1. EXECUTIVE SUMMARY

Based on the information provided in the application and other scientific data, as described in this Technical Project Lead review, I find that permitting the marketing of the new products listed above ("new products" or "subject ENDS") is appropriate for the protection of the public health (APPH) (subject to certain marketing restrictions) and that none of the other denial grounds specified in section 910(c)(2) apply. Accordingly, I recommend that marketing granted orders be issued for the new products, subject to the marketing restrictions and post-market requirements.

1.1. APPH STANDARD

Section 910 of the FD&C Act requires that, for a product to receive a PMTA marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute specifies that, in assessing APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products. Section 910(c)(4). FDA interprets the APPH standard to require a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. In determining whether permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching).

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

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

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

of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Whether other products, such as tobacco-flavored ENDS, give adult smokers comparable options for switching or cigarette reduction bears on the extent of the public health benefit that the subject ENDS arguably provide to that population. Therefore, in making the APPH determination for a flavored ENDS, FDA considers whether the applicant has provided acceptably strong evidence of an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers in completely switching from or significantly reducing their smoking.

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

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

1.2. SUBJECT APPLICATIONS

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

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

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

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

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

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

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

2. BACKGROUND

2.1. NEW TOBACCO PRODUCTS

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

2.2. REGULATORY ACTIVITY

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

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

2.3. SCOPE OF REVIEW

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

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Regulatory	Kristopher Van Amburg	3/17/2020	Dyamond Govan	select date
Engineering	Nashaat Rasheed	7/27/2020	Pritesh Darji	4/21/2022
Chemistry	Selena Russell	7/27/2020	Yougbang Liu	select date
Microbiology	David Craft	7/27/2020	Prashanthi Mulinti	select date
Toxicology	Kamau Peters	7/28/2020	Ryan Haskins	select date
Behavioral and Clinical Pharmacology	Babita Das/ Marzena Spindle	7/27/2020	Arit Harvanko	4/21/2022
Medical	Edna Termilus	7/27/2020	Kathy Jackson	select date
Epidemiology	Rebecca Jackson	7/27/2020	Maria Cooper	select date
Social science	Elisabeth Donaldson	7/27/2020	Lisa Lagasse	select date
Environmental Science	Rudaina Alrefai-Kirkpatrick	7/27/2020	Ron Edwards	select date