2; however, these estimates are lower than what the literature suggests, and so should be interpreted with caution. In the applicant's Youth Prevalence studies, NJOY was the second most popular brand after JUUL.
  - Evidence from the peer-reviewed literature suggests that, while ENDS use among former tobacco users (predominantly former combusted cigarette smokers) has been observed across studies, prevalence is generally low (<5%), and one prospective study estimated the three-year transition probability of ENDS initiation among previous tobacco users was 3.2%. There is some evidence to suggest that former smokers who begin to use ENDS may relapse to combusted cigarette smoking.
  - National surveillance data suggest that, within the ENDS category, there is variability in the popularity of device types among youth, suggesting there may be differential appeal of certain product styles. Still, across these different device types, the role of flavor is consistent. As described above, the majority of youth ENDS use involves flavored products: in 2020, the majority of high school and middle school current e-cigarette users reported use of non-tobacco-flavored products (82.9%) (Wang et al., 2020) and flavored use was favored among both users of closed (87%) and open (76%) ENDS (internal analysis). In particular, across device types, including prefilled pods/cartridges, disposables, tanks, and mod systems, fruit was the most commonly used flavor type among youth, with 66.0% for prefilled pods/cartridges, 82.7% for disposables, 81.7% for tanks, and 78.9% for mod systems among youth reporting using a fruit flavor (Wang et al., 2020). It is also worth noting that the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace, that is, the options, especially flavors, that are available for consumers to choose from. Some evidence for this was observed in the trends both leading up to, and coinciding with, the shifting marketplace following the 2020 Enforcement Priorities Guidance. In particular, the enormous rise in youth ENDS use from 2017-2019 coincided with the ascendance of JUUL (and copy-cat devices) in the marketplace, suggesting a relationship between the availability of JUUL as an option, and the sudden popularity of pod-based devices. Then, as noted earlier, when FDA changed its enforcement policy to prioritize pod-based flavored ENDS, which were most appealing to youth at the time, we subsequently observed a substantial rise in use of disposable flavored ENDS--a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users (Wang et al., 2021). This trend illustrates that the removal of one flavored product option prompted youth to migrate to

another ENDS type that offered the desired flavor options, underscoring the fundamental role of flavor in driving appeal.

- Overall, the available evidence to date does not adequately address whether new product use in youth and young adults leads to regular smoking.

3.4.1.4. Vulnerable populations (other than youth)

- Epidemiology: 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. 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; Buchting et al. 2016; Hawkins et al. 2020; Obisesan et al. 2020; Wheldon et al. 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 combusted cigarette smokers from vulnerable populations to switch or reduce cigarettes per day (CPD).
- 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 ACE 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 the new products than females. In addition, White and Black non-users were less likely to intend to try than Hispanic and 'other' non-user race respondents.
- BCP:
    - BCP's review of ENDS use in vulnerable populations is based solely on published literature and is limited to smokers with diagnosed mental illness.
    - Vulnerable populations have higher rates of current ENDS use compared to non-vulnerable populations suggesting they find ENDS appealing and may initiate and continue using the new products (Huang et al., 2016; Kasza et al., 2017; Miller et al., 2018).
    - Vulnerable populations have increased difficulties with smoking cessation (Bowden et al., 2011; Cook et al., 2014; McClave et al., 2010). ENDS may serve as a harm reduction approach if users are able to completely switch or dramatically reduce combusted tobacco product use. However the impact of the new products on vulnerable populations is unknown.
    - Studies have not been conducted to assess the abuse liability of pod-based ENDS and e-liquids containing nicotine salts and/or flavors in vulnerable populations.

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

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

OHCE reviewed the marketing information submitted as part of the PMTA applications for NJOY ACE products and finds that the applicant proposes directing its marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion. However, it is noted that the applicant could alter its marketing plans following authorization. OHCE noted that if the products are authorized, this concern may be addressed by incorporating the marketing restrictions and reporting requirements described in section V of OHCE consult. Relatedly, OHCE supports certain aspects of the applicant's marketing plan, as described in the PMTAs, that are intended to help address the potential for youth use of the new products. Specifically, the applicant stated their intent to use the following measures to help reduce youth appeal of their marketing materials, restrict youth access to the new products, and limit youth exposure to their labeling, advertising, marketing, and promotion:

- 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 ACE products;
- Prohibiting the sale of NJOY ACE products on third-party websites;
- Limiting the number of products that can be purchased in a given time period or transaction;
- Using competent and reliable third-party sources to verify the age and identity of users against public records before granting access to the product website or conducting online

sales;

- Requiring retailers to only place NJOY ACE products in non-self-service areas of the store; and
- Conducting quarterly audits of point-of-sale signage located in retail chains that carry NJOY to determine whether only NJOY-approved trade marketing materials are being utilized.

OHCE encourages the applicant to implement these measures because they are likely to help further mitigate risks to youth.

3.4.1.6. Labeling and advertising

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

3.4.2. Synthesis

The applicant stated that adult current tobacco users (including cigarette smokers and ENDS users) are the intended user population for the new products. The new e-liquid products are classic tobacco and rich tobacco flavored ENDS pods. The applicant conducted 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.

Per Social Science and Epidemiology reviews, the applicant's adult Prevalence and Perception Study showed that the prevalence of the new NJOY products use was low among adult combusted cigarette smokers, with 2.3% reported use of the new products. In adult current smokers, curiosity about and intention to try the NJOY ACE products were low (b)(4) (b)(4) respectively). Based on ratings of curiosity and intentions to try, the applicant's adult Prevalence and Perception data suggest that current adult smokers had the most interest in the Classic Tobacco 5% nicotine product (b)(4) (b)(4) (b)(4) The Rich Tobacco and Classic Tobacco flavors showed similar curiosity and intentions to try among adult smokers. The applicant's studies also demonstrated that a greater proportion of adult current smokers were curious about Rich and Classic Tobacco flavors as compared to youth.

In the applicant's NJOY User Study, the estimated complete switching or abstinence rates at three months are 32%. These switching rates are higher than what is reported in published literature (3.4-5.9%). Per Epidemiology review, there were limitations to the NJOY User Study which may contribute to the high switching rates. The study limitations included: 1) the NJOY User Study recruited new purchasers of NJOY products using a convenience sampling approach and had a low enrollment rate, creating a likely source of selection bias in which the study population may not represent the target population; 2) the NJOY User Study had considerable loss-to-follow-up—i.e, incomplete follow-up observations were removed from the analyses which has the potential to bias results. Only 3,949 NJOY users out of 8,002 NJOY users (49.4%) completed the baseline survey and all follow-up time points. The incomplete surveys, which were excluded, were more likely from the participants who weren't completely switching to ENDS use. Even though the actual

switching rate may be lower than what is reported in the study, the NJOY User Study demonstrated that switching from combusted cigarettes to ENDS does occur among current adult smokers—typically through a period of dual use. In addition, current established cigarette smokers are more likely to prefer tobacco flavor relative to other flavors. In Wave 2 of the PATH Study, tobacco flavor was used by 50.5% of adult ENDS users aged 25 years and older who used a single flavor while menthol/mint was used by 23.3%, fruit by 15.9%, and candy or sweets by 7.8% (Soneji et al., 2019). In addition, among adult dual users (18+) who used nonmenthol cigarettes, 32.3% reported exclusive tobacco flavor use (Rostron et al., 2020). I agree with the Social Science review that these tobacco-flavored ENDS products may provide an important option for adult smokers who want to transition away from smoking.

The applicant's youth prevalence and perception studies showed that 18.0% of youth who reported ever ENDS use started with tobacco-flavored ENDS, 41.5% started with menthol or mint flavor, and 40.5% of youth who reported ever ENDS use started with "something other" than tobacco or mint/menthol flavors. (b)(4) (b)(4) (b)(4). Rich and Classic Tobacco flavors had similar levels of curiosity in the studies, though the intention to try was higher for Rich Tobacco flavor. As we discussed in this section, evidence shows that tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors. The findings from the 2020 Monitoring the Future (MTF) survey provide evidence that youth use of tobacco-flavored ENDS is less common compared to other flavored ENDS including mint (Miech et al., 2021). According to the 2020 MTF data, the prevalence of tobacco flavor use was 2.9% among 10th and 12th graders while mint was the second most often used flavor (26.9%) after fruit (59.3%). Though youth use of ENDS is concerning, as previously discussed, the published literature shows that prevalence of youth use of tobacco-flavored ENDS is low and that tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors.

With respect to youth appeal and mitigation, I agree with OHCE's evaluation of the applicant's marketing plans and all recommendations in the OHCE consult. The marketing information submitted by the applicant proposes directing marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion. However, since the applicant could alter their marketing plans following authorization, I recommend that the MGO letter include those marketing requirements and recommendations in section V of OHCE consult.

Product-specific information on vulnerable populations is lacking. However, based on published literature, vulnerable populations, such as lesbian, gay, and bisexual individuals and people with mental illness, have higher rates of ENDS use. I agree with BCP review that vulnerable populations have increased difficulties with smoking cessation (Bowden et al., 2011; Cook et al., 2014; McClave et al., 2010). ENDS may serve as a harm reduction approach if users are able to completely switch or dramatically reduce combusted tobacco product use. However the impact of the new products on vulnerable populations is unknown.

The evidence summarized in this section describes relatively high interest among adult smokers in using the tobacco-flavored products and demonstrates that switching from combusted cigarettes to ENDS does occur among current adult smokers—typically through a period of dual use. Use of these products would benefit smokers who switch completely or substantially reduce their cigarette smoking due to significant reductions in HPHCs of the new products compared to cigarettes (discussed in details in Section 3.5). In addition, the abuse liability of NJOY ACE products is somewhat lower than or comparable to combusted cigarettes, mitigating concern of greater nicotine exposure (addiction potential) than combusted cigarettes. The available information also shows that youth appeal/uptake of tobacco-flavored products is generally low among youth. Overall, I agree that the benefit of the new products to adult smokers is significant enough to overcome the risk to youth.

3.5. TOXICANT EXPOSURE

3.5.1. Discipline key findings

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

3.5.1.1. Toxicity

- Overall, there were significant reductions in aerosol HPHCs tested using the device (PM0000613.PD1) withte-liquids (PM0000614.PD1, PM0000615.PD1, PM0000622.PD1) stored for up to [(b)(4)] compared to cigarette comparison data under both non-intense and intense puffing regimens. Elevations in glycerin, propylene glycol, chromium and nickel of the new products aerosols are outweighed by decreases in other respiratory toxicants (e.g., acetaldehyde, diacetyl, acetyl propionide, acrolein, [(b)(4)], formaldehyde, [(b)(4)] and ethylene glycol) in the cigarette comparators. Observed glycerin, propylene glycol, chromium and nickel levels are comparable to levels seen in other ENDS market comparisons.
- Overall, in comparisons of combusted cigarette smoke HPHC concentrations to the products, combusted cigarette smoke has a higher number of HPHCs and many of the HPHCs present in cigarette smoke have comparatively higher potencies (i.e., higher magnitude or severity of toxicological effect, at a given dose or exposure level) than HPHCs in the aerosols of the new products. Therefore, these HPHC increases for chromium, nickel and nicotine in the new products in comparison to combusted cigarettes are outweighed by the increased number and potency of HPHCs in cigarette smoke and are unlikely to raise toxicology concerns for users of the products in comparison to average combusted cigarette yields.

3.5.1.2. Biomarkers of exposure

- Biomarker data submitted from a survey study conducted by the applicant found that participants who had recently used only the new tobacco products had lower levels of biomarkers of exposure (e.g., CO, cotinine, CEMA, 3-HPMA, and NNAL) relative to recent dual users of the new tobacco products and combusted cigarettes (i.e., dual-users).
- Published studies suggest that cotinine levels (i.e., nicotine exposures) in pod-style ENDS users are comparable or higher than that of cigarette smokers (Goniewicz et al., 2019) and non-pod-ENDS users (Boykan, Messina, et al., 2019).

- In youth, cotinine levels increase over time, particularly with increases in ENDS use frequency (Vogel et al., 2019).
- Cigarette smokers will likely experience significant reductions of VOC exposure upon complete switching to NJOY ACE products (Goniewicz et al., 2017; Oliveri et al., 2020; Round et al., 2019).
- Dual users likely will have comparable tobacco-specific nitrosamine (TSNA) and VOC biomarkers of exposure (BOE) as cigarette smokers, or they may experience low to modest reductions in these BOE (Pulvers et al., 2018).
- Exclusive users of NJOY ACE likely will be exposed to greater levels of TSNA and VOC BOE compared with non-tobacco users.
- Based on published literature, heavy metal exposure is likely to stay the same or decrease upon complete switching to NJOY ACE (Goniewicz et al., 2018; Jain, 2019; Prokopowicz et al., 2019).

3.5.2. Synthesis

Toxicology review concludes that there were significant reductions in aerosol HPHCs of the new NJOY ACE products compared to the combusted cigarettes. Although the applicant-provided data showed elevations in glycerin, propylene glycol, chromium and nickel of the new products, these increases are outweighed by large decreases in other respiratory toxicants (e.g., acetaldehyde, diacetyl, acetyl propionide, acrolein, (b)(4) formaldehyde, (b)(4) and ethylene glycol) in the cigarette comparators. Therefore, the overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in HPHC yields in the new products compared to cigarette comparators.

BCP review states that, based on biomarker data submitted from a survey study conducted by the applicant, participants who had recently used only the new products had lower levels of biomarkers of exposure (e.g., CO, cotinine, CEMA, 3-HPMA, and NNAL) compared to the dual users of the new products and combusted cigarettes. The data is consistent with other publications.

As TPL, I agree with the Toxicology and BCP conclusions that smokers who completely switch to or significantly reduce cigarette consumption with the new NJOY ACE products can reduce overall exposures to HPHCs compared to users of combusted cigarettes.

3.6. HEALTH EFFECTS

3.6.1. Discipline key findings

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

3.6.1.1. Toxicology

- Nonclinical studies
  - The new product aerosols and the ENDS comparison product, Vuse Alto Original 5%, demonstrated no mutagenic (Ames assay), no genotoxic (ivMN assay in IVGT cells), nor cytotoxic (NRU assay) potential at the

concentrations and under the conditions tested. Meanwhile, under the conditions tested, the combusted cigarette comparison product, 1R6F Reference cigarette, showed:

- Significant mutagenicity in Salmonella typhimurium strains TA98 and TA1537.
- Significant cytotoxicity and genotoxicity in IVGT cells.

- The applicant submitted a hazard analysis for in vitro studies comparing HPHCs (at 1 month to 9 months) and leachable compounds (at 1 month to 6 months) to HPHCs and leachable compounds at 0 month (which were used in the in vitro studies), and used a toxicology literature review to compare the highest ineffective dose (HID) and the lowest effective dose (LED) for Ames test and ivMN studies to the stability testing HPHC concentrations. Based on relative stability of e-liquids up to (b)(4) of storage under various conditions, and lack of mutagenicity, cytotoxicity, and genotoxicity at 0 month, the in vitro study hazard analysis of aerosol from the new product e-liquids (PM0000614.PD1-PM0000615.PD1 and PM0000622.PD1) stored for up to (b)(4) under various conditions is acceptable from a toxicological perspective.

3.6.1.2. BIMO inspection findings

BIMO inspection was not conducted at this time by FDA because the reported adverse effects (AEs) did not raise clinically significant concerns.

3.6.1.3. Addiction as a health endpoint

Per the BCP review:

- Clinical study data submitted by the applicant suggests that, based on subjective effects and nicotine exposure, the new products have a somewhat lower or comparable addiction potential than combusted cigarettes among inexperienced ENDS users.
- Clinical study data submitted by the applicant suggests that, based on subjective effects and nicotine exposure, PM0000615.PD1 has an addiction potential comparable to combusted cigarettes among experienced ENDS users.
- Current cigarette smokers, (i.e., one of the applicant's stated intended user populations) who switch partially or completely to NJOY ACE products, are initially likely to achieve somewhat lower or comparable nicotine exposures and likely will maintain their nicotine addiction. After some period of experience with the applicant's products, however, nicotine exposure may become comparable to combusted cigarettes.
- Dual users are likely to achieve slightly lower or comparable nicotine exposures from NJOY ACE products; some smokers may titrate, over time, to their preferred nicotine exposures (St Helen et al., 2020). Dual users are likely to maintain nicotine addiction, as with exclusive cigarette smoking.
- Based on published literature and the applicant-submitted survey study, dual users of NJOY ACE and cigarettes likely will reduce their cigarette consumption, however the extent of the reduction is unclear (Czoli et al., 2019).
- E-liquids with nicotine salts are easier (i.e. less irritating) to inhale at high nicotine concentrations (Caldwell et al., 2012; Omaiye et al., 2019; Prochaska & Benowitz,

2019; Talih et al., 2019) and may facilitate use and progression to regular use by naïve users such as youth. Published literature suggest that youth who initiate use of nicotine salt-containing pod-style ENDS may have comparable or higher nicotine exposures compared with youth cigarette smokers and non-pod-ENDS users. Youth who use nicotine salt-containing pod-style ENDS may experience increased cotinine levels over time which may correspond with increases in nicotine dependence and progression to regular use. However, based on data from the applicant submitted clinical studies, BCP concluded that the abuse liability of NJOY ACE products is somewhat lower than or comparable to combusted cigarettes, mitigating concern of greater nicotine exposure than combusted cigarettes.

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 Behavioral Risk Factor Surveillance System (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. E-cigarette users have higher exposure to constituents such as VOCs than do non-tobacco users.
  - Dual Use: In general, data from the biomarker literature suggests that dual users have sometimes been found to have higher levels of certain biomarkers of exposure including nicotine and its metabolites compared to combusted cigarette 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 combusted cigarettes to e-cigarettes, but levels of all other biomarkers significantly decreased after one week of using e-cigarettes (Goniewicz et al., 2017). Further information on possible benefits of switching from combusted cigarettes to e-cigarettes can be seen in the biomarker literature

showing researchers have generally found that e-cigarette users have lower levels of exposure to some constituents including TSNAs than do combusted cigarette smokers. Nicotine levels among e-cigarette users have usually been found to be somewhat lower or comparable to levels among smokers.

- Medical:
  - Based on the literature review, the impact of ENDS use on CVD, cancer, respiratory outcomes, developmental, and reproductive health outcomes, oral health, mental health, and other health topics are largely inconclusive. Risk of injury and poisonings have been consistently reported in the literature; however, no specific reports related to use of the new product were identified.
  - The applicant provided minimal data on biomarkers of potential harm; the information provided did not inform the health effects assessment.
  - Clinical studies submitted by the applicant did not identify short or long term health effects specific to the NJOY products. However, the studies have limitations, including small sample sizes and relatively short time periods of product exposure, thereby limiting the generalizability of the health effects data to a larger user population and extrapolation of the long-term health effects of the NJOY products. Despite these limitations, the applicant's data and published literature suggest that adult smokers who switch to these products (either completely or with a significant reduction in cigarette consumption) would benefit from reduced exposure to many HPHCs.

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 ACE products. Despite the lack of clinical data assessing product misuse (using the product in ways other than intended such as product modifications, dripping, and stealth use), BCP concludes that the likelihood of misuse is low for NJOY ACE products because they are closed-system pod-style ENDS. NJOY ACE power settings are non-adjustable, and thete-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.
- Medical:
  - The applicant did not report any serious health outcomes related to misuse. Though reports of ENDS-related poisonings among children have increased in the literature, the closed-system design of NJOY ACE pods may mitigate the risk of accidental exposure. The majority of ENDS related injuries among children and adults have been minor with more extensive injuries related to the use of lithium batteries as a power source for devices; however, no serious adverse events related to lithium battery use was reported by the applicant.

- Warnings against use of this product in children and adolescents appear on the label to mitigate the risk of misuse but does not include the potential risk of poisoning.
- The proposed labeling does not include recommendations for frequency of product use for these nicotine-containing products.

3.6.1.6. Adverse experiences

- Engineering: The AEs were discussed in the first cycle, where applicant evaluated the failure modes of the pods, device, and the complete system by calculating a risk priority number (RPN) to establish a standard risk scale. The medical discipline did not refer or defer any engineering-related design parameters associated with the adverse experiences of the NJOY ACE products. From an engineering perspective, no more information is needed.
- Medical:
  - There were no deaths or other serious AEs reported in the two clinical studies. Subject 13 reported a moderate headache after receiving the study product and it is unclear if this AE contributed to the subject's withdrawal from the study.
  - Nineteen AEs were reported in the clinical studies and assessed as at least possibly related to NJOY products. The AEs reported were either mild or moderate in severity, with the majority being mild.
  - The most commonly reported AEs across all studies were gastrointestinal (nausea, vomiting, dyspepsia, and stomach ache) followed by neurological (dizziness and headache). All AEs resolved prior to the end of the study.
  - The four categories in the applicant's Adverse Experiences Summary Report containing the highest number of AEs were Respiratory System (n=71), Digestive System (n=48), General (n=30), and Nervous System (n=11). The top four AEs across all organ systems were Sore Throat (n=23), Mouth Irritation (n=22), Cough/Sputum (n=19), and Feeling Sick (n=17).
  - The reports of gastrointestinal and neurological effects in clinical studies and in the Adverse Experiences Summary Report could indicate the potential for health effects of this nature when generalized to a larger population. These effects could potentially lead to further health complications or exacerbate underlying medical conditions in subpopulations of users (e.g., immunocompromised, diabetic, cardiac disease, respiratory disease).
  - In the applicant-submitted literature review on ENDS, AEs reported in published studies of ENDS products included cough, dry or irritated mouth or throat, dizziness or lightheadedness, headache or migraine, shortness of breath, change in or loss of taste, nausea, tight chest, and congestion. Several of these AEs were reported in the applicant-sponsored clinical studies.
  - FDA is aware of several health issues regarding the use of ENDS, specifically e-cigarette or vaping use-associated lung injury (EVALI), seizures, and overheating/fire/explosion-related thermal burn injuries (OH/F/Exp):
    - EVALI is a potential respiratory health effect that could occur in individuals who use vaping products. There were no reports of EVALI in the applicant's clinical studies and there did not appear to

be any subjects who experienced the constellation of symptoms indicative of EVALI as an AE that required hospitalization. However, since EVALI is associated with use of vaping products, CTP is interested in evaluating any additional information related to respiratory illness in association with ENDS and specifically the new products.

- There were no seizures reported as an AE in the applicant-submitted clinical studies. CTP is interested in monitoring an on-going evaluation of this potential health consequence of ENDS use.
- No OH/F/Exp were reported in the PMTAs. However, the risk is still an issue regarding ENDS use overall.

Therefore, to further monitor and evaluate potential ENDS health effects such as EVALI, seizures, and OH/F/Exp, medical recommends that post-market reporting include a specific plan to monitor respiratory-related illnesses, neurological symptoms, and AEs related to overheating and thermal burns associated with the products in the PMTAs.

3.6.2. Synthesis

As TPL, I agree with the BCP conclusions that the new tobacco products have a lower or comparable addiction potential than combusted cigarettes. Current cigarette smokers who switch partially or completely to NJOY ACE products will likely maintain their nicotine addiction. In terms of short- and long-term health effects, I agree with Epidemiology and Medical's conclusion that the association of ENDS use and CVD, cancer, respiratory disease, developmental, and reproductive health outcomes, oral health, mental health, and other health topics is largely inconclusive due to the limitations of clinical studies, such as small sample sizes and relatively short periods of product exposure. However, adult smokers who switch to these products (either completely or with a significant reduction in cigarette consumption) would benefit from reduced exposure to many HPHCs.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

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

3.7.1.1. Toxicology

- The applicant provided risk assessments for ingredients in the e-liquids for the new products (PM0000614.PD1, PM0000615.PD1, PM0000622.PD1), HPHCs in the aerosol for the new products, leachables and extractables from the NJOY ACE device (PM0000613.PD1), and alternative exposures (secondhand exposure to NJOY ACE aerosol; oral and intentional ingestion of NJOY ACE e-liquids; and incidental and accidental dermal exposures to NJOY ACE).
- The increases in chromium, nickel, acrolein, and formaldehyde in the new product compared to average combusted cigarette smoke levels suggest that they would increase the cancer risk for users of the new products. Assuming that a potential user will be switching completely from combusted cigarette smoking to using the

new tobacco products, exposures to HPHCs such as NNK, NNN, acrylonitrile, cadmium and lead are expected to be decreased. HPHCs from cigarette smoke (NNK, NNN, acrylonitrile, cadmium and lead), for which exposure levels would be decreased with switching completely, have increased potencies (i.e., higher magnitude or severity of toxicological effect, at a given dose or exposure level) compared to the HPHCs from aerosols from the new product. Based on the comparatively increased potency of HPHCs from cigarette smoke, and the number and concentrations of HPHCs from cigarette smoke and new product aerosol yields, the reduction in cancer risk from switching completely from combusted cigarettes to the products would likely outweigh the increase in cancer risk in the products due to chromium, nickel and formaldehyde. Overall, it is likely that the total cancer risk for the new products, NJOY ACE (PM0000614.PD1- PM0000615.PD1, PM0000622.PD1), assuming additivity, is less than the cancer risk posed by the commercially marketed combusted cigarette comparison products (e.g., the applicant submitted average MSS HPHC levels from the literature, and FDA50).

- Overall, the risk assessments conclude that with complete switching from use of other tobacco products (i.e., other ENDS and combusted cigarettes) to use of the new products, NJOY ACE, the potential health risks are likely to be similar (to use of other ENDS) and reduced (compared to combusted cigarettes) when compared to continued exclusive use of those tobacco products. In addition, secondhand exposures to HPHCs from ENDS aerosol are likely to be less harmful than secondhand combusted cigarette smoke exposures, and although there is an increased risk of adverse health effects with exposures to the new product e-liquids from alternate sources (i.e., dermal, oral, and ingestion), the likelihood of being exposed through these pathways is low due to the design of the product (i.e., it is a closed ENDS product). Based on the proposed new product use scenarios, switching completely from combusted cigarette smoking to the new products will result in the greatest reduction in HPHC exposures. Dual use of combusted cigarettes and the new products may offer decreases in HPHC exposures if combusted cigarettes per day is reduced. Switching completely from smoking combusted cigarettes to using the new product may result in similar or greater reductions compared to switching completely to products such as the comparison product, Vuse Alto.

3.7.1.2. Population health impact (PHI) model

- The data inputs used in the applicant's population health modeling scenarios for ENDS generally and NJOY ACE 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 combusted cigarette smoking to exclusive ENDS use. The scenarios also did not consider the possibility of ENDS use among young people, even though such use has become a matter of considerable public health concern. Given these limitations, the population modeling projections are not particularity informative to the overall assessment.

3.7.2. Synthesis

As TPL, I agree with Toxicology conclusions that switching completely from combusted cigarette smoking to the new products will result in large reduction in HPHC exposures. I also agree with Epidemiology review on the limitations of the applicant's population health modeling methodology. The limitations include overestimating actual switching rate from combusted cigarette smoking to exclusive ENDS use, as well as overlooking the scenarios of ENDS use among young people. Therefore, given the limitations associated with the model inputs described in the epidemiology review, the model is not particularly informative in the evaluation of whether the new products are 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, I find that permitting the marketing of the new products in accordance with the requirements in the marketing granted orders is APPH.

3.8.2. Tobacco product manufacturing practices

The PMTAs contain sufficient information to characterize the 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 proposed labeling is false or misleading in any particular.

3.8.4. Product standards

There are no applicable product standards for these PMTAs.

4. ENVIRONMENTAL DECISION

4.1. DISCIPLINE FINDINGS

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

4.2. ENVIRONMENTAL CONCLUSION

For PM0000613.PD1 – PM0000615.PD1, and PM0000622.PD1, a finding of no significant impact (FONSI) was signed by Luis G. Valerio on 4/22/2022. The FONSI was supported by an environmental assessment prepared by FDA on 4/22/2022.

5. CONCLUSION AND RECOMMENDATION

In making a determination about whether permitting the marketing of a product is APPH, Section 910(c)(4) directs FDA to consider the risks and benefits to the population as a whole, including users and nonusers of tobacco, taking into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to considering only information in a PMTA, but also extends to any other information before the Agency, including the relevant existing scientific literature (see Section 910(c)(2)).

Based on its evaluation of these PMTAs, FDA determined that these PMTAs contain sufficient information to characterize the new products' design and that there are adequate process controls and quality assurance procedures to help ensure both the device and e-liquids are manufactured consistently. FDA's evaluation also concluded that chemical testing was sufficient to determine that overall HPHC levels in the aerosol of these products are lower than in combusted cigarette smoke. Further, biomarker data provided by the applicant demonstrated that participants who had used only the NJOY ACE products had lower levels of biomarkers of exposure to HPHCs (e.g., CO, cotinine, CEMA, 3-HPMA, and NNAL) compared to the dual users of the new products and combusted cigarettes. In the applicant's Perception Study, current adult smokers had the most interest in the Classic Tobacco 5% nicotine product. Further, the NJOY User Study and published literature demonstrated that switching from combusted cigarettes to ENDS does occur among current adult smokers. The applicant has therefore demonstrated the potential for these products to benefit adult smokers who switch completely or significantly reduce their cigarette consumption as compared to continued exclusive cigarette use.

In terms of the risks to non-users, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. Although ENDS products are the most widely used tobacco products among youth, use of tobacco-flavored ENDS products by youth is reported to be significantly less common than flavored ENDS products in the published literature. Consistent with these findings, in the applicant's Youth Perception study, curiosity to use the tobacco-flavored products (b)(4) (b)(4). The same study also showed that the percentage of youth reporting ever ENDS use who initiated tobacco use with tobacco flavored ENDS was much lower than that of other flavors. Despite the lower appeal of tobacco-flavored products to youth, a marketing authorization order for these products should include postmarket requirements to help ensure that youth exposure to tobacco marketing is being minimized, given the strong evidence regarding the impact of youth marketing exposure to youth appeal and initiation of tobacco use. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit adult smokers who switch completely or significantly reduce their cigarette use would outweigh the risk to youth, provided the applicant follows post-marketing requirements aimed at reducing youth exposure and access to the products.

Regarding product stability, the applicant proposed a (b)(4) shelf life for the new products, but only provided (b)(4) of finished product chemical stability data under ambient

conditions. In addition, the applicant provided (b)(4) of microbial stability data for the e-liquids in PM0000614.PD1-PM0000615.PD1 and (b)(4) of microbial stability data for the e-liquid in PM0000622.PD1. Because the stability data provided by the applicant is acceptable and indicates that the products are low-risk for chemical stability and microbial growth over the period tested and because there are no other stability concerns, the lack of stability data for (b)(4) does not preclude an APPH finding for the new products.

Based on my review of the subject PMTAs, I find that permitting the marketing of the new products, as described in the applications and specified in Appendix, Table 3, is 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 products, in accordance with the marketing order requirements outlined in the marketing granted orders.

FDA has examined the environmental effects of finding the new tobacco products appropriate for the protection of public health 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

Adriaens, K., Gucht, D. V., & Baeyens, F. (2018). IQOS(TM) vs. e-cigarette vs. tobacco cigarette: A direct comparison of short-term effects after overnight-abstinence. *Int J Environ Res Public Health, 15*(12). doi:10.3390/ijerph15122902

Anic G, Cullen KA, Gardner LD, Liu ST. E-Cigarette Device Types Used by Middle School Students and High School Students-The U.S., 2019. J Adolesc Health. Feb 16 2021; doi:10.1016/j.jadohealth.2021.01.001

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. doi:10.1016/j.drugalcdep.2019.04.037

Azagba S, Latham K, Shan L. Cigarette smoking, e-cigarette use, and sexual identity among high school students in the USA. Eur J Pediatr. Sep 2019;178(9):1343-1351. doi:10.1007/s00431-019-03420-w

Bao W, Liu B, Du Y, Snetselaar LG, Wallace RB. Electronic Cigarette Use Among Young, Middle-Aged, and Older Adults in the United States in 2017 and 2018. JAMA Intern Med. 2019;180(2):313-314.

Barrington-Trimis, J. L., Kong, G., Leventhal, A. M., Liu, F., Mayer, M., Cruz, T. B., . . . McConnell, R. (2018). E-cigarette Use and Subsequent Smoking Frequency Among Adolescents. *Pediatrics, 142*(6). doi:10.1542/peds.2018-0486

Biglan M, Gilpin EA, Rohrbach LA, Pierce JP. Is there a simple correction factor for comparing adolescent tobacco-use estimates from school- and home-based surveys? Nicotine Tob Res 2004;6:427-437

Bowden, J. A., Miller, C. L., & Hiller, J. E. (2011). Smoking and mental illness: a population study in South Australia. *Aust N Z J Psychiatry, 45*(4), 325-331. doi:10.3109/00048674.2010.536904

Boykan, R., Goniewicz, M. L., & Messina, C. R. (2019). Evidence of Nicotine Dependence in Adolescents Who Use Juul and Similar Pod Devices. *Int J Environ Res Public Health, 16*(12). doi:10.3390/ijerph16122135

Boykan, R., Messina, C.tR., 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). doi:10.1542/peds.2018-3531

Buchting FO, Emory KT, Scout, et al. Transgender Use of Cigarettes, Cigars, and E-Cigarettes in a National Study. Am J Prev Med. Jul 2017;53(1):e1-e7. doi:10.1016/j.amepre.2016.11.022

Caldwell, B., Sumner, W., & Crane, J. (2012). A systematic review of nicotine by inhalation: is there a role for the inhaled route? *Nicotine Tob Res, 14*(10), 1127-1139. doi:10.1093/ntr/nts009

Chaffee BW, Couch ET, Urata J, Cash D, Werts M, Halpern-Felsher B. Electronic cigarette and moist snuff product characteristics independently associated with youth tobacco product perceptions. Tob Induc Dis. 2020;18:71. doi:10.18332/tid/125513

Cho J, Goldenson NI, Stone MD, et al. Characterizing Polytobacco Use Trajectories and Their Associations With Substance Use and Mental Health Across Mid-Adolescence. Nicotine Tob Res. Aug 14 2018;20(supplt 1):S31-S38. doi:10.1093/ntr/ntx270

Chopyk J, Chattopadhyay S, Kulkarni P, et al. Temporal Variations in Cigarette Tobacco Bacterial Community Composition and Tobacco-Specific Nitrosamine Content Are Influenced by Brand and Storage Conditions. Front Microbiol. 2017;8:358. doi:10.3389/fmicb.2017.00358

Coleman B, Rostron B, Johnson SE, et al. 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. 2019;28(1):50-59.

Conway KP, Green VR, Kasza KA, et al. 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. Addict Behav. Jan 2018;76:208-217. doi:10.1016/j.addbeh.2017.08.009

Cook, B. L., Wayne, G. F., Kafali, E. N., Liu, Z., Shu, C., & Flores, M. (2014). Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA, 311*(2), 172-182. doi:10.1001/jama.2013.284985

Cullen, K. A., Ambrose, B. K., Gentzke, A. S., Apelberg, B. J., Jamal, A., & King, B. A. (2018). Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students - United States, 2011-2018. *MMWR. Morbidity and mortality weekly report, 67*(45), 1276-1277. doi:10.15585/mmwr.mm6745a5

Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. JAMA. Dec 3 2019;322(21):2095-2103. doi:10.1001/jama.2019.18387

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. doi:10.1093/ntr/nty174

Dawkins, L., Kimber, C. F., Doig, M., Feyerabend, C., & Corcoran, O. (2016). Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology (Berl), 233*(15-16), 2933-2941. doi:10.1007/s00213-016-4338-2

Denlinger-Apte, R. L., Cassidy, R. N., Carey, K. B., Kahler, C. W., Bickel, W. K., O'Connor, R., . . . 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 and Alcohol Dependence, 218*, 108390.

Djordjevic MV FJ, Bush LP, Brunnemann KD, and Hoffmann D. Effects of storage conditions on levels of tobacco-specific n-nitrosamines and n-nitrosamino acids in U.S. moist snuff. . J Agric Food Chem 1993;41:1790-1794

Farsalinos, K. E., Spyrou, A., Stefopoulos, C., Tsimopoulou, K., Kourkoveli, P., Tsiapras, D., . . . Voudris, V. (2015). Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naive users (smokers). *Sci Rep, 5*(1), 11269. doi:10.1038/srep11269

Fuochi, V., Caruso, M., Emma, R., Stivala, A., Polosa, R., Distefano, A., & Furneri, P. M. (2020). Investigation on the antibacterial activity of electronic cigarette liquids (ECLs): a proof of concept study. Curr Pharm Biotechnol. doi:10.2174/1389201021666200903121624

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. doi: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. doi:10.1093/ntr/ntw160

Goniewicz, M. L., Smith, D. M., Edwards, K. C., Blount, B. C., Caldwell, K. L., Feng, J., . . . Hyland, A. J. (2018). Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. *JAMA Netw Open, 1*(8), e185937. doi:10.1001/jamanetworkopen.2018.5937

Groom AL, Vu TT, Kesh A, et al. Correlates of youth vaping flavor preferences. Prev Med Rep. Jun 2020;18:101094. doi:10.1016/j.pmedr.2020.101094

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. doi:10.1111/add.14936

Hammond, D., Wackowski, O. A., Reid, J. L., & O'Connor, R. J. (2020). Use of JUUL E-cigarettes Among Youth in the United States. *Nicotine Tob Res, 22*(5), 827-832. doi:10.1093/ntr/nty237

Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. Prev Med Rep. Mar 2017;5:33-40. doi:10.1016/j.pmedr.2016.11.001

Hawkins SS, Wylie BJ, Hacker MR. Use of ENDS and Cigarettes During Pregnancy. Am J Prev Med. Jan 2020;58(1):122-128. doi:10.1016/j.amepre.2019.08.031

Hiler, M., Breland, A., Spindle, T., Maloney, S., Lipato, T., Karaoghlanian, N., . . . Eissenberg, T. (2017). Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience. *Exp Clin Psychopharmacol, 25*(5), 380-392. doi:10.1037/pha0000140

Huang, J., Kim, Y., Vera, L., & Emery, S. L. (2016). Electronic Cigarettes Among Priority Populations: Role of Smoking Cessation and Tobacco Control Policies. *Am J Prev Med, 50*(2), 199-209. doi:10.1016/j.amepre.2015.06.032

Hughes, J. R., Peters, E. N., Callas, P. W., Peasley-Miklus, C., Oga, E., Etter, J. F., & Morley, N. (2020a). Withdrawal symptoms from e-cigarette abstinence among adult never-smokers: A pilot experimental study. *Nicotine Tob Res, 22*(5), 740-746. doi:10.1093/ntr/ntz169

Hughes, J. R., Peters, E. N., Callas, P. W., Peasley-Miklus, C., Oga, E., Etter, J. F., & Morley, N. (2020b). Withdrawal symptoms from e-cigarette abstinence among former smokers: A pre-post clinical trial. *Nicotine Tob Res, 22*(5), 734-739. doi:10.1093/ntr/ntz129

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. doi:10.1016/j.envpol.2019.05.041

Kasza, K. A., Ambrose, B. K., Conway, K. P., Borek, N., Taylor, K., Goniewicz, M. L., . . . Hyland, A. J. (2017). Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014. *N Engl J Med, 376*(4), 342-353. doi:10.1056/NEJMsa1607538

Leventhal AM, Miech R, Barrington-Trimis J, Johnston LD, O'Malley PM, Patrick ME. Flavors of e-Cigarettes Used by Youths in the United States. JAMA. Dec 3 2019;322(21):2132-2134. doi:10.1001/jama.2019.17968

Leventhal, A. M., Goldenson, N. I., Cho, J., Kirkpatrick, M. G., McConnell, R. S., Stone, M. D., . . . Barrington-Trimis, J. L. (2019). Flavored e-cigarette use and progression of vaping in adolescents. *Pediatrics, 144*(5). doi:10.1542/peds.2019-0789

Leventhal, A. M., Strong, D. R., Sussman, S., Kirkpatrick, M. G., Unger, J. B., Barrington-Trimis, J. L., & Audrain-McGovern, J. (2016). Psychiatric comorbidity in adolescent electronic and conventional cigarette use. *J Psychiatr Res, 73*, 71-78. doi:10.1016/j.jpsychires.2015.11.008

Lin, C., Baiocchi, M., & Halpern-Felsher, B. (2020). Longitudinal trends in e-cigarette devices used by Californian youth, 2014-2018. *Addict Behav, 108*, 106459. doi:10.1016/j.addbeh.2020.106459

Loukas, A., Marti, C. N., Cooper, M., Pasch, K. E., & Perry, C. L. (2018). Exclusive e-cigarette use predicts cigarette initiation among college students. *Addict Behav, 76*, 343-347. doi:10.1016/j.addbeh.2017.08.023

Martinez, U., Martinez-Loredo, V., Simmons, V. N., Meltzer, L. R., Drobes, D. J., Brandon, K. O., . . . Brandon, T. H. (2020). How does smoking and nicotine dependence change after onset of vaping? A retrospective analysis of dual users. *Nicotine Tob Res, 22*(5), 764-770. doi:10.1093/ntr/ntz043

McClave, A. K., McKnight-Eily, L. R., Davis, S. P., & Dube, S. R. (2010). Smoking characteristics of adults with selected lifetime mental illnesses: results from the 2007 National Health Interview Survey. *Am J Public Health, 100*(12), 2464-2472. doi:10.2105/ajph.2009.188136

McKelvey, K., Baiocchi, M., & Halpern-Felsher, B. (2018). Adolescents' and Young Adults' Use and Perceptions of Pod-Based Electronic Cigarettes. *JAMA Netw Open, 1*(6), e183535. doi:10.1001/jamanetworkopen.2018.3535

Miech R, Leventhal A, Johnston L, O'Malley PM, Patrick ME, Barrington-Trimis J. Trends in Use and Perceptions of Nicotine Vaping Among US Youth From 2017 to 2020. JAMA Pediatr. Feb 1 2021;175(2):185-190. doi:10.1001/jamapediatrics.2020.5667

Miller, M. E., Tidey, J. W., Bunn, J. Y., Gaalema, D. E., Scott-Sheldon, L. A. J., Pericot-Valverde, I., & Japuntich, S. J. (2018). Self-perceived Mental Health and Population-level Tobacco Use Disparities. *Tob Regul Sci, 4*(4), 3-11. doi:10.18001/trs.4.4.1

Morean, M. E., Butler, E. R., Bold, K. W., Kong, G., Camenga, D. R., Cavallo, D. A., . . . 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. doi:10.1371/journal.pone.0189015

Morean, M. E., Krishnan-Sarin, S., & O'Malley, S. S. (2018). Assessing nicotine dependence in adolescent E-cigarette users: The 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for electronic cigarettes. *Drug Alcohol Depend, 188*, 60-63. doi:10.1016/j.drugalcdep.2018.03.029

Morean, M. E., Krishnan-Sarin, S., Sussman, S., Foulds, J., Fishbein, H., Grana, R., & O'Malley, S. S. (2019). Psychometric evaluation of the e-cigarette dependence scale. *Nicotine Tob Res, 21*(11), 1556-1564. doi:10.1093/ntr/ntx271

Obisesan OH, Osei AD, Uddin SMI, et al. E-Cigarette Use Patterns and High-Risk Behaviors in Pregnancy: Behavioral Risk Factor Surveillance System, 2016-2018. Am J Prev Med. Aug 2020;59(2):187-195. doi:10.1016/j.amepre.2020.02.015

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. doi:10.1007/s11739-019-02053

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. doi:10.1093/ntr/ntz185

Omaiye, E. E., McWhirter, K. J., Luo, W., Pankow, J. F., & Talbot, P. (2019). High-nicotine electronic cigarette products: Toxicity of JUUL fluids and aerosols correlates strongly with nicotine and some flavor chemical concentrations. *Chem Res Toxicol, 32*(6), 1058-1069. doi:10.1021/acs.chemrestox.8b00381

Park-Lee E, Ren C, Sawdey MD, et al. Notes from the Field: E-Cigarette Use Among Middle and High School Students — National Youth Tobacco Survey, United States, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1387–1389.

Patskan, G. J., Podraza, K. F., Meurrens, K., Coggins, C.tR., Friedrichs, B., Gerstenberg, B., ... & Weber, S. (2008). Toxicological comparisons of three styles of a commercial US cigarette (Marlboro®) with the 1R4F reference cigarette. *Inhalation toxicology, 20*(7), 695-721.

Piper ME, Baker TB, Benowitz NL, Jorenby DE. Changes in Use Patterns Over 1 Year Among Smokers and Dual Users of Combustible and Electronic Cigarettes. Nicotine Tob Res. 2020;22(5):672-680.

Prochaska, J. J., & Benowitz, N. L. (2019). Current advances in research in treatment and recovery: Nicotine addiction. *Sci Adv, 5*(10), eaay9763. doi:10.1126/sciadv.aay9763

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. doi: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. *Nicotine Tob Res, 20*(2), 206-214. doi:10.1093/ntr/ntw333

Riehm KE, Young AS, Feder KA, et al. Mental Health Problems and Initiation of E-cigarette and Combustible Cigarette Use. Pediatrics. Jul 2019;144(1)doi:10.1542/peds.2018-2935

Roemer E, Stabbert R, Rustemeier K, Veltel DJ, Meisgen TJ, Reininghaus W, Podraza KF. (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.

Rostron BL, Cheng YC, Gardner LD, Ambrose BK. 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. Jan 1t2020;44(1):76-81. doi:10.5993/AJHB.44.1.8

Rostron BL, Chang JT, Chang CM, Jackson RA, Ambrose BK. ENDS Flavor Preference by Menthol Cigarette Smoking Status among US Adults, 2018-2019. Int J Environ Res Public Health. Dec 31 2020;18(1)doi:10.3390/ijerph18010240

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. doi:10.1093/ntr/nty140

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. *Tobacco regulatory science, 6*(1), 66-80.

Soneji, S., Barrington-Trimis, J. L., Wills, T. A., Leventhal, A. M., Unger, J.tB., Gibson, L.tA., . . . Sargent, J. D. (2017). Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr, 171*(8), 788-797. doi:10.1001/jamapediatrics.2017.1488

Soneji, S.tS., Knutzen, K. E., & Villanti, A. C. (2019). Use of Flavored E-Cigarettes Among Adolescents, Young Adults, and Older Adults: Findings From the Population Assessment for Tobacco and Health Study. *Public Health Rep, 134*(3), 282-292. doi:10.1177/0033354919830967

Stanton CA, Sharma E, Edwards KC, et al. 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. 2020;29(Suppl 3):s147-s154.

St Helen, G., Nardone, N., Addo, N., Dempsey, D., Havel, C., Jacob, P., 3rd, & Benowitz, N. L. (2020). Differences in nicotine intake and effects from electronic and combustible cigarettes among dual users. *Addiction, 115*(4), 757-767. doi:10.1111/add.14884

Stiles, M. F., Campbell, L. R., Graff, D. W., Jones, B. A., Fant, R. V., & Henningfield, J. E. (2017). Pharmacodynamic and pharmacokinetic assessment of electronic cigarettes, combustible cigarettes, and nicotine gum: implications for abuse liability. *Psychopharmacology (Berl), 234*(17), 2643-2655. doi:10.1007/s00213-017-4665-y

Stiles, M. F., Campbell, L. R., Jin, T., Graff, D. W., Fant, R. V., & Henningfield, J. E. (2018). Assessment of the abuse liability of three menthol Vuse Solo electronic cigarettes relative to combustible cigarettes and nicotine gum. *Psychopharmacology (Berl), 235*(7), 2077-2086. doi:10.1007/s00213-018-4904-x

Talih, S., Salman, R., El-Hage, R., Karam, E., Karaoghlanian, N., El-Hellani, A., . . . Shihadeh, A. (2019). Characteristics and toxicant emissions of JUUL electronic cigarettes. *Tob Control, 28*(6), 678-680. doi:10.1136/tobaccocontrol-2018-054616

Vogel, E. A., Prochaska, J. J., Ramo, D. E., Andres, J., & Rubinstein, M. L. (2019). Adolescents' E-Cigarette Use: Increases in Frequency, Dependence, and Nicotine Exposure Over 12 Months. *J Adolesc Health, 64*(6), 770-775. doi:10.1016/j.jadohealth.2019.02.019

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 US cigarettes. Chem Res Toxicol, 28(8), 1616-1626. doi:10.1021/acs.chemrestox.5b00190

Wang TW, Gentzke AS, Neff LJ, et al. Disposable E-Cigarette Use among U.S. Youth — An Emerging Public Health Challenge. New England Journal of Medicine. 2021;384(16):1573-1576.

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. *MMWR. Morbidity and mortality weekly report, 69*(37), 1310-1312. doi:10.15585/mmwr.mm6937e1

Wheldon CW, Wiseman KP. Tobacco Use Among Transgender and Gender Non-conforming Adults in the United States. Tob Use Insights. 2019;12:1179173X19849419. doi:10.1177/1179173X19849419

U.S. Department of Health and Human Services (HHS). Preventing Tobacco Use Among Youth and Young Adults. 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, 2012. https://www.ncbi.nlm.nih.gov/books/NBK99237/

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

Zevin, S., Gourlay, S. G., & Benowitz, N. L. (1998). Clinical pharmacology of nicotine. *Clin Dermatol, 16*(5), 557-564. doi:10.1016/s0738-081x(98)00038-8

7. APPENDIX

7.1. APPENDIX A: NEW PRODUCTS AND AMENDMENTS

Table 3. New tobacco products subject to Granted Orders[8]

Common Attributes of PMTAs	
Date of Submission:	March 10, 2020
Date of Receipt:	March 10, 2020
Product Manufacturer:	NJOY LLC
Product Category:	ENDS (VAPES)
P00000613.PD1 : NJOY ACE Device	
Product Sub-Category:	Closed E-Cigarette
Package Type:	Box
Package Quantity:	1 E-Cigarette
Length:	74.12 mm
Diameter:	29.8 mm
Wattage:	6.5W
Battery Capacity:	400 mAh
E-liquid Volume:	Not applicable
Nicotine Concentration:	Not applicable
PG/VG Ratio:	Not applicable
Characterizing Flavor:	None
Additional Properties:	Thickness: 13.5 mm Universal Serial Bus (USB)
PM0000614.PD1t NJOY ACE POD Classic Tobacco 2.4%	
Product Sub-Category:	Closed E-Liquid
Package Type:	Cartridge
Package Quantity:	2 Cartridges
Characterizing Flavor:	Tobacco
E-liquid Volume:	1.9ml
Nicotine Concentration:	2.4%w/w
PG/VG Ratio:	0.83[9]
Additional Properties:	Length: 34.75 mm Thickness: 11.57 mm Width: 29.59 mm

[8] Brand/sub-brand or other commercial name used in commercial distribution.
[9] Applicant provided value. Additionally, applicant provided PG and VG values as percentages of ingredient formula for each product.

PM0000615.PD1 : NJOY ACE POD Classic Tobacco 5%	
Product Sub-Category:	Closed E-Liquid
Package Type:	Cartridge
Package Quantity:	2 Cartridges
Characterizing Flavor:	Tobacco
E-liquid Volume:	1.9 ml
Nicotine Concentration:	5%tw/w
PG/VG Ratio:	0.75[9]
Additional Properties:	Length: 34.75 mm Thickness: 11.57 mm Width: 29.59 mm

PM0000622.PD1t: NJOY ACE POD Rich Tobacco 5%	
Product Sub-Category:	Closed E-Liquid
Package Type:	Cartridge
Package Quantity:	2 Cartridges
Characterizing Flavor:	Tobacco
E-liquid Volume:	1.9 ml
Nicotine Concentration:	5%tw/w
PG/VG Ratio:	0.77[9]
Additional Properties:	Length: 34.75 mm Thickness: 11.57 mm Width: 29.59 mm

Table 4. Amendments received

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
June 16, 2020	June 16, 2020	PM0000824	All	Yes	Technical update to new adverse experiences reporting, updated user survey, and updated population model
August 11, 2020	August 11, 2020	PM0000882	All	Yes	Response to July 29, 2020 Deficiency Letter
August 26, 2020	August 26, 2020	PM0000906	All	Yes	Follow up phone call for July 29, 2020 Deficiency Letter
September 30, 2020	September 30, 2020	PM0003401	All	Yes	Clarification to previously submitted data
December 17, 2020	December 17, 2020	PM0004434	All	Yes	Notification of new/current literature to support PMTA applications