



Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review ¹	
STNs	PM0000630-PM0000631
Common Attributes	
Submission date	March 30, 2020
Receipt date	March 30, 2020
Applicant	NJOY, LLC
Product manufacturer	NJOY, LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	Closed E-Cigarette
Cross-Referenced Submissions	
All new products	(b)(4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	<ul style="list-style-type: none"> • Statistical Consultation finalized on May 6, 2021 • Tobacco Product Surveillance Team Consultations finalized on September 30, 2020 and on February 2, 2022 • OHCE Consultation finalized on February 24, 2022
Recommendation	
Issue marketing granted orders for the new products subject of this review.	

Technical Project Lead (TPL):

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Signatory Decision:

Concur with TPL recommendation and basis of recommendation

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Matthew R. Holman, Ph.D.
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¹ Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application(s).

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1. EXECUTIVE SUMMARY

Based on the information provided in the application and other scientific data, as described in this Technical Project Lead (TPL) review, I find that permitting the marketing of the new products listed above (“new products” 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 premarket tobacco product application (PMTA) marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute specifies that, in assessing APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products. Section 910(c)(4). FDA interprets the APPH standard to require 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 increase or decrease, the burden of demonstrating a substantial enough benefit likewise increases or decreases. For flavored ENDS² (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

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 “menthol-flavored ENDS” or “menthol ENDS” to refer to ENDS flavored to impart a menthol flavor and the term “tobacco-flavored ENDS” or “tobacco ENDS” to refer to ENDS flavored to impart a tobacco flavor.

type 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 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.

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.

1.2. SUBJECT 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. The new products have UL 1642 Certification for the battery cell, and Engineering concluded there is a reduced risk of battery rupture. Based on the information provided in the PMTAs, the new products' abuse liability—i.e., ability to promote continued use, addiction, or dependence—is lower than combusted cigarettes and is similar to, or lower than, that of other ENDS. The overall toxicological risk to the users of the new products is lower compared to combusted cigarette smoke due to significant reductions in aerosol harmful and potentially harmful constituents (HPHCs) of the new products compared to cigarettes, as evidenced by results of nonclinical and aerosol studies. The biomarker data provided by the applicant demonstrated that participants who had used only the new products had lower levels of measured biomarkers of exposure (*e.g.*, carbon monoxide (CO), cotinine, 2-cyanoethylmercapturic acid (CEMA), 3-hydroxypropylmercapturic acid (3-HPMA), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)) compared to the dual users of the new tobacco products and combusted cigarettes. Based on applicant submitted survey studies, curiosity and intention to try the new products was higher in current adult smokers compared to former adult smokers and never smokers. Estimates by the applicant of complete switching from cigarettes to the new products for current adult smokers at three months was 26.5%, a level higher than what is typically seen in the literature for estimates of complete switching to ENDS products. The applicant submitted an observational study, from which the epidemiology review estimated that more current smokers at baseline reported using the new tobacco-flavored products compared to non-tobacco flavored NJOY products. Therefore, the applicant has demonstrated that some current adult smokers are interested in the new products to assist in decreasing or quitting their cigarette use, and these products have the potential to benefit that group.

Regarding human adverse experiences (AEs) with the new products, the applicant's submitted clinical studies did not have serious AEs or deaths. In addition, the applicant did not report any serious health outcomes related to misuse of the product. No definitive AEs related to the new products were found in FDA's Safety Reporting Portal.

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. In addition, the applicant's study findings demonstrated low intention to try and curiosity about using the new products among adult former smokers and never smokers. 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 post-market requirements to help ensure that youth exposure to tobacco marketing is limited. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit smokers who switch completely or significantly reduce their cigarette use would outweigh the risk to youth, provided the applicant follows postmarket 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. The applicant provided complete chemical stability study data including test data for bulk e-liquids,

finished product e-liquids, and aerosols; extractables and leachables data for components, parts and container closure system (CCS) meeting product specifications. The applicant-provided data supports microbial stability of the products over (b) (4). The stability data provided by the applicant is acceptable and indicates that the products are low-risk for chemical instability and microbial growth over the period tested and there are no stability concerns. Therefore, the applicant's stated shelf life of (b) (4) for the new products is supported by the submitted testing data.

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

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

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the two new products listed on the cover page and with more detail in the Appendix, sold under the product names NJOY DAILY Rich Tobacco 4.5% and NJOY DAILY EXTRA Rich Tobacco 6%. Briefly, the new products are disposable ENDS products with a prefilled e-liquid reservoir containing Rich Tobacco as a characterizing flavor with 4.5% nicotine (PM0000630) and 6% nicotine (PM0000631). The units are powered by a lithium ion, non-rechargeable battery with UL 1642 certification and atomizer subsystem. The power unit and cartridge settings are not adjustable by the user.

2.2. REGULATORY ACTIVITY

On March 30, 2020, FDA received two PMTAs (PM0000630-PM0000631) from NJOY LLC. FDA issued an Acceptance letter to the applicant on April 8, 2020. FDA issued a Filing letter to the applicant on April 21, 2020. FDA issued a Deficiency letter to the applicant on December 17, 2020.

Refer to the Appendix 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 of this review, as well as TPMFs (b)(4) and (b)(4). The TPMFs were referenced to support the new products in this application.

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewers	Review Date	Reviewers	Review Date
Engineering	Jim Melchiors	12/17/2020	Jim Melchiors	6/9/2022
Chemistry	Tianrong Cheng	12/14/2020	Tianrong Cheng	6/9/2022
Microbiology	Wen Lin	12/14/2020	Kristy HuynhNgo	6/9/2022
Toxicology	Prince Awuah	12/16/2020	Prince Awuah	6/9/2022
Behavioral and Clinical Pharmacology	Tyler Nighbor	12/14/2020	Steven Meredith	6/9/2022
Medical ⁵	Kathy Jackson	12/17/2020	Not assigned	N/A
Epidemiology	Arpi Terzian	12/16/2020	Amy Gross	6/9/2022
Social science	Dannielle Kelley	12/16/2020	Dannielle Kelley	6/9/2022
Environmental Science	Dilip Venugopal	12/16/2020	Dilip Venugopal	6/8/2022

Table 2. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Statistics	Not assigned	N/A	Sapna Thakur	5/6/2021
OCE – BIMO ⁵	Tara Singh	11/23/2020	Not assigned	N/A
OCE – Manufacturing/Lab	Hiwot Kesi	11/19/2020	Hiwot Kesi	04/30/2021
OCE – DPAL ⁵	Adeola Obajemu	11/5/2020	Not assigned	N/A
OHCE	Emily Talbert	10/14/2020	Allison O'Donnell Emily Talbert	02/24/2022
Tobacco Product Surveillance Team	Susan Rudy	09/30/2020	Susan Rudy	02/02/2022

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

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

- Engineering:
 - The applicant provided limited information on the comparator products STIG Cubano and STIG Mighty Mint. They have the same wick material and coil resistance as the new products, although the comparator products are slightly bigger, with 34% more e-liquid at 1.2 mL and 30% more battery at 260 mAh. The STIG Cubano and STIG Mighty Mint are similar products to

⁵ A second cycle review was not necessary as there was no new information or data to review for this discipline.

the new products with respect to the product design and are disposable ENDS like the new products. Therefore, they are appropriate comparators to the new products with respect to the product design.

- Chemistry:
 - All PMTAs provided aerosol constituent concentrations (generated from applicant-conducted testing) for Leap Go Smooth Tobacco 5% as a comparison product. Leap is a prefilled disposable tobacco flavored ENDS containing 5% nicotine salt. The rationale for this comparison was that Leap Go Smooth is also a disposable closed system ENDS with a non-rechargeable battery and single-use pod that is filled by the manufacturer with nicotine salt-containing e-liquid. Because the applicant also identified combusted cigarettes to compare to the new products, the chemistry reviewer also compared constituent yields from the new tobacco product aerosols to the mainstream smoke yields of 50 commercially available combusted cigarettes (FDA50 products).
- Toxicology:
 - The applicant provided comparisons between the new products and combusted cigarettes as a product category. The applicant used the average combusted cigarette mainstream smoke (MSS) concentration data from peer-reviewed scientific literature to represent the combusted cigarette category. This comparison was presented in the HPHC data. The applicant's rationale for this comparison is based on the premise of reduction of risk of overall adverse health effects from combusted cigarette for smokers who switch 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 recently published and peer-reviewed, measured many of the same HPHCs, included cigarettes that are currently on the market, and were tested using common puffing protocols (e.g., International Organization of Standardization (ISO) and Health Canada Intense (HCI)) across the studies. In addition, aerosol HPHC yields from the new products compared to mainstream smoke (MSS) concentration data from FDA50 products was provided by the applicant (Section 2.3 in cycle 1 review). Based on the applicant-submitted data, an additional analysis was conducted by Chemistry comparing HPHCs in the MSS of FDA50 products and in the aerosols of the new products. The additional analysis by Chemistry found the level of the HPHC, acetaldehyde, to be higher in the MSS of FDA50 products compared to that in the aerosols of the new products. The HPHCs acrylonitrile, benzene, NNN, NNK, and toluene were quantifiable (> limit of quantification) in the MSS of FDA50 products and were below the limit of detection in the aerosols of the new product PM0000631. The applicant did not measure acrylonitrile, benzene, NNN, NNK, and toluene in aerosols of the new products in PM0000630 because the measurement of these HPHCs from product shelf-life stability testing in PM0000631 was found to be below the limit of detection in the aerosols. The chemistry review found the shelf-life stability testing the applicant provided on PM0000631 to be acceptable. Since the only ingredient difference between PM0000631 and PM0000630 is the percentage of nicotine, 6% and 4.5%, respectively, the

toxicology review concluded that the levels of these HPHCs in PM0000630 would be expected to be lower or at least similar (below the limit of detection) in comparison to PM0000631. Therefore, from a toxicological perspective, the applicant's rationale for using combusted cigarettes as a comparison product is appropriate because the data show the comparator is representative of the combusted cigarette category, and current adult cigarette smokers are the applicant's stated intended users. Moreover, the use of average combusted cigarette MSS concentration data from the published toxicology literature is an appropriate 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 that reference cigarettes have 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., 2008). 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 mutagenicity, cytotoxicity, and genotoxicity in a combusted tobacco product.
- The applicant provided comparisons between the new products and the ENDS comparison product, Leap Go Smooth Tobacco with 5% nicotine. This comparison was presented in the HPHC data (Section 2.3 in cycle 1 review) and in the in vitro mutagenicity, cytotoxicity, and genotoxicity studies. The rationale for this comparison was that Leap Go Smooth 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 Leap Go Smooth Tobacco 5% flavor (Smooth Tobacco) and nicotine content (5% w/w nicotine) are similar to NJOY DAILY Rich Tobacco at 4.5% and 6% nicotine. From a toxicological perspective, the applicant's rationale for using Leap Go Smooth Tobacco with 5% nicotine is adequate.
- The applicant provided comparisons between the new products and other ENDS products (i.e., cig-a-like, fixed pods, variable pods, fixed tanks, and variable tanks). The applicant used the average nicotine-adjusted aerosol concentration data from peer-reviewed scientific literature to represent the other ENDS products categories. The applicant states that the rationale for using this comparison was to give insight into HPHC comparison between the new products and other ENDS products, and to allow for the consideration of possible HPHC exposures for non-users who may initiate use of the new products or other ENDS products. Overall, comparison of HPHCs from the new products and other ENDS products showed lower levels in the new products. From a toxicological perspective, the applicant's rationale for using average nicotine-adjusted HPHC levels from other ENDS products as a comparison product is adequate because this would allow for an ingredient normalized comparison since there are ingredient and design differences between the different ENDS products and the new products.

This method allows for a direct comparison of the new tobacco products and 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 used observational studies with comparison groups of both never users and current combusted cigarette users to support their application. According to the applicant, the intended user population is: “current adult users of nicotine-containing products who cannot or choose not to discontinue use of nicotine, particularly current combustible cigarette users and ENDS users”. However, some non-users will likely use the product as well. Considering the applicant-submitted youth prevalence studies, although these studies had small sample sizes, the data suggest that 40.5% of youth who reported ever ENDS use started with “something other” than tobacco/menthol flavored products, compared to 41.5% of every ENDS users who reported initiating with mint or menthol, and 18% reported using tobacco flavored ENDS. The applicant’s Youth Perceptions Study also indicated results specific to NJOY DAILY youth users. The applicant’s study indicated 45.6% of ever NJOY DAILY youth users reported starting with Blue + Black Berry, Tropical Twist, or Watermelon flavored NJOY DAILY products. The remaining respondents used tobacco flavored (13.3%), or menthol or mint flavored (32.8%) NJOY DAILY products, and 8% indicated they don’t remember.. These data provide some evidence that the new products are less appealing to youth compared to other types of flavored products. Based on the applicant’s description of the intended user population as current adult users of nicotine-containing products who cannot or choose not to discontinue use of nicotine, particularly current combustible cigarette users and ENDS users , , combusted cigarettes are an appropriate comparison product.
- Medical:
 - NJOY DAILY products were of the same product category (ENDS) as other products used as comparators in the applicant’s clinical studies to collect data on adverse experiences (AE) and health effects (NJOY ACE Tobacco 5%, NJOY LOOP Rich Tobacco 4.5%, and JUUL Virginia 5%). Combusted cigarettes were also used as a comparator in clinical studies. All comparator products used by the applicant are appropriate as they provide AE and health effects data on products that represent the current tobacco market and generally contain similar amounts of nicotine as the new products, 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 (Leap Go Smooth Tobacco 5%) 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. The new tobacco 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 non-NJOY ENDS and nicotine replacement therapies (NRTs). Based upon available data on perceptions, curiosity about and intentions to try the new products, the likely users of the new products will include current adult smokers. The applicant examined perceptions of the tobacco products and measured intentions to try the new products among cigarette smokers. The data in the application support the applicant's assertion that the intended population of current adult smokers is a likely user population. Overall, the comparisons of the new products made by the applicant to cigarettes, non-NJOY ENDS, and NRTs are appropriate from a social science perspective because the intended user populations are users of nicotine-containing products, particularly adult cigarette users and adult ENDS users, and data from other ENDS and NRTs allows for a comparison where the new products fall on the risk continuum.
- Behavioral & Clinical Pharmacology (BCP):
 - Combusted cigarettes served as the comparison product in a clinical study submitted by the applicant. Other ENDS were also used as the comparison products in another clinical study. Results from the clinical study provided by the applicant suggest that the new products may have lower nicotine exposure and subjective effects than combusted cigarettes. Overall, these findings suggest that the abuse liability of the new products is likely sufficient to sustain addiction in nicotine-dependent populations, and thus the comparison products are appropriate.

3.1.2. Synthesis

The applicant used combusted cigarettes and other ENDS products in the same category as the new products and a variety of other products outside the same category to compare to the new products. As TPL, I agree with the toxicology, engineering, chemistry, microbiology, medical, behavioral and clinical pharmacology, epidemiology, and social science conclusions that the comparison products selected by the applicant and the rationale for selection as well as the data from these products are appropriate. The principal comparator products were combusted cigarettes and ENDS products of the same category often with similar flavors. The comparators are appropriate because the applicant's stated intended user populations for the new products are current users of nicotine-containing products, including current ENDS users. Overall, the applicant provided adequate justification, rationale, and data to support the selections and comparisons made between the new products and their chosen representative and comparison products.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

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

3.2.1.1. Product design and composition

- Engineering:
 - Each new tobacco product is a closed non-rechargeable ENDS. The new products are not serviceable by the user for any purpose, including, but not limited to, customizing the atomizer, or modifying or refilling the e-liquid. For a 3-second puff, the new products heat an e-liquid to produce 3 to 5 mg of inhalable aerosol.
 - The new products contain an absorbent pad saturated with 0.84 to 0.94 mL of e-liquid consisting of propylene glycol, vegetable glycerin, lactic acid, and either 4.5% (PM0000630) or 6% (PM0000631) nicotine. A wick comprised of (b) (4) utilizes capillary action within the space between the (b) (4) to transport e-liquid from the absorbent pad to a (b) (4) heating element positioned diametrically across the airway where airflow transports the aerosol to the user. When the user draws air through the device (activation threshold is (b) (4) cc/minute), the pressure differential activates an airflow sensor with an Application Specific Integrated Circuit (ASIC) that outputs 3.4 VRMS from the non-rechargeable 200 mAh lithium-ion battery cell to the coil for 0.4 seconds, after which 3.0 VRMS is output. The airflow sensor limits the maximum puff duration to (b) (4). In order to consume for longer than that, a user must take multiple puffs. When airflow is stopped, the negative pressure within the housing returns to atmospheric and the sensor deactivates the output, returning the device to standby mode. When the battery cell is depleted (b) (4) V, the airflow sensor flashes the LED to notify the user that the cell is depleted, and the device is no longer usable.
 - The device always remains on in standby mode with activation controlled by the ASIC residing in the airflow controller waiting to detect airflow. The ASIC on the new products does not require software or firmware, as the required logic is integrated into the device. It has no user-adjustable parameters and stores no data. The device cannot be accessed, altered, or adjusted through any external connection.
 - Specifications were provided for all of the components of the new products that help to adequately characterize the new products. From an engineering perspective, the information submitted regarding design and principles of operation fully characterize the new products from an engineering perspective.
 - The new products have UL 1642 Certification for the battery cell reducing the risk of fire and explosion. The devices also have short circuit protection. The battery presents a minimal risk from an engineering perspective.
 - The design minimizes the risk of poisoning by containing the e-liquid in a manner that results in the e-liquid being inaccessible through customary or reasonably foreseeable handling or use, consistent with the Child Nicotine Poisoning Prevention Act of 2015. In addition, the e-liquid quantity is only 0.94 mL and it is contained in a sponge and is not free-flowing. Poisoning presents a minimal risk from an engineering perspective. Although the possibility of accidental exposure remains, these concerns have been reduced by the product design (i.e., closed, pod-based, non-refillable

- system). In addition, post-market manufacturer reporting obligations will allow FDA to monitor and assess any issues with accidental exposure.
- The new products have packaging components that could present a small choking hazard if not properly disposed of. They have a silicon end tip side cap and silicon mouthpiece side cap that are 9.2 mm in diameter. This risk is being monitored by the applicant and no adverse experiences have been recorded. Although this represents a potential concern, per the engineering review, the risk is small and is being monitored by the applicant. Post-market manufacturer reporting obligations will allow FDA to monitor and assess any potential issues with accidental exposure.
 - The new products do not have temperature control on the coil which could result in elevated HPHCs under certain conditions (“dry puff”). These conditions are that the atomizer fibers could deliver insufficient liquid to heated zone, the e-liquid viscosity could be too high for wicking transport, or an incorrect function of ASIC could cause over voltage at the atomizer. This risk is being monitored by the applicant. This risk is minimal from an engineering perspective.
 - The new products have a coil resistance between (b) Ω and (b) Ω with a target of (b) Ω. The overall atomizer resistance is the same (b) Ω to (b) Ω which is a reasonable design of the atomizer.. The applicant does provide data that demonstrates that the coil resistance meets the specification.
 - The applicant performed a design failure modes and effects analysis (dFMEA) for the new products. A risk assessment was completed by the applicant to identify potential risks in the design of the product including battery rupture. The engineering review concluded that the applicant’s risk assessment identified and implemented control measures that adequately mitigate foreseeable hazards.
- Chemistry:
 - The source of nicotine is cross referenced to Tobacco Product Master Files (TPMFs). According to the applicant, the nicotine used is extracted from *Nicotiana tobacum* plant. Per the TPMFs (b)(4), the nicotine specifications meet those in US Pharmacopeia monograph 41. The new products contain nicotine salt (nicotine lactic acid).
 - The 4.5% nicotine e-liquids contain 2.1% lactic acid, 40-44% (w/w) propylene glycol (PG), and 42-44% (w/w) vegetable glycerin (VG). The 6.0% nicotine e-liquids contain 3.2% lactic acid, 37-42% (w/w) PG, and 42-46% (w/w) VG. With regard to nicotine salts in the new products, the applicant used lactic acid to reduce e-liquid pH and protonate the nicotine to create a nicotine salt. The applicant indicated the main purpose is to partition more nicotine into the droplet phase of the aerosol for effective delivery and palatability. The applicant stated lactic acid is a weak acid naturally occurring in the human body, is safe, and is able to vaporize during heating, and compatible with the e-liquid formulation. Chemistry noted the nicotine concentration and nicotine form are comparable between the new products and the comparison ENDS product (Leap Go Smooth Tobacco 5% nicotine salts). Leap Go Smooth Tobacco 5% nicotine salts is in the same category and subcategory (closed, non-rechargeable ENDS) as the new products. Chemistry review found the applicant’s justification for technical use of

lactic acid in the formulation acceptable. Toxicity from exposure to the ingredients including nicotine salt, was evaluated by toxicology; they had no concern based on the applicant's use of literature information and toxicology reference values. Regarding potential toxicity from lactic acid, toxicology evaluated estimates from the applicant for daily inhalation exposures to the new products. Toxicology estimated lactic acid to be 3700-fold and 370-fold lower than established toxicology reference values for a no-effect level in humans under acute and chronic periods of exposure, respectively. With this information and considering lactic acid is naturally occurring in the human body, toxicology concluded there was no concern from use of lactic acid in the new products. Further, as discussed in Sections 3.3-3.6, the behavioral pharmacology review of clinical studies on the new products did not find any potential concerns in abuse liability specific to the nicotine salts that are used in the new products.

- All PMTAs included single chemical and complex ingredient information for e-liquids and the information is acceptable. All PMTAs included ingredient information and extractables and leachables (E&L) study results for the product structure materials that are in contact with e-liquids/aerosols. The ingredient information and E&L study results did not raise concerns from a chemistry perspective because chemistry concluded it is unlikely that product characteristics negatively impact the aerosol constituent levels of the new products as the aerosol constituent levels are significantly lower than those of combusted cigarettes.
- The applicant provided uniquely identifying information for materials and ingredients for the CCS, and the information is acceptable from a chemistry perspective. For all PMTAs, the applicant provided the material/ingredient quantities in percentages without providing the absolute quantity of the materials/ingredients. This limitation does not impact the outcome of this review, because the applicant provided the time zero leachable data for all bulk e-liquids.
- Microbiology:
 - The new products contain humectants (propylene glycol and vegetable glycerin), which may impact microbial activity during product shelf life. The stability of the new products is discussed in Section 3.2.1.3 of this review.

3.2.1.2. Manufacturing

- Engineering:
 - The applicant subcontracts the manufacturing of the products to (b) (4). (b) (4). The applicant provided a description of the manufacturing process at (b) (4) including the manufacturing steps, the sources of the components assembled, the packing processes, and the associated quality control (QC) and safety mechanisms that are in place. (b) (4)
 - (b) (4). Then, the assembly is completed, and the product is packaged.
 - The applicant states it audits the (b) (4) of the suppliers and contract manufacturers periodically to ensure compliance with applicable internal and external standards and regulations. The

- applicant supplied the relevant documentation for their (b)(4) including the (b)(4) documentation for (b)(4). The information on the manufacturing steps and the quality control measures in place demonstrate that the products meet manufacturing specifications for the new products and that the products are manufactured in a consistent manner that minimizes the variability in product quality.
- The above information submitted regarding the manufacturing process and quality control measures is acceptable from an engineering perspective.
 - Chemistry:
 - The information submitted regarding manufacturing procedures for the new product e-liquids (b)(4) and all e-liquids cartridge filling (by (b)(4)) is acceptable from a chemistry perspective. All PMTAs included representative ingredient certificates of analysis (CoA), raw ingredient quality control test results, batch verifications, liquid properties, and constituent measurements.
 - Quality control test data provided for all PMTAs are within the acceptance criteria indicating batch consistency with respect to the provided e-liquid properties. The applicant provided the test information (methods, validation reports, and test laboratory quality management system) for the (b)(4) in-process and batch release testing and a valid laboratory ISO9001 certificate for (b)(4) that generates comparable data in quality compared to ISO 17025 accredited laboratory (b)(4) for the targeted analysis. The applicant provided pH and specific gravity acceptance criteria and included specific gravity as a product quality measure for the new products manufactured by (b)(4). The information provided demonstrated that each new product's quality was controlled in a consistent manner and, therefore, is acceptable from a chemistry perspective.
 - The remote regulatory assessment (RRA) memo regarding inspections stated that the RRA did not find any significant observations. The applicant provided 22 exhibits, 14 of which address the chemistry relevant items listed in the Firm Specific Package (FSP). All 14 exhibits were acceptable from a chemistry perspective.
 - The applicant provided "representative" data for in-process/batch release testing and specifications for all PMTAs and the test information (test methods, validation reports, and testing laboratory quality management system) for manufacturing batches of the new products. There were minor limitations in the testing results such as the slight difference between the pH CoA specification range and the test data range. Chemistry found these limitations negligible and not adversely impacting the batch release and accepting testing. Overall, from a chemistry perspective, the data quality information in the submission on in-process/batch release testing, liquid properties, and constituent measurements demonstrates there is suitable quality, data accuracy and reliability in test results, and therefore, the data quality information provided by the applicant is acceptable from a chemistry perspective.
 - Microbiology:
 - Bulk e-liquid manufacturers conduct e-liquid blending and filling operations by (b)(4) an A2LA ISO 17025:2005 certified laboratory, and (b)(4) an on-site

laboratory, in an ISO (b)(4) and (b)(4) perform release testing on the finished bulk e-liquids. The released finished bulk e-liquids are dispensed into (b)(4) and sealed (b)(4) (b)(4) and shipped to the GMP certified (b)(4), to manufacture and package into finished new products. At (b)(4) site, (b)(4) (ISO 9001:2015 certified) personnel sample and test the finished new products (organoleptic testing for e-liquids only). The new products that are compliant with NJOY specifications are released for shipment. This information submitted regarding manufacturing of the new products is acceptable from a microbiology perspective.

3.2.1.3. Product stability

- Chemistry:

- The applicant originally intended an (b)(4) shelf-life for finished product, and (b)(4) shelf-life for bulk e-liquids. The applicant provided complete stability study data including test data for bulk e-liquids, finished product e-liquids, and aerosols; extractables and leachables data for components and parts and CCS; the stability specifications; justifications for the specifications; and justifications for bridging the bulk e-liquid stability data from NJOY Daily Extra Rich Tobacco 6% nicotine to NJOY Daily Rich Tobacco 4.5% product for sealed e-liquid shelf-life. In response to first cycle deficiency, the applicant revised their intended shelf-life from (b)(4) to (b)(4) for all finished new products and the sealed bulk e-liquid in Extra Rich Tobacco 6% and from (b)(4) to (b)(4) for sealed bulk e-liquid in Rich Tobacco 4.5%. All stability data show that the finished products (e-liquids and aerosols) and bulk e-liquids in all PMTAs meet the stability specifications at the proposed shelf-life demonstrating that the shelf-life for finished products in all PMTAs is (b)(4) whereas the shelf-life for sealed bulk e-liquids in NJOY Daily Extra Rich Tobacco 6% is (b)(4) and for NJOY Daily Rich Tobacco 4.5% is (b)(4).
- The applicant provided homogeneity data demonstrating that the new products remain homogeneous for up to (b)(4) during the (b)(4) process (b)(4).
- For all PMTAs, one justification for bridging the bulk e-liquid shelf-life of NJOY Daily Extra Rich Tobacco 6% nicotine to NJOY Daily Rich Tobacco 4.5% is that the nicotine content in NJOY Daily Extra Rich Tobacco is the highest (6.0%) and, therefore, is expected to generate the highest amount of nicotine related substances (NRS). This justification is acceptable and is supported by the bulk e-liquid stability data of the same flavor and of time zero. Additionally, the specification of total NRS (b)(4) µg/g) in 4.5% nicotine content bulk e-liquid is lower compared to 6.0% nicotine content bulk e-liquids (b)(4) µg/g) and thus, is not a concern.

- Microbiology:

- The microbial stability data is necessary for the proposed shelf life as bacterial communities change as a function of storage time. Increased microbial growth over time can impact stability of the product and may result in an increased risk to public health as the product sits in storage

(Chopyk et al. 2017; Djordjevic et al. 1993). The applicant provided stability testing data (water content, and total aerobic microbial count (TAMC)/ total yeast and mold count (TYMC)) that supports (b)(4) of shelf life following new product storage at (b)(4) % RH. Therefore, the data provided are sufficient to demonstrate the microbial stability of the finished products over (b)(4).

3.2.1.4. Product test data

- Engineering:
 - The product performance testing provided demonstrates conformance with the finished product release specifications set for the new products. The applicant has provided adequate information to demonstrate that the new products can be manufactured consistently and meet the manufacturer's pre-defined quality controls and specifications, and they will operate consistently throughout the life of the product.
- Chemistry:
 - The aerosol HPHC yields of the new products are tested under intense and non-intense regimens. There are significant reductions in HPHCs from the new products' aerosols compared to combusted cigarette comparison data under intense and non-intense regimens.
 - All analytical methods and validations for chemical characterizations (of e-liquids and aerosols) and product stability studies of all PMTAs are sufficient to support the provided test data.
 - The aerosol generation regimens (non-intense and intense) selected for all PMTAs are appropriate and represent the range of emissions including the emissions that could occur during heavy use of the new products.
 - The constituents with increased yields in the new products relative to combusted cigarette comparison data under both non-intense and intense puffing regimens are discussed in Section 3.5.1.
- Toxicology:
 - The toxicology review evaluated the increases of constituents in the aerosols of the new products relative to combusted cigarette comparison data noted by chemistry. The toxicology evaluation of the constituents with increased yields in the new products relative to combusted cigarette comparison data is discussed in Sections 3.5.1 and 3.7.1.1.
- Microbiology:
 - Stability testing data (Water content, TAMC, TYMC) that supports (b)(4) (b)(4) of shelf life were provided at time points (0, (b)(4) and (b)(4) (b)(4) following new product storage at (b)(4) % RH. From a microbiology perspective, the provided stability testing is sufficient to demonstrate the microbial stability of the products over the applicant-proposed shelf life of (b)(4).
 - Endotoxin testing data at zero and (b)(4) were provided for all new products. All new products endotoxin content data are below acceptable limits (≤ 0.5 EU/mL or ≤ 20 EU/device) as established by USP<161> and consistent with recommendations set out in FDA Guidance for Industry

Pyrogen and Endotoxins Testing: Questions and Answers, June 2012 (<https://www.fda.gov/media/83477/download>).

- The information submitted regarding endotoxin content levels in the new products is acceptable from a microbiological standpoint.

3.2.2. Synthesis

As TPL, I agree with engineering, chemistry, and microbiology conclusions that these PMTAs contain sufficient information to characterize the product design and adequate manufacturing processes and controls to help ensure that the new products meet the manufacturer's specifications. The product characterization information submitted by the applicant fully characterizes the new products from an engineering, chemistry and microbiological standpoint.

The engineering review found that these PMTAs contain sufficient information to characterize the product design, composition, manufacturing, and test data. The engineering review concluded that the devices were designed and tested to minimize the risk of fire, explosion, and accidental poisoning. A small choking hazard for packaging components was identified as a potential concern; however, no adverse experiences have been recorded and it is being monitored by the applicant. Because the risk cannot be eliminated, this small choking hazard represents a limitation on the new product from an engineering perspective. This limitation represents a low risk and is not significant enough to raise a concern. Post-market manufacturer reporting obligations will allow FDA to monitor and assess any potential issues with accidental exposure. A risk assessment for design failure modes was performed by the applicant which strengthened the evidence that there is a reduced risk of product malfunction, as well as safety or regulatory concerns resulting from materials of construction, system interactions, specification tolerances, degradation, and others as discovered during the design failure modes and effects analysis (dFMEA) process. The microbiology information submitted for manufacturing and stability data was found to be adequate. The applicant-provided stability testing for TAMC and TYMC and supports (b)(4) of shelf life for finished product, and the endotoxin testing data was found to be below USP acceptable limits as well as FDA Guidance for Industry Pyrogen and Endotoxins Testing. Stability specification and justifications for bridging the bulk e-liquid stability data from NJOY Daily Extra Rich Tobacco 6% nicotine to NJOY Daily Rich Tobacco 4.5% product for sealed e-liquid shelf-life was found to be adequate by chemistry. For chemistry and microbiology, materials and ingredient information was adequately described. A notable feature of the product composition is the presence of nicotine salt (nicotine lactate). The applicant indicated the main purpose of creating the nicotine salt is for delivery of nicotine in the droplet phase of the aerosol for effective nicotine delivery and palatability. The applicant stated the creation of nicotine salt reduces the pH of the nicotine solution and aerosolized vapor resulting in less throat irritation for the user. The applicant indicated that lactic acid is a weak acid that is naturally occurring in the human body, is able to vaporize upon heating, and is compatible with the e-liquid formula. The comparison ENDS product Leap Go Smooth Tobacco 5% also contains a nicotine salt at a similar nicotine strength compared to the new products. Chemistry found the applicant's provided information (source, quantity, grade, form, and function) for use of the nicotine salt adequate. Toxicology had no concerns with use of nicotine lactate noting lactate is endogenously produced at low levels in the body and found the applicant's use of literature

information and toxicology reference values for ingredients to be adequate and to show no significant increased risk. As discussed in the Abuse Liability Section 3.3.1.1 below, BCP assessed whether the high nicotine salt formulations in the e-liquids of the new products would facilitate initiation and use of ENDS with high amounts of nicotine. Based on the applicant's submitted clinical studies, the abuse liability of the new products is somewhat lower than combusted cigarettes. Therefore, the use of nicotine salt in the new products is not a concern for enhancing addiction liability any greater than the comparator tobacco product, combusted cigarettes. Manufacturing procedures information provided by the applicant showed that the new products have consistent quality control with only negligible limitations regarding e-liquid batch release specification. The chemical stability data that was provided by the applicant for the new products support the applicant's intended (b)(4) (b)(4) shelf-life for the finished products and sealed bulk e-liquid in Extra Rich Tobacco 6.0%, and the applicant's intended (b)(4) shelf-life for sealed bulk e-liquid in Rich Tobacco 4.5%. Microbiological stability testing data supports a (b)(4) shelf life for the finished product.

3.3. ABUSE LIABILITY

3.3.1. Discipline key findings

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

3.3.1.1. Current tobacco users

- Behavioral and Clinical Pharmacology:
 - '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.
 - The behavioral and clinical pharmacology review evaluated two applicant-sponsored clinical studies on the new products and literature bridging information submitted in the application to the new products and concluded that current tobacco users who use the new products in these PMTAs are likely to be dual users of the new products and combusted cigarettes. The review further concluded the new products may produce lower nicotine exposure and subjective effects than combusted cigarettes. This conclusion is based on results of an acute clinical study submitted by the applicant measuring nicotine pharmacokinetic data and urinary biomarkers of exposure (BOE) information.
 - According to the behavioral and clinical pharmacology review, the new products have an abuse liability lower than combusted cigarettes among experienced ENDS users. Together with the published literature, the submitted data for the new products suggests that individuals will maintain their nicotine dependence and will have a low likelihood of complete cessation from tobacco products. Results from a clinical study involving acute exposure to the new products suggest that the new products may

produce lower nicotine exposure and subjective effects than combusted cigarettes, suggesting lower abuse liability for these new products than that of combusted cigarettes. This conclusion is based on clinical testing of the new product, Extra Rich Tobacco 6% nicotine (PM0000631), which was tested for nicotine pharmacokinetics and biomarkers of exposure. Bridging information on the tested Extra Rich Tobacco 6% nicotine concentration product was provided by the applicant to approximate the concentration of plasma nicotine measured by area under the curve over 120 minutes for the untested Rich Tobacco 4.5% nicotine concentration (PM0000630) new tobacco product. Based on the bridging information provided, compared to the tested product, the untested product is assumed to have nicotine C_{max} approximating 96%, mean nicotine $AUC_{0-120min}$ approximating 99%, and mean nicotine T_{max} approximating 128% of the tested product. Because the untested product has the same or lower amount of nicotine as the tested product, it is expected to have a similar mean plasma nicotine exposure to the tested products. Collectively, the information from the tested product and bridged product suggests that abuse liability for these products would be lower than combusted cigarettes. Furthermore, with respect to the bridged product, the information suggests that abuse liability would be no higher than the tested 6% nicotine product.

- Results from the applicant's clinical study involving acute exposure to the new products PM0000630 and PM0000631 suggest these products may have lower nicotine exposure than the representative ENDS that were tested. However, it is unclear how the abuse liability of the new products compares to other ENDS.
- Published literature shows that e-liquids with nicotine salts, like the new products in PM0000630 and PM0000631, 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 et al., 2019; O'Connell et al., 2019; Yingst et al., 2019). However, based on data from the applicant submitted clinical studies, BCP concluded that the abuse liability of the new products is lower than combusted cigarettes, mitigating concern of greater nicotine exposure (addiction potential) than combusted cigarettes among youth.

3.3.2 Synthesis

Clinical studies measured nicotine pharmacokinetics for the new product, Extra Rich Tobacco 6%, which was appropriately selected by the applicant to bridge to the lower nicotine containing product, Rich Tobacco 4.5%. The data from these studies demonstrated an abuse liability that approaches that of combusted cigarettes. A study was submitted by the applicant demonstrating use of the new products by combusted cigarette smokers who had past month experience using ENDS suggesting that abuse liability would be lower than or comparable to combusted cigarettes for experienced users. Results from the applicant's clinical study provided evidence that the new products may have lower nicotine exposure than comparative ENDS products. Since nicotine exposure from the new products did not exceed that of combusted cigarettes, this supports a lower abuse liability for users of the new products which may be beneficial to population health. In addition, given that the submitted clinical evidence

on the new product Extra Rich Tobacco 6%, which was bridged to Rich Tobacco 4.5%, which collectively shows an abuse liability approaching that of combusted cigarettes, there is support for a potential benefit of smokers trying to switch to the new products. Studies have demonstrated that experienced users can attain higher plasma nicotine concentrations than inexperienced users (Farsalinos et al., 2015; Hiler et al., 2017); however, there is also evidence that inexperienced ENDS users may also achieve plasma nicotine levels similar to own brand cigarettes (Hiler et al., 2017; Lopez et al., 2016; Maloney et al., 2019; O'Connell et al., 2019). Taken together, the inherent risk of addiction of the new products appear to be no higher than other currently available tobacco products. As TPL, I agree with the behavioral and clinical pharmacology conclusions that, based on data from the applicant's studies and published literature, the abuse liability of the new products is likely sufficient to sustain dependence in already nicotine-dependent populations.

3.4. USER POPULATIONS

3.4.1. Discipline key findings

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

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

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

3.4.1.2. Current tobacco users

- Social Science:
 - Based on data submitted by the applicant, curiosity about using NJOY products in general was 8.3% among current adult smokers, which was greater than curiosity among former smokers (3.5%) and never smokers (5.1%). Regarding curiosity, specific to the new products, the curiosity of current adult smokers was 7.2% for Rich Tobacco and 6.0% for Extra Rich Tobacco. Curiosity among former smokers for Rich Tobacco and Extra Rich Tobacco was at 1.9% and 2.6% respectively. Curiosity among never smokers for Rich Tobacco and Extra Rich Tobacco was 1.2% and 2.3% respectively.
 - Intention to try any of the new products in the next year was 5.2% among adult current smokers and greater than intention to try among former smokers (0.8%) and never smokers (0.5%). A similar proportion of current adult smokers intended to try Rich Tobacco (5.2%) and Extra Rich Tobacco (7.0%)
- Behavioral and Clinical Pharmacology:
 - Based on a survey study provided by the applicant and findings in the literature, current tobacco users who use the new products in these PMTAs are likely to be dual users of the new products and combusted cigarettes.
 - Based on the literature submitted by the applicant, current tobacco users may learn to titrate their use of the new products in these PMTAs

- to their preferred nicotine exposures over time, thereby maintaining their nicotine dependence.
- Based on a limited survey study provided by the applicant and findings in the literature, current tobacco users are unlikely to switch completely to the new products in the current PMTAs. Additional details were reviewed by epidemiology (discussed below).
 - Clinical data provided by the applicant suggest the new products have abuse liability lower than, but perhaps approximating, combusted cigarettes among experienced ENDS users. Together with the published literature, this suggests users of the new products will maintain their nicotine dependence and have a low likelihood of complete cessation from tobacco products.
- **Epidemiology:**
 - The prevalence of the use of NJOY DAILY products was approximately 0.3% among adults in the applicant's Adults Prevalence Study. Overall, ENDS use prevalence in the Adult Prevalence Study (3.2%) was lower but generally similar to estimated national prevalence of ENDS use in adults from the 2018 National Health Interview Survey (NHIS) (4.1%). Similar to the published literature, ENDS use, specifically NJOY DAILY use, among adults was more common in current than former and never smokers. The evidence showed that the proportion of adult combusted cigarette users who reported NJOY ENDS use is 2.3%.
 - Based on the data presented by the applicant, a large number of NJOY DAILY users (78.6% baseline will dual use with combusted cigarettes, which is higher than other ENDS product dual use patterns reported in the literature (43.5%-54.1%). While the NJOY User Study suggests there may be a reduction in combusted cigarette use seen by NJOY DAILY users, data from the literature is mixed (Berry et al., 2019; Benmarhnia et al., 2018; Adriaens et al., 2017; Gomajee et al., 2019; Jackson et al., 2020; Sweet et al., 2019). Published literature also currently shows that many adult dual users will discontinue ENDS use over time (43.5%-54.1%), and few (3.4-5.9%) will transition to ENDS only use (Coleman et al., 2019; Stanton et al., 2020; Piper et al., 2020).
 - The applicant's estimates for current smokers completely switching to NJOY use at one month was 24.6%, three months was 26.5%, and six months was 39%, 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). In support of the PMTAs, the applicant originally submitted five observational studies. The applicant submitted a flavor analysis (Primary Outcomes cohort, n=2103) to address a deficiency identified in the first cycle review of the lack of evidence of NJOY DAILY products assisting current smokers switching to ENDS use. Among current smokers at baseline, 24% reported using Rich Tobacco as their initial flavor, which is higher than each of the individual non-tobacco flavored NJOY DAILY

products⁶. It was also found from the study that 23% of current smokers reported using Rich Tobacco as their most used flavor at baseline (calculations by FDA epidemiology reviewers).

3.4.1.3. Tobacco Non-users (including youth)

- Social Science:
 - Overall, the data submitted by the applicant on reported curiosity and intention to try NJOY DAILY among adult never (5.1% and 0.5%, respectively) and former (3.5% and 0.8%) smokers suggest that former and never smoking adults are not interested in trying the new products.
 - Among youth (age 13-17), curiosity to try Rich Tobacco was 11.26%, which is lower compared to non-tobacco flavored NJOY DAILY products. In 2021, 11.3% of high school students and 2.8% of middle school students reported current ENDS 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., 2020). These published findings indicate risk of ENDS use among youth. However, youth are less likely to initiate tobacco-flavored ENDS and subsequently progress to regular use than with non-tobacco flavored ENDS. For instance, in Wave 1 of the Population Assessment of Tobacco Health (PATH) Study, which is a longitudinal and nationally representative study covering the time period 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 (Rose et al. 2020). 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 54.9% 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

⁶ "Rich tobacco" and "Extra Rich tobacco" refer to the applicant-provided characterizing flavor for PM0000630-631, respectively. FDA determined that no additional information regarding characterizing flavor was necessary.

Philadelphia, PA found initial use of a non-tobacco flavored vs. non-flavored ENDS (which is a flavor category not defined by the authors) was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months (Audrain-McGovern et al., 2019). 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 (Villanti et al, 2015). 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.

- For the new products, the proportion of youth reporting both curiosity about and intention to try the new products is higher than the proportion of adult current smokers ($p < 0.05$). However, the interest in tobacco flavor is low among youth according to the literature. The available evidence (NYTS 2021) indicates that a higher percentage of middle and high school current users reported using flavored ENDS than tobacco-flavored ENDS (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 cartridge device, and 53.7% used a disposable device as the ENDS device types they used most often. Sleek design, ability to use products discreetly, and user-friendly nature make pod mod products appealing among youth. Although the new products are not pod mods, they are sleek and small in design, and appear to be user friendly. Although there is some risk of youth uptake of these 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 (Morean et al., 2018; Harrell et al., 2017; Groom et al., 2020). Moreover, the evidence indicates that tobacco flavored ENDS are less likely to be used by youth who initiate with or regularly use such ENDS compared to non-tobacco flavored ENDS. 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 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, Social Science anticipates that the digital marketing and TV and radio restrictions recommended by OHCE will help to mitigate the risk of youth initiation.

- Behavioral and Clinical Pharmacology:
 - Based on a survey study provided by the applicant, minimal use of the new products in the current PMTAs was observed among youth and non-tobacco users.
 - Due to the lower abuse liability of these products compared to cigarettes, former and non-tobacco users (including youth) who initiate use of the new products are less likely to progress to regular use of the new products than products with higher addiction potential (e.g., cigarettes).
 - Although tobacco non-users including youth were not included in the applicant-submitted clinical studies, the comparably low abuse liability of the new products relative to combusted cigarettes suggests initiation and sustained use of the new products among tobacco non-users is likely to be lower than initiation and sustained use of tobacco products with greater abuse liability (e.g., combusted cigarettes).
 - 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 and 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 DAILY products is somewhat lower than combusted cigarettes, mitigating concern of greater nicotine exposure (addiction potential) than combusted cigarettes among youth.
- Epidemiology:
 - FDA and Centers for Disease Control and Prevention's analysis of the 2020 National Youth Tobacco Survey (NYTS) data found that, 33.2% of high school ENDS users reported using NJOY brand products in the past 30 days, and 16.4% of high school ENDS users indicated that NJOY was their usual brand. However, it is not known which specific NJOY products were used. Analysis of the 2021 NYTS found that NJOY brand products were no longer in the top five usual brands used by high school and middle school ENDS users. In regard to youth initiation, the applicant analyzed the 2019 and 2020 NYTS findings. The applicant's analysis of the 2019 NYTS, found that no respondents indicated that they had used the new products. They argue that this is consistent with their Youth Prevalence Studies, which found only two respondents reported using the new products in the past 30 days. The applicant further cites results from the 2020 NYTS in which 8 respondents reported both that NJOY was their most frequently used brand in the past 30 days and that they most commonly used disposable ENDS. This represents 0.055% of unweighted respondents using NJOY DAILY. The 2019 NYTS demonstrated a preference for fruit, mint, and menthol products among high school and middle school aged users of ENDS. No specific NJOY product is specified in these analyses, and it was noted by the epidemiology review that any given brand preference is subject to change as the market changes. As previously discussed, however, 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.

- Overall, the available evidence to date does not adequately address whether ENDS use and specifically use of the new products by youth and young adults leads to regular smoking. While the literature supports an association between ever ENDS use and initiation of ever using combustible cigarettes or past 30-day cigarette use in youth, the available evidence to-date does not adequately address whether ENDS use in youth and young adults leads to regular established cigarette smoking. Additionally, cigarette smoking is now at an all-time low among youth, which suggests that the impact of tobacco-flavored e-cigarette use on youth current, established smoking is likely minimal. The applicant did not include any evidence regarding combustible cigarette initiation among youth following use of their products.

3.4.1.4. Vulnerable populations (other than youth)

- Social Science and Epidemiology:
 - It is possible, based on the applicant's submitted data, that there are gender and race/ethnicity differences in intention to try NJOY DAILY among adults. The applicant summarizes what appears to be intention to try data that they call "initiation" in a logistic regression model in their Adult Perceptions Study. The model findings suggest that males were more likely to intend to try NJOY than females. In addition, White and Black non-users were less likely to intend to try than Hispanic and 'other' non-user race respondents. However, the applicant did not provide information on use of the new products among other 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. 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., 2017; Hawkins et al., 2020; Obisesan et al., 2020; Wheldon and Wiseman, 2019). While the evidence indicates that some vulnerable populations experience disproportionate ENDS use, there is a lack of currently available evidence to show whether the new products would help facilitate adult combusted cigarette smokers from vulnerable populations to switch or reduce cigarettes per day (CPD).
- Behavioral and Clinical Pharmacology:
 - No clinical studies were provided or reviewed by the applicant addressing use of the new products among 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. Due to insufficient information, from a BCP perspective, the impact of the new products in these PMTAs on abuse liability and product use behavior in vulnerable populations other than youth is unknown.

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

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

OHCE reviewed the relevant marketing submissions and drafted a consult dated February 24, 2022. 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 Daily products;
- Prohibiting the sale of NJOY Daily products on third-party websites;
- Limiting the number of products that can be purchased in a given time period or transaction;
- Using competent and reliable third-party sources to verify the age and identity of users against public records before granting access [to] the product website or conducting online sales;
- Requiring retailers to only place NJOY Daily products in non-self-service areas of the store; and
- Conducting “quarterly audits of point-of-sale signage located in retail chains that carry NJOY to determine whether only NJOY-approved trade marketing materials are being utilized”

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 BCP, social science, and epidemiology reviews indicate that the applicant states that current adult users of nicotine-containing products including combusted cigarette smokers and ENDS users are the intended users for the new products. As TPL, I agree with the reviews that the applicant has identified intended users to be adult users of nicotine-containing products, particularly current combustible cigarette users and ENDS users. In making the APPH determination, it is important to understand population effects such as behavioral intentions, perceptions of harm and addiction, actual product use from clinical study, and the potential for switching from combusted cigarettes to the new products as well as potential for discontinuation from tobacco products. Effects on non-tobacco users including youth and vulnerable populations are also important to understand in a determination if the new products are appropriate for the protection of public health.

To address how the new products are used by current smokers, the applicant conducted analyses from their study, “Additional Flavor Analysis”. Current smokers were those who reported smoking combusted cigarettes during the past thirty days. Switching was assessed as the percentage of current smokers at baseline who became former smokers at one, two, three, and six months, respectively. Former smokers were those who either self-identified as a former smoker (baseline measure) or who reported no smoking during the past thirty days [30-day point prevalence abstinence (PPA)] at follow-up. A limitation to the study was that the applicant’s analysis of switching did not provide information whether the participant was currently using NJOY DAILY. There was no way to distinguish between complete switching (cessation of combusted cigarettes and continued ENDS use) and cessation of combusted cigarettes while also discontinuing NJOY DAILY. However, the applicant reported that at three months, 35% of current smokers at baseline had

transitioned to former smokers, and at six months, 48% of current smokers at baseline had switched to former smokers. These data show a possible benefit from the use of the new products in adult current smokers. To further estimate measures of change in smoking status, the applicant used different types of analyses on missing outcomes and showed that 11.9-13.5% of everyday users and 26.3-32.3% of somedays users of the new products achieved 30-day PPA. According to the epidemiology review, these results are higher than what is typically reported in the literature for estimates of switching (3.4-5.9%) from other tobacco products to ENDS tobacco products and concludes the discrepancy is related to issues of study design.

Similar to the published literature on ENDS use, use of the new products among adults was more common in current smokers than former and never smokers, and as the prevalence data in the application suggests, initiators are more likely to be current or former users than never users. Some of this could be due to cohort effects or generational differences in the marketplace when most adults initiated tobacco use. Overall, epidemiology found that the applicant presented several different measures of the association of the tobacco-flavored new products with smoking behaviors, including switching. Switching was defined as the percentage of current smokers at baseline who became former smokers at one, two, three, and six months. The measures of switching did not account for whether the participant was currently using the new products; therefore, the estimates did not distinguish between complete switching (cessation of combusted cigarettes and continued ENDS use) and cessation of combusted cigarettes while also discontinuing the new products. In addition, there was significant loss to follow-up. Despite limitations detailed in the epidemiology review, there was evidence of switching from current cigarette smokers to Rich Tobacco flavor NJOY DAILY product as assessed by z-tests and logistic regressions. Based on the applicant's User Study report, the percentage of baseline current smokers who reported former smoking and switched to NJOY DAILY Rich Tobacco product at one month was 24.6%, two months 38.6%, three months 26.5%, and six months 39.0%.

The 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 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). The applicant asserted that a very small proportion of youth who use ENDS reported NJOY as their preferred brand citing the 2019 and 2020 NYTS, and therefore, youth use of the new product poses a minimal public health risk. The applicant's analysis of the 2019 NYTS found that no respondents indicated that they had used the new products which are tobacco flavored. The applicant states this is consistent with their Youth Prevalence Studies, which found only two respondents reported using the new products in the past 30 days. The applicant further cites results from the 2020 NYTS in which 8 respondents reported both that NJOY was their most frequently used brand in the past 30 days and that they most commonly used disposable ENDS. However, as noted in the epidemiology review, the popularity of any given brand is subject to change as the market changes.

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 flavored ENDS.

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. Accordingly, I recommend that the MGO letter include additional marketing requirements and recommendations.

The evidence summarized in this section describes relatively high interest among smokers in using tobacco-flavored products generally. Although nicotine delivery is lower than for cigarette smoking, available evidence indicates that experienced ENDS users can increase nicotine uptake compared to inexperienced users, which increases the likelihood of switching. Use of these products could benefit smokers who switched completely or substantially reduced their cigarette smoking. The available information also shows that youth appeal/uptake of tobacco-flavored ENDS products is generally low among youth. Overall, I agree that the possible benefit of the new products to adult smokers is significant enough to overcome the risk to youth.

Consistent with the epidemiology review, the behavioral and clinical pharmacology review suggests that current tobacco users are unlikely to switch completely to the new products. However, the applicant's data show that some smokers may completely switch. The behavioral and clinical pharmacology review concluded that, based on the submitted clinical study data, the new products do not have an abuse liability exceeding combusted cigarettes and that users of the new products will maintain their nicotine dependence and will have a low likelihood of complete cessation from tobacco products. As TPL, I agree with the conclusions of epidemiology, behavioral and clinical pharmacology.

3.5. TOXICANT EXPOSURE

3.5.1. Discipline key findings

The following key findings were provided in discipline reviews.

3.5.1.1. Toxicity

- Overall, there were significant reductions in aerosol HPHCs tested using the new products with their corresponding e-liquids (PM0000630, PM0000631) which had been stored for up to (b)(4) compared to cigarette comparison data under both non-intense and intense puffing regimens. Toxicology evaluated the applicant's submitted data on HPHC yields for the new products, combusted cigarettes, Leap Go Smooth Tobacco 5% nicotine salt, and other ENDS products. In the new products, compared to combusted cigarettes, HPHC increases for chromium, nickel, nicotine, PG, and VG are offset by HPHC decreases for acetaldehyde, diacetyl, acetyl propionyl, acrolein, (b)(4) formaldehyde (b)(4) and ethylene glycol, and are unlikely to raise toxicology concerns for users of the new products compared to average combusted cigarette yield. In comparisons of aerosols from the new products to the applicant's selected ENDS comparator product, Leap Go Smooth

Tobacco 5% nicotine salt, the HPHCs are comparable. In addition, all the nicotine-adjusted HPHC yields (i.e., HPHC:nicotine ratios) were similar or decreased in the aerosols of the new products compared to average HPHC:nicotine ratios for other ENDS products (i.e., cig-a-like, pod, and tank systems). Overall, these comparisons showing similar or reduced exposures to HPHCs from the new products do not raise toxicology concerns.

3.5.1.2. Biomarkers of exposure (BOE)

- BOE data submitted from a survey study conducted by the applicant found that participants who had recently used only the new products had lower levels of the measured BOE (i.e., CO, cotinine, CEMA, 3-HPMA, and NNAL) relative to recent users of the new products and combusted cigarettes (i.e., dual users).
- The published literature suggests combusted cigarette smokers will likely experience significant reductions in volatile organic compound (VOC) exposure upon complete switching to ENDS (Goniewicz et al., 2017; Oliveri et al., 2020; Round et al., 2019). The applicant did provide yields of some VOC HPHCs (e.g., acrylonitrile, benzene, propylene oxide, toluene) using mainstream smoke (MSS) concentration data derived from peer-reviewed scientific literature to represent the combusted cigarette category and the levels of these VOCs from the new products. Overall, the differences show lower levels of these VOC yields from the new products compared to the combusted cigarette MSS data.
- Heavy metal exposure is likely to stay the same or decrease upon complete switching to ENDS (Goniewicz et al., 2018; Jain, 2019; Prokopowicz et al., 2019). Dual users who do not significantly reduce combusted cigarette use will likely have comparable tobacco-specific nitrosamine (TSNA) and VOC BOE as combusted cigarette smokers, or if cigarette use is reduced, they may experience low to modest reductions in these BOE (Pulvers et al., 2018).
- Changes in BOE and the associated health risks of dual use of cigarettes and the new products in the PMTAs have not been evaluated in longitudinal studies or under extended exposure conditions, thus conclusions on such long-term health risks cannot be made at this point

3.5.2. Synthesis

The toxicology review concludes that the majority of HPHC yields measured in the aerosols of the new products were decreased compared to literature-reported yields from combusted cigarettes, ENDS products of the same category (disposable ENDS) and subcategory (closed e-cigarette), and other ENDS products from different categories (i.e., cig-a-like, pod, and tank systems). NNK and NNN as well as volatile organic chemicals (acrylonitrile, benzene, propylene oxide, and toluene) were reported for the average combusted cigarette comparison product, however, these HPHCs were below the limit of detection or not quantifiable in the aerosol of the new products. Other HPHCs and toxicants such as acetaldehyde, diacetyl, acetyl propionyl, acrolein, (b)(4), formaldehyde, (b)(4) and ethylene glycol yields in the aerosols of the new products were 65.3-100% lower than average combusted cigarette smoke under both intense and non-intense puffing regimens. (b)(4) and therefore, it is unknown as to why it was detected in the aerosol of PM0000631. Diacetyl was not quantifiable but detected in PM0000630. The applicant provided supporting literature and

analysis that indicates exposure to diacetyl from NJOY DAILY is at least two orders of magnitude lower than exposure to diacetyl from combusted cigarettes, and therefore, would represent a reduction in risk from acute exposure to diacetyl. In addition, the applicant demonstrated that the average of the 95th percentile of exposure to diacetyl from the new product (PM0000631) is several hundred fold lower compared to the average level of diacetyl documented in the literature for other comparator ENDS products including, heat not burn, tank fixed power, and tank variable power devices. Diacetyl was not quantifiable but was detected in the applicant's ENDS comparator Leap Go Smooth 5%. However, based on the applicant's risk evaluation and comparisons demonstrating higher levels of diacetyl from combusted cigarettes and other ENDS products compared to the new products, and considering that diacetyl is not added as such to the new products, toxicology concluded the low level of diacetyl detected in the aerosol of testing PM0000631 to be acceptable. Metals and humectants, chromium, nickel, nicotine, PG and VG yields were increased in aerosols of the new products compared to combusted cigarettes. However, the applicant's risk evaluation was found to be adequate in the toxicology review with no concerns. Overall, comparison of combusted cigarette smoke to the new products showed that combusted cigarette smoke has a higher number of HPHCs and many of the HPHCs present in cigarette smoke have comparatively higher potencies than HPHCs in the aerosols of the new products. In addition, compared to combusted cigarettes, the HPHC increases in the new products for chromium, nickel, nicotine, PG and VG are offset by HPHC decreases for acetaldehyde, diacetyl, acetyl propionyl, acrolein, (b)(4), formaldehyde (b)(4) and ethylene glycol, and are unlikely to raise toxicology concerns for users of the new products compared to average combusted cigarette yield. Comparisons of HPHC yields from the new products and the applicant's selected ENDS comparator product as well as other ENDS from different product categories, showed the aerosols from the new products have similar or reduced levels of HPHCs. Biomarkers of exposure (BOE) data were submitted from a survey study conducted for subjects that recently used only the new products. These subjects had lower levels of the measured BOE (i.e., CO, cotinine, CEMA, 3-HPMA, and NNAL) relative to recent users of both the new products and combusted cigarettes (i.e., dual users).

I agree with the conclusion that available toxicological data, the demonstrated reductions in measured HPHC levels, other toxicants, and the reductions in measured BOEs indicate the potential for a relative benefit compared to cigarette smoking for smokers who completely or partially switch to the new products.

3.6. HEALTH EFFECTS

3.6.1. Discipline key findings

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

3.6.1.1. Toxicology

- Aerosols from the new products and the ENDS comparison product, Leap Go Smooth Tobacco 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. However, under the conditions tested, the combusted cigarette comparison product, 1R6F Reference cigarette, showed significant mutagenicity, cytotoxicity, and genotoxicity.

- The applicant submitted a hazard analysis for in vitro studies comparing HPHCs (at (b)(4) to (b)(4) ambient and (b)(4) accelerated versus (b)(4) ambient) and leachable compounds (at (b)(4) to (b)(4)) to HPHCs and leachables compounds at (b)(4) (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 (b)(4), the in vitro study hazard analysis of aerosol from the new product e-liquids stored for up to (b)(4) under various conditions is acceptable from a toxicological perspective.

3.6.1.2. Bioresearch Monitoring (BIMO) inspection findings

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

3.6.1.3. Addiction as a health endpoint

- Results from a clinical study provided by the applicant suggest that the new product in PM0000631 produced statistically significant lower area under the curves (AUCs) for nicotine exposure compared to combusted cigarettes, indicating lower nicotine exposure. However, overall, the data suggest that the abuse liability of the new products is likely sufficient to sustain dependence in nicotine-dependent populations.
- Based on a survey study provided by the applicant and findings in the literature, current adult cigarette smokers may maintain their nicotine addiction severity via dual use of the new products and combusted cigarettes and are unlikely to quit using tobacco products overall.
- 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 and Benowitz, 2019; Talih et al., 2019) and may facilitate use and progression to regular use by naïve users such as youth. However, based on data from the applicant submitted clinical studies, BCP concluded that the abuse liability of NJOY DAILY products is lower than combusted cigarettes, mitigating concern of greater nicotine exposure than combusted cigarettes among youth.

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 bias due to loss to follow-up, 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 associations between ENDS use and some health outcomes (e.g., cardiovascular disease, respiratory disease, 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 adjusting 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.

- Battery-related adverse experiences and e-liquid nicotine poisonings are serious issues that have been reported with certain ENDS products. The new products have UL 1642 Certification for their integrated battery cells; battery cells that comply with UL 1642 have a reduced risk of fire and explosion. With respect to potential for e-liquid poisoning from the new products. Per the applicant information and engineering review, the new products are a closed system and non-refillable device or serviceable. Therefore, by design the risk of poisoning is comparably low. Another health risk is that ENDS users may have higher exposure to some chemical constituents such as VOCs than do non-tobacco users.
- Dual Use: In general, data from the biomarker literature suggests that dual users have been found to have higher levels of certain biomarkers of exposure associated with combusted cigarette use, including nicotine and its metabolites, compared to combusted cigarette smokers. This information is useful for discerning some biomarkers of exposure associated with dual use of ENDS and combusted cigarettes relative to users who completely switch to ENDS from combusted cigarettes.
- 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 ENDS, but levels of all other biomarkers significantly decreased after one week of using ENDS. Further information on possible short-term benefits of switching from combusted cigarettes to ENDS can be seen in published literature showing that ENDS users have lower levels of exposure to some constituents including TSNA than combusted cigarette smokers.
- Medical:
 - Overall, the applicant submitted clinical studies which provided limited data to evaluate the short and long-term health effects of NJOY DAILY products. The applicant did not measure biomarkers of potential harm in any of the submitted studies.
 - Clinical studies submitted by the applicant did not identify short or long-term health effects specific to the NJOY products. The studies have small sample sizes and relatively short time periods of product exposure, limiting the generalizability of the health effects data to larger user populations 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.
- Limitations of the applicant's literature review included lack of NJOY-specific data and inclusion of ENDS products with various chemical compositions and testing methods with no rationale for bridging health effects data.
 - Based on review of the literature submitted by the applicant, the impact of ENDS use on cardiovascular disease, cancer, respiratory outcomes, developmental, and reproductive health outcomes, oral health, mental health, and other health topics are mixed and largely inconclusive. The risks of injury and poisonings have been consistently reported in the literature; however, no specific reports of serious injury related to use of the new products were identified.
 - The applicant provided limited data on biomarkers of potential harm; the information provided did not inform the health effects assessment.
 - There were no deaths, serious adverse experiences (AEs), or discontinuations due to AEs reported in the clinical studies. A few AEs associated with the new products were reported; those reported were found by the medical reviewer to be possibly related to the study product. Light headedness, mild nausea and vomiting were reported in one clinical study and no AEs in another study sponsored by the applicant. Reported AEs for the comparison products in the clinical studies were related to mild neurological (e.g., light headedness) or gastrointestinal symptoms (e.g., nausea, vomiting). No safety concerns were identified in these studies.

3.6.1.5. Likelihood and effects of product misuse

- Behavioral and Clinical Pharmacology:
 - The new products are closed, disposable "cigalike" ENDS with non-adjustable power settings. These device characteristics reduce the likelihood that users will manipulate ENDS device settings and e-liquid constituents, including nicotine. As discussed in the product design and composition section (see Section 3.2.1.1), the engineering review concluded the new products have UL 1642 certification for the battery cell and the devices have short circuit protection reducing the risk of fire and explosion. Regarding accidental e-liquid nicotine poisoning, the engineering review concluded the design of a closed pod-based, non-refillable system minimizes the risk of poisoning because the system is inaccessible through customary or reasonably foreseeable handling or use (see Section 3.2.1.1).
 - Design features of the new products make "stealth vaping" possible (i.e., discreet use of ENDS such as inhaling deeply to avoid forming visible aerosol clouds or swallowing of aerosol during exhalation) and based on findings in the literature, this behavior can influence nicotine and toxicant exposure.
 - The applicant-submitted clinical studies and literature review did not provide data evaluating the likelihood of misusing NJOY DAILY products.
 - Despite the lack of clinical data assessing product misuse, BCP concludes that the likelihood of misuse is low for NJOY DAILY products because they are closed-system ENDS. NJOY DAILY power settings are non-adjustable, and

the e-liquid is enclosed in a pod, thereby reducing chances that users may manipulate ENDS product settings and e-liquid constituents, including nicotine levels, which may influence exposure to nicotine and other HPHCs in the aerosol.

3.6.1.6. Adverse experiences

- Engineering:
 - The applicant supplied the consumer complaints (adverse experiences) for the new products for the calendar year 2020. The engineering related adverse experiences were reviewed and they were not significant or serious.
- Medical:
 - There were no deaths, serious adverse experiences, or discontinuations of use due to AEs reported by the applicant in the two clinical studies.
 - Thirteen AEs were reported in the clinical studies. Eleven AEs were described by the applicant as mild and two were moderate. All AEs resolved prior to the end of the study.
 - Overall, gastrointestinal AEs were the most commonly reported and were consistent with the AEs reported in the literature related to nicotine intake.
 - In the applicant-submitted literature review on ENDS, AEs reported in published studies of ENDS products included cough, dry or irritated mouth or throat, dizziness or 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 and were mostly minor in severity.
 - Analysis of FDA's Safety Reporting Portal data was performed on 09/20/2020 with search inclusion dates 01/01/2014 to 09/21/2020, and a second search performed 02/02/2022 with search inclusion dates 09/01/2020 to 01/31/2022. There were five reports related to NJOY products: one seizure while driving, one pulmonary embolism, one serious lung injury, and two respiratory issues (coughing and productive cough/sore throat). Product details were scant in the reports; hence it was unclear which NJOY ENDS products were used, the nicotine content or flavor of the products, and if the products were used in combination with other products. No definitive adverse experiences related to NJOY DAILY could be identified from the provided information.
 - Nine AEs were reported with the consumer report data provided by the applicant. One case of chest pain and one incident of difficulty breathing were reported by the applicant but were reported as non-serious experiences. Three reports of non-serious burns related to NJOY DAILY were reported by the applicant.
 - FDA is aware of several health issues regarding the use of ENDS, specifically ENDS, or vaping, product 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 foundational 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, FDA 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. One seizure was reported with NJOY products in FDA's Safety Reporting Portal. However, it is unclear which NJOY ENDS products were used with the provided reports. While this data is insufficient to fully evaluate the potential association of the new products with seizures, FDA 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. Three reports of non-serious burns related to NJOY DAILY were reported by the applicant. 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 toxicology review that the aerosols of the new products have an overall lower level of toxicants and HPHCs compared to combusted cigarettes. Comparison toxicity testing demonstrated the aerosols to be less toxic under the conditions tested compared to the research 1R6F combusted cigarette. The aerosols of the new products and smoke from a research combusted cigarette comparator were tested in short-term studies using in vitro mutagenicity, cytotoxicity, and DNA damage assays with and without metabolic activation. The results convincingly showed that the combusted cigarette comparator was more toxic than the new products. After (b)(4) storage, the e-liquids from the new products showed a lack of genetic toxicity potential. Genetic toxicity is a commonly used toxicity endpoint used under short-term exposure conditions to help predict chronic cancer hazard potential. No long-term toxicology studies were submitted in the application.

As TPL, I also agree with the behavioral and clinical pharmacology review which concluded from clinical studies that the addiction potential when assessing AUCs for nicotine exposure of the new product (PM0000631) is lower than that of combusted cigarettes. Bridging information provided by the applicant for the untested new product (PM0000630) suggested that the nicotine exposure could be as high as, but no higher than, the tested product. The basis for this suggestion is that the nicotine concentration is lower in the bridged new product (4.5%) compared to the tested new product (6%). This conclusion is based on acute clinical pharmacokinetic data and biomarkers of exposure in which the findings overall suggest the new products would support nicotine-dependence for users who choose to completely switch from combusted cigarettes to the new products.

In an applicant-sponsored clinical study, biomarkers of exposure (e.g., CO, cotinine, CEMA, 3 HPMA, and NNAL) were found at lower levels in users of the new products compared to dual users of the new products and combusted cigarettes. No biomarkers of harm were measured or reported in the applicant-sponsored clinical studies. No applicant-sponsored long-term clinical studies on addiction liability were submitted in the application.

The applicant provided limited data on observational health outcomes from an epidemiological standpoint, and there are no data in the literature regarding long-term health effects of NJOY DAILY specifically.

The medical review noted limitations with the applicant's sponsored studies in terms of the small sample size and short-term period of exposure. In addition, the medical review noted a lack of NJOY DAILY specific clinical data in the application. Although the applicant included assessment of various chemical compositions of other ENDS products, there was no rationale to bridge the information to the new products. The medical review also pointed out that based on literature findings, the impact of ENDS use on cardiovascular disease, cancer, respiratory outcomes, developmental, and reproductive health outcomes, oral health, mental health, and other health topics are mixed and largely inconclusive. The medical review indicated that the applicant reported non-serious burns in the provided consumer reports. As noted by epidemiology, battery-related adverse experiences and e-liquid nicotine poisonings are serious issues that have been reported with certain ENDS products. However, as discussed in the product design and composition section (see Section 3.2.1.1), the engineer review concluded the new products have UL 1642 certification for the battery cell and the devices have short circuit protection reducing the risk of fire and explosion. Regarding accidental e-liquid nicotine poisoning, the engineering review concluded the design as a closed pod-based, non-refillable system minimizes the risk of poisoning because the system is inaccessible through customary or reasonably foreseeable handling or use (see Section 3.2.1.1).

Overall, there is a lack of available data to demonstrate a comprehensive health effects profile from chronic use of the new products. From a chemical toxicology standpoint, there is potential that use of these new products, along with significant reduction or quitting cigarettes, will result in a reduction in exposure to many HPHCs. This benefit will likely be greater for smokers who are able to switch completely to the new products. However, the applicant's switching studies did not assess the effects of long-term use and the impact of dual use which would be more likely to occur in real-world conditions. There are limited data about the long-term health effects of ENDS from large clinical studies or long-term epidemiological studies. In addition, the study design limitations (e.g., small sample size, generally healthy participants, short exposure periods) in the published literature make it difficult to draw definitive conclusions related to health effects of ENDS, specifically the new products. Therefore, the long-term health effects of completely switching to the new products and potential short and long-term health effects from dual use of the new products with combusted cigarettes could not be evaluated. However, based on available information, as TPL, I agree that adult smokers who switch to these products (either completely or with a significant reduction in cigarette consumption) could benefit from reduced exposure to many HPHCs. While the effects of dual use were not assessed, significant reductions in systemic exposures after short-term switching and the available

evidence suggest that daily use of the new products with concomitant reduction in CPD may provide health benefits from a harm reduction perspective in terms of reducing exposure to HPHCs relative to continued use of cigarette smoking alone.

From the standpoint of findings from clinical testing of the specific new products, I agree with the medical conclusion that there is inconclusive information for long-term health effects due to the limitations of clinical studies and lack of such specific information on NJOY DAILY products. Although adverse experiences (AEs) were reported in the applicant-sponsored clinical studies and possibly related to the NJOY products, there were few and they were mostly mild involving gastrointestinal (e.g., nausea, vomiting) and neurological symptoms (e.g., headache and lightheadedness). Two AEs of moderate severity were reported, 1 per study. No serious AEs or deaths were reported in any of the applicant sponsored short-term clinical studies. Due to the product design as a closed ENDS product, there is minimal risk for accidental ingestion of the e-liquids. The applicant provided minimal information on observational health outcomes and the literature is limited regarding long-term health effects of use of NJOY DAILY products and other ENDS products. However, the epidemiology review points out that there is some epidemiologic evidence suggesting associations between ENDS use and some health outcomes including cardiovascular disease, respiratory disease, and oral health.

For dual users of ENDS and combusted cigarettes, certain biomarkers of exposure may be similar or higher compared to combusted cigarette smokers. There is published literature reporting short-term benefits of switching from combusted cigarettes to ENDS with users showing lower levels of toxic and carcinogenic constituents such as tobacco specific nitrosamines. In the nonclinical testing, the toxicology endpoints measured are not indicators or predictors of short-term health effects. Genetic toxicity is designed to help predict cancer hazard and therefore, does not align with the AEs reported in the short-term clinical study. However, genetic toxicity assessment is accepted to understand carcinogenic potential of substances and products since DNA damage is the measured endpoint. The new products did not induce the DNA damage seen in the comparator combusted cigarettes in the studies conducted.

As TPL, I agree that the nonclinical data suggest that use of the new products have the potential to have better outcomes for genetic damage compared to smoking combusted cigarettes. Given the lack of health effects information for long-term use and exposure to the new products, I agree with the medical review that, for the marketed new products, post-market reporting is needed to further monitor and evaluate potential health effects including EVALI, seizures, and OH/F/Exp.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

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

3.7.1.1. Toxicology

- The applicant provided a risk assessment for ingredients in the e-liquids of the new products (PM0000630, PM0000631), HPHCs in the aerosol for the new products, leachables and extractables for the new products, and alternative exposures

- (secondhand exposure to NJOY DAILY aerosol; oral and intentional ingestion of NJOY DAILY e-liquids; and incidental and accidental dermal exposures to NJOY DAILY).
- 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 DAILY, the potential health risks are likely to be similar (to use of other ENDS) or reduced (compared to combusted cigarettes) when compared to continued exclusive use of those tobacco products. In addition, secondhand exposures to HPHCs from ENDS aerosol is 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 means using these new products 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 depending on 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 other ENDS products, such as the comparison product, Leap Go Smooth Tobacco 5%, and other pods, cig-a-likes, and tank systems.

3.7.1.2. Population health impact (PHI) model

- The data inputs used in the population health modeling scenarios for ENDS use generally and NJOY DAILY use specifically 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 particularly informative to the overall assessment.

3.7.2. Synthesis

As TPL, I agree with the toxicology conclusions that switching completely from use of combusted cigarettes to use of the new products will result in the greatest reduction in HPHC exposures. Dual use of combusted cigarettes and the new products or dual use of other ENDS and the new products would also likely result in decreases in HPHC exposures overall. Limited chronic inhalation toxicity data for the product ingredients are available in the public domain. However, the applicant assessed published toxicological studies to provide an understanding of the current state-of-the-science with respect to the toxicology and health effects associated with ENDS products. The systematic scientific literature searches provided by the applicant show that exposure to ENDS resulted in respiratory, cardiovascular, and immunological toxicity. However, the adverse events noted are comparatively less than those related to the use of combusted cigarettes. The applicant provided conservative risk assessments for ingredients in the e-liquids, HPHCs in the

aerosol, and extractables and leachable compounds from the new products. PG, VG, chromium, and nickel levels are higher in the aerosols of the new products than in the ENDS comparator. Additionally, for nickel and chromium, the reference exposure levels were higher than the California Office of Environmental Health Hazard Assessment (OEHHA) reference exposure level (REL) and the Agency for Toxic Substances and Disease Registry (ATSDR) acute toxicity minimum risk level (MRL) but below other reported regulatory reference values (Texas Commission on Environmental Quality and ICH Permitted Daily Exposure). Increases in chromium and nickel in the new products compared to average combusted cigarette smoke mainstream smoke levels were noted and suggest increased cancer risk. However, a user who completely switches from combusted cigarettes to the new products is expected to have lower exposures to several potent carcinogens (e.g., NNK, NNN, acrylonitrile, cadmium, lead) that will result in a large reduction in HPHC exposures to outweigh the increases in cancer risk in the new products due to chromium and nickel. Extractable and leachable organic and inorganic compounds were identified in some products but not all and highest levels were seen under accelerated conditions. There was no toxicology concern for the levels of these compounds due to genotoxicity testing results from the literature, the levels found in the e-liquid being below health-based guidance values (HGVs), and exaggerated conditions of the testing. Overall, as TPL, I agree with toxicology that based on the data submitted by the applicant on toxicants and HPHCs, switching from combusted cigarettes to the new products or dual use of combusted cigarettes and the new products with substantive reduction in combusted cigarette use is likely to result in significant reductions in HPHC exposures. Secondhand exposure studies were evaluated and showed increased indoor air nicotine, VOCs, particulate matter (i.e., PM_{2.5}), polycyclic aromatic hydrocarbons (PAHs), aluminum, nickel, and silver concentrations after ENDS use, compared to background levels. However, several literature studies provided by the applicant reported that airborne black carbon, PAHs and TSNA were not detected after ENDS use. In studies comparing secondhand ENDS aerosol exposure to secondhand combusted cigarette smoke exposure, airborne nicotine, VOCs, carbonyls, metals, nitrosamines, polyaromatic amines, PAH and carbon monoxide concentrations were low or undetected in ENDS aerosol, compared to combusted cigarette smoke. These secondhand exposures after ENDS use are not thought by the applicant to pose a risk for adverse health effects. The applicant concluded that secondhand exposures to HPHCs in aerosol of the new products are likely to not pose a risk for adverse health effects. As TPL, I do not unilaterally agree with the applicant that secondhand exposures to HPHCs in the aerosol does not pose a risk for adverse health effects as I believe this risk is still unknown. With respect to the new products, I find that secondhand exposure is likely to be much less harmful for this product than for cigarettes.

The applicant developed a population health impact model for NJOY DAILY and ENDS use in general. As TPL, I agree with the epidemiology review on the limitations of the applicant's population health modeling methodology. The epidemiology review concluded that the applicant's model does not reflect real world data and likely overestimates whole population health benefits of the new products if marketed. Therefore, given the limitations associated with the model inputs, it is not particularly informative in the evaluation of whether marketing of the new products would be appropriate for the protection of the public health. However, the applicant provided data demonstrating some current cigarette smokers may switch completely to the new products which is supportive of an APH determination.

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 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 PM0000630-PM0000631, a finding of no significant impact (FONSI) was signed by Hans Rosenfeldt, PhD on June 9, 2022. The FONSI was supported by an environmental assessment prepared by FDA on June 9, 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 products, 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 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. 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. Based on the information provided in the PMTAs, the abuse liability of the new products is lower than combusted cigarettes. Results from an applicant-submitted clinical study with the new products suggest that the new products may have lower nicotine exposure than the representative ENDS that were tested in the applicant's study. However, it is unclear how the abuse liability of the new products compares to other ENDS. Further, clinical biomarker data submitted by the applicant found statistically significant lower levels of biomarkers of exposure to HPHCs (e.g., CO, cotinine, CEMA, 3-HPMA, and NNAL) for exclusive users of the new products compared to dual users of the new products and combusted cigarettes. A body of published literature suggests combusted cigarette smokers will likely experience significant reductions in volatile organic chemical (VOC) exposure upon complete switching to ENDS products. Consistent with this notion, the applicant provided VOC HPHCs (e.g., acrylonitrile, benzene (b)(4) toluene) using mainstream smoke (MSS) concentration data derived from peer-reviewed scientific literature to represent the combusted cigarette category. The applicant demonstrated lower levels of these VOCs from the new products compared to the combusted cigarette MSS literature data. 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 and as evidenced by results of nonclinical studies. The consideration of HPHC information provides compelling evidence that the new products have the potential to benefit smokers who switch completely or significantly reduce their cigarette consumption. The basis for this conclusion is that the biomarkers of exposure data to HPHCs and the HPHC aerosol yields suggest reduced exposure to carcinogens and other toxicants. Therefore, the applicant has demonstrated the potential for these new products to benefit adult smokers who switch completely or significantly reduce their cigarette consumption as compared to continued exclusive cigarette use.

The applicant's Adult Prevalence Study on NJOY DAILY use among adults showed use was more common in current than former and never smokers. Complete switching from combusted cigarettes to NJOY DAILY was estimated in the applicant's NJOY User Study with 39% of 2,533 adults using the tobacco flavored products at 6 months, a rate that is much higher than typically seen (3-6%) in the published literature. Based on data presented by the applicant, dual use of the new products with combusted cigarettes was also observed (78.6% baseline) which is higher than other ENDS products reported in the literature (44-54%).

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 than use of flavored ENDS among youth. The applicant submitted youth prevalence studies and although these studies had small sample sizes, the data suggest that 40.5% of youth who reported ever ENDS use started with "something other" than tobacco or menthol flavored products, and 45.6% of ever NJOY DAILY youth users reported starting with non-tobacco/non-menthol flavored NJOY DAILY products. The remaining respondents used tobacco flavored (13.3%) or Menthol or Mint flavored (32.8%) NJOY DAILY products. These data provide some evidence that the new products which are tobacco-flavored are less appealing to youth compared to other types of flavored products. Nonetheless, given the strong evidence regarding the impact of youth marketing exposure to youth appeal and initiation of tobacco use, a marketing authorization should include post-market requirements to help ensure that youth exposure to tobacco marketing is

limited. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit adult smokers who switch completely or significantly reduce their cigarette use would outweigh the risk to youth, provided the applicant follows post-market 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. The applicant provided complete chemical stability study data including test data for bulk e-liquids, finished product e-liquids, and aerosols and extractables and leachables data for components, parts, and CCS meeting product specifications. The applicant's data supports microbial stability of the products over (b)(4). The stability data provided by the applicant is acceptable and indicates that the products are low-risk for chemical instability and microbial growth over the period tested and there are no stability concerns. Therefore, the applicant's stated shelf life of (b)(4) for the new products is supported by the submitted testing data.

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 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 of this review, as identified on the cover page of this review.

6. REFERENCES

- Adriaens K, Van Gucht D, Baeyens F. Differences between Dual Users and Switchers Center around Vaping Behavior and Its Experiences Rather than Beliefs and Attitudes. *Int J Environ Res Public Health*. 2017;15(1).
- Audrain-McGovern J, Rodriguez D, Pianin S, Alexander E. Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents. *Drug Alcohol Depend*. Sep 1 2019;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
- Benmarhnia T, Pierce JP, Leas E, et al. Can E-Cigarettes and Pharmaceutical Aids Increase Smoking Cessation and Reduce Cigarette Consumption? Findings From a Nationally Representative Cohort of American Smokers. *Am J Epidemiol*. 2018;187(11):2397-2404.
- Berry KM, Reynolds LM, Collins JM, et al. E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013-2015. *Tob Control*. 2019;28(1):42-49.
- 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
- Boykan R, Goniewicz, ML, and Messina CR. Evidence of Nicotine Dependence in Adolescents Who Use Juul and Similar Pod Devices. *Int J Environ Res Public Health*. 2019; 16(12). doi:10.3390/ijerph16122135
- 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, and Crane J. A systematic review of nicotine by inhalation: is there a role for the inhaled route? *Nicotine Tob Res*. 2012; 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 Poly tobacco Use Trajectories and Their Associations With Substance Use and Mental Health Across Mid-Adolescence. *Nicotine Tob Res*. Aug 14 2018;20(suppl_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

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 KE, Spyrou A, Stefopoulos C, Tsimopoulou K, Kourkouveli P, Tsiapras, et al. Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naive users (smokers). *Sci Rep*. 2015; 5(1):11269. doi:10.1038/srep11269

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

Goniewicz M L, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J, et al. Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. *JAMA Netw Open*. 2018; 1(8), e185937. doi:10.1001/jamanetworkopen.2018.5937

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

Gomajee R, El-Khoury F, Goldberg M, et al. Association Between Electronic Cigarette Use and Smoking Reduction in France. *JAMA Intern Med*. 2019;179(9):1193-1200.

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

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

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, et al. Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience. *Exp Clin Psychopharmacol*. 2017; 25(5):380-392. doi:10.1037/pha0000140

Jackson A, Green B, Erythropel HC, Kong G, Cavallo DA, et al. Influence of menthol and green apple e-liquids containing different nicotine concentrations among youth e-cigarette users. *Exp Clin Psychopharmacol*. 2020; 29(4):355–365. doi:10.1037/pha0000368

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

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*. 2019; 322(21):2132-2134. doi:10.1001/jama.2019.17968

Liu B, Xu G, Rong S, et al. National Estimates of e-Cigarette Use Among Pregnant and Nonpregnant Women of Reproductive Age in the United States, 2014-2017. *JAMA Pediatr*. 2019; 173(6):600-602

Maloney SF, Breland A, Soule EK, Hiler M, Ramôa C, Lipato T, and Eissenberg T. Abuse liability assessment of an electronic cigarette in combustible cigarette smokers. *Experimental and Clinical Psychopharm*. 2019; 27(5), 443–454. <https://doi.org/10.1037/pha0000261>

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. (2021). *JAMA Pediatr*. 2021; 175(2):185-190. doi:10.1001/jamapediatrics.2020.5667

Morean ME, Butler ER, Bold KW, et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PLoS One*. 2018;13(1):e0189015. doi:10.1371/journal.pone.0189015

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 JD, Prue C, Thompson J, Verron T, Graff D, and Walele T. 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*. 2019; 14(6):853-861. doi:10.1007/s11739-019-02025-3

Oliveri D, Liang Q, and Sarkar M. 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*. 2020; 22(7):1114-1122. doi:10.1093/ntr/ntz185

Omaiye EE, McWhirter KJ, Luo W, Pankow JF, and Talbot P. High-nicotine electronic cigarette products: Toxicity of JUUL fluids and aerosols correlates strongly with nicotine and some flavor

chemical concentrations. *Chem Res Toxicol*. 2019; 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 GJ, Podraza KF, Meurrens K, Coggins CR, Friedrichs B, et al. Toxicological comparisons of three styles of a commercial US cigarette (Marlboro®) with the 1R4F reference cigarette. *Inhalation Toxicology*. 2008; 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 JJ and Benowitz NL. Current advances in research in treatment and recovery: Nicotine addiction. *Sci Adv*. 2019; 5(10), eaay9763. doi:10.1126/sciadv.aay9763

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

Pulvers K, Emami AS, Nollen NL, Romero DR, Strong DR, Benowitz NL, and Ahluwalia JS. Tobacco Consumption and Toxicant Exposure of Cigarette Smokers Using Electronic Cigarettes. *Nicotine Tob Res*. 2018; 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. Chemical composition, cytotoxicity and mutagenicity of smoke from US commercial and reference cigarettes smoked under two sets of machine smoking conditions. *Toxicology*. 2004; 195(1):31-52.

Rose SW, Johnson AL, Glasser AM, et al. Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2014-2015. *Tob Control*. 2020;29(4):432-446. doi:10.1136/tobaccocontrol-2018-054852

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 1 2020;44(1):76-81. doi:10.5993/AJHB.44.1.8

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

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, Dempsey DA, Havel CM, Jacob P, 3rd, and Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug Alcohol Depend.* 2017;178:391-398. doi:10.1016/j.drugalcdep.2017.05.042

Sweet L, Brasky TM, Cooper S, et al. Quitting Behaviors Among Dual Cigarette and E-Cigarette Users and Cigarette Smokers Enrolled in the Tobacco User Adult Cohort. *Nicotine Tob Res.* 2019;21(3):278-284.

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

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/>

Villanti, A. C., Johnson, A. L., Glasser, A. M., Rose, S. W., Ambrose, B. K., Conway, K. P., ... & Hyland, A. (2019). Association of flavored tobacco use with tobacco initiation and subsequent use among US youth and adults, 2013-2015. *JAMA network open*, 2(10), e1913804-e1913804.

Voos N, Smith D, Kaiser L, Mahoney MC, Bradizza CM, Kozlowski, L. T. et al. Effect of e-cigarette flavors on nicotine delivery and puffing topography: results from a randomized clinical trial of daily smokers. *Psychopharmacology (Berl)*. 2020; 237(2):491-502. doi:10.1007/s00213-019-05386-x

Vu AT, Taylor KM, Holman MR, Ding YS, Hearn B, and Watson CH. Polycyclic aromatic hydrocarbons in the mainstream smoke of popular US cigarettes. *Chem Res Toxicol.* 2015; 28(8):1616-1626. doi:10.1021/acs.chemrestox.5b00190.

Wheldon CW and 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

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

7. APPENDIX⁷

Table 3. New products

Common Attributes	
Submission date	March 30, 2020
Receipt date	March 30, 2020
Applicant	NJOY, LLC
Product manufacturer	NJOY, LLC
Product category	ENDS (VAPES)
Product subcategory	Closed E-Cigarette
Attributes	New Product
STN	PM0000630.PD1⁸
Product name	NJOY DAILY Rich Tobacco 4.5%
Package type	Box
Package quantity	1 E-cigarette
Characterizing flavor	Tobacco
Length	106.9 mm
Diameter	8.4 mm
Nicotine concentration	4.5% w/w
PG/VG ratio	46.56/46.00
E-liquid volume	0.9 mL
Wattage	4 W
Battery capacity	200 mAh (lithium ion; non-rechargeable)
Additional Properties	Disposable E-Liquid Reservoir
STN	PM0000631.PD1
Product name	NJOY DAILY EXTRA Rich Tobacco 6%
Package type	Box
Package quantity	1 E-cigarette
Characterizing flavor	Tobacco
Length	106.9 mm
Diameter	8.4 mm
Nicotine concentration	6% w/w
PG/VG ratio	43.96/46.00
E-liquid volume	0.9 mL
Wattage	4 W
Battery capacity	200 mAh (lithium ion; non-rechargeable)
Additional Properties	Disposable E-Liquid Reservoir

⁷ Brand/sub-brand or other commercial name used in commercial distribution.

⁸ PD numbers were not used in previously issued letters

Table 4. Amendments

Submission Date	Receipt Date	Applications being amended	Reviewed	Status	Brief Description
June 16, 2020	June 16, 2020	All ⁹	Yes	Active	Correction or clarification to update report: Adverse Events – NJOY Report DAILY – Qtr. 1 2020 Update: Adverse Experience (Module 5.5)
July 13, 2020	July 14, 2020	All ⁹	Yes	Active	Correction or clarification to Study Reports: NJOY User Survey (Module 6.2.4) & Population Module (Module 6.6)
November 25, 2020	November 25, 2020	All ⁹	Yes	Active	Response to November 12, 2020 FDA Information Request
March 04, 2021	March 04, 2021	All ⁹	Yes	Active	Response to December 17, 2020 Deficiency Letter

⁹ This amendment applies to all STN subject of this review.