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 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 of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in

[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.

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.

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. 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)). 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	select date