Contains Nonbinding Recommendations

Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications – Considerations Related to Youth Risk

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Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications – Considerations Related to Youth Risk; Draft Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist persons submitting premarket tobacco product applications (PMTAs) for electronic nicotine delivery systems (ENDS) under section 910 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387j). This guidance communicates FDA's current thinking on these applications to improve the efficiency of application submission and review; however, the recommendations in this guidance are non-binding. When FDA reviews PMTAs for ENDS, it will base decisions on the obligations that arise from the FD&C Act and its implementing regulations. FDA anticipates that the experience gained through the implementation of this guidance, if finalized, and review of PMTAs may contribute to future rulemaking and guidance.

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 "appropriate for the protection of the public health."[2] FDA's current approach to PMTA review for determining whether a flavored ENDS product is "appropriate for the protection of the public health" (APPH) includes evaluating the risks and benefits, considering all relevant evidence and circumstances associated with the new product to the population as whole. To show that the marketing of an ENDS is APPH, an applicant must show that the benefits, including those to adults who smoke combusted cigarettes, outweigh the risks, including those to youth, resulting in a net benefit to the public health.[3] As the known risks of the

[1] This guidance was prepared by the Center for Tobacco Products at FDA.
[2] 21 U.S.C. 387j(c)(2)(A).
[3] See, for e.g., Technical Project Lead (TPL) Review of PMTAs for Juul Products, available at https://www.accessdata.fda.gov/static/searchtobacco/7-10-25/Juul-TPL-Rev-Multiple-STNs.pdf

product increase or decrease, the amount of benefit that the applicant must establish likewise increases or decreases.

FDA has gained considerable experience in regulating ENDS and has determined that the evidence shows that flavored ENDS products pose a substantial risk to youth, and they pose a greater risk to youth than tobacco-flavored ENDS. Among other things, existing literature suggests that flavors facilitate initiation among youth and promote established regular ENDS use. Although flavored ENDS may offer a public health benefit in leading adult smokers to completely switch or significantly reduce their use of combusted cigarettes, tobacco-flavored ENDS may offer the same public health benefit. Due to the known and substantial risk of youth initiation and use associated with flavored ENDS products relative to tobacco-flavored ENDS,[4] an applicant seeking to market a flavored ENDS product would therefore need to show that its product provides an added benefit compared to tobacco-flavored ENDS to establish that the likely benefits to adults who smoke combusted cigarettes outweigh the added risk to youth. This is the approach that the FDA has long applied in reviewing PMTAs for flavored ENDS products, and the Supreme Court considered and affirmed this approach in *FDA* v. *Wages and White Lion.*[5] Under that approach, FDA reviews flavored ENDS applications for the types of studies that could demonstrate an added benefit over tobacco-flavored ENDS. That approach remains unchanged and is not affected by this guidance.

This guidance addresses a subsequent question that arises in reviewing PMTAs for flavored ENDS products—specifically, how much of an added benefit compared to a tobacco-flavored ENDS must an applicant demonstrate, via appropriate studies, for its flavored ENDS to be found to be APPH. As discussed in this guidance, the extent of the benefit that will need to be shown will depend on the risk of the product and will vary among different flavors. In order to demonstrate a net public health benefit, ENDS with flavors that pose a higher risk of youth initiation and use would need to show greater benefits than ENDS with flavors that appeal less to youth. Given the substantial public health risks flavored ENDS products that have greater appeal to youth (e.g., fruit and candy/dessert/other sweet) pose to American youth, these products face a correspondingly high evidentiary burden to demonstrate that the benefits to adult smokers in

[4] Park-Lee E, Jamal A, Cowan H, et al. Notes from the Field: E-Cigarette and Nicotine Pouch Use Among Middle and High School Students — United States, 2024. *MMWR Morb Mortal Wkly Rep* 2024;73:774–778. Available at http://dx.doi.org/10.15585/mmwr.mm7335a3; 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. Available at https://doi.org/10.5993/AJHB.44.1.8.

[5] See *FDA v. Wages & White Lion Invs*., 604 U.S. 542 (2025) (finding that FDA's decisions denying marketing authorization to flavored ENDS were sufficiently consistent with the APPH standard, with the agency's guidance regarding the scientific evidence needed to support a premarket tobacco application, and with the need to compare proposed products to other products).

terms of quitting or significantly reducing cigarette use outweigh the risks of youth initiation and use.

FDA recognizes that ENDS products with flavors other than tobacco may, in certain circumstances, provide benefits to adults who smoke combusted cigarettes, including by facilitating switching away from combusted tobacco products, increasing quit attempts, supporting sustained smoking abstinence, and reducing cigarette consumption among adults who would otherwise continue smoking. Emerging evidence indicates that many adult smokers who use an ENDS product to transition away from combusted cigarettes report a preference for non-tobacco flavors, but whether or how much benefit a flavored product may provide depends, in part, on how the characteristics of the particular products affect users.[6] FDA will review the information an applicant submits about the product's ability to facilitate adult switching and cessation, as well as other relevant information. FDA remains committed to supporting the development of potentially less harmful alternatives for adults who smoke combusted cigarettes, while ensuring that authorized products meet the APPH standard and that appropriate oversight is maintained throughout the product lifecycle to protect youth and other vulnerable populations.

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[6] See, e.g., Mok, Y., J. Jeon, D.T. Levy, and R. Meza. "Associations Between E-Cigarette Use and E-Cigarette Flavors With Cigarette Smoking Quit Attempts and Quit Success: Evidence From a U.S. Large, Nationally Representative 2018–2019 Survey." *Nicotine & Tobacco Research* 25, no. 3 (2023): 541-552. Available at https://doi.org/10.1093/ntr/ntac241 (finding higher odds of quit attempts (adjusted odds ratio (AOR) 2.9) and quit success (AOR 1.7) among adults using nontobacco-flavored ENDS compared to non-users, with stronger associations among frequent users); Smith TT, et al. "The Impact of Non-Tobacco E-Cigarette Flavoring on E-Cigarette Uptake, Cigarette Smoking Reduction, and Cessation: A Secondary Analysis of a Nationwide Clinical Trial." *Addictive Behaviors,* Vol.163, (2025): 108240. Available at https://doi.org/10.1016/j.addbeh.2024.108240 (finding greater ENDS uptake and cigarette reduction among participants using nontobacco flavors compared to tobacco flavor only); Lindson, N., J. Livingstone-Banks, A.R. Butler, et al. "An Update of a Systematic Review and Meta-Analyses Exploring Flavours in Intervention Studies of E-Cigarettes for Smoking Cessation." *Addiction*, Vol.120 (4), (2025): 770-778. Available at https://doi.org/10.1111%2Fadd.16736 (meta-analysis finding that while sweet flavors were often preferred during quit attempts, flavor switching also occurred during quit attempts; subgroup meta-analyses of interventional studies showed that there was no clear association between flavor provision and smoking cessation or longer-term product use, highlighting ongoing evidence gaps and that the findings remain mixed). See also Chang, J.T., Mayer, M., et al. Characteristics and Patterns of Cigarette Smoking and Vaping By Past-Year Smokers Who Reported Using Electronic Nicotine Delivery System to Help Quit Smoking in the Past Year: Findings From the 2018–2019 Tobacco Use Supplement to the Current Population Survey. *Nicotine & Tobacco Research* 25 (2023): 596-601. Available at https://doi.org/10.1093/ntr/ntac199 (cross-sectional data finding that ENDS users trying to quit by switching to ENDS were more likely to use menthol/mint flavors exclusively but less likely to use tobacco-flavored ENDS compared to dual users who tried to quit by switching to ENDS); Liber AC, Knoll M, Cadham CJ, et al. The role of flavored electronic nicotine delivery systems in smoking cessation: A systematic review. *Drug Alcohol Depend Rep* 7 (2023): 100143. Available at https://doi.org/10.1016/j.dadr.2023.100143 (systematic review finding that evidence about the role of different flavored ENDS use and smoking cessation outcomes is inconclusive due to methodological limitations of the available literature). FDA notes that much of the available evidence is subject to methodological limitations, and FDA evaluates the totality of scientific evidence in assessing whether a product meets the APPH standard.

To date, we have not more explicitly distinguished among ENDS products with flavors other than tobacco regarding the relative degree of risk their flavors may pose to youth (e.g., low, medium, high) or the added adult benefit that may be needed to offset such differential risks. This document aims to provide further clarity around the FDA's current approach to assessing and characterizing risk to youth posed by non-tobacco flavors (e.g., fruit and candy/dessert/other sweet) and the way FDA generally intends to consider such risks in assessing whether a product's benefits to adult users offset such risks. FDA reaffirms its concerns regarding youth risk—particularly initiation associated with particularly youth-appealing flavors, e.g., fruit and candy/dessert/other sweet flavored ENDS products—and this guidance reflects FDA's updated and current thinking regarding the evidentiary considerations applicable to non-tobacco flavored ENDS products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Pub. L. 111-31) was enacted on June 22, 2009, amending the FD&C Act and providing FDA with the authority to regulate tobacco products. Specifically, section 101(b) of the Tobacco Control Act amends the FD&C Act by adding a new chapter that provides FDA with authority over tobacco products. In 2016, to better protect the public health, FDA issued a final rule, "Deeming Tobacco Products to Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products" (final deeming rule) (81 FR 28974, May 10, 2016). The final deeming rule extended FDA's tobacco product authorities to all products, other than accessories of deemed tobacco products, that meet the statutory definition of "tobacco product" in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)). With the final deeming rule, ENDS (including, but not limited to, e-liquids, e-cigarettes, e-pens, e-cigars, e-hookah, vape pens, personal vaporizers, and electronic pipes) became subject to chapter IX of the FD&C Act on the effective date of the final deeming rule.

All regulated tobacco products that meet the definition of a "new tobacco product," including ENDS products, are subject to the requirements of premarket review in sections 910(a)(2) of the FD&C Act. Manufacturers must receive authorization from the FDA before marketing their

product as set forth in sections 910(a)(2) of the FD&C Act.[7] The PMTA pathway is most likely to be the appropriate pathway for ENDS products.

An applicant seeking marketing authorization through a PMTA must show, among other things, that the marketing of the new product would be APPH.[8] In applying that standard, FDA must consider "the risks and benefits to the population as a whole."[9] Specifically, it must consider both 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."[10] In other words, that standard requires the agency to weigh (1) the likelihood that the new product will help existing tobacco users quit altogether, completely switch to potentially less harmful alternatives, or significantly reduce the amount of combusted tobacco products they smoke, against (2) the risk that the new product will entice non-tobacco users (including youth) to begin using tobacco products. It is possible for certain ENDS products to potentially reduce risks to current smokers if they facilitate complete switching and/or significant reduction in combusted cigarette use. FDA's determinations for APPH are specific to the characteristics of individual products.

The APPH standard requires that a firm seeking premarket authorization demonstrate that the marketing of a new tobacco product would have a net benefit to the public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at a particular risk of tobacco initiation. In making the APPH assessment specifically for a noncombusted tobacco product such as an ENDS, FDA weighs, among other things, the negative public health impact stemming from youth initiation and use of the product against the potential positive public health impact stemming from adults who use combusted cigarettes transitioning away, i.e., completely switching, from combusted cigarettes to the ENDS product or significantly reducing smoking of combusted cigarettes. In order to show that the marketing of an ENDS is APPH, an applicant must show that the benefits, including those to adults who use combusted cigarettes, outweigh the risks, including those to youth, resulting in a net benefit to public health.

[7] 21 U.S.C. 387j(a)(2).

[8] 21 U.S.C. 387j(c)(2)(A).

[9] 21 U.S.C. 387j(c)(4).

[10] 21 U.S.C. 387j(c)(4)(A) and (B).

Additionally, as discussed in Section III.C of this document, FDA also considers novel device access technology to assess whether a new tobacco product is APPH.[11]

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 health impacts (e.g., harm from initiation and use among non-users, particularly youth) against potential positive public health outcomes. FDA's determination regarding the likely effects of a new product must, "when appropriate," be based on "well-controlled investigations."[12] But the agency may rely on "valid scientific evidence" apart from "well-controlled investigations" if such evidence "exists" and "is sufficient to evaluate the tobacco product."[13]

III. DISCUSSION

ENDS products with fruit and candy/dessert/other sweet flavors that appeal to youth pose a substantial public health risk[14]. Given the substantial public health risks these products pose to American youth, these products face a correspondingly high evidentiary burden to demonstrate that the benefits to adult smokers in terms of quitting or significantly reducing cigarette use outweigh the risks of youth initiation and use. Notably, while PMTA marketing orders have been granted for tobacco- and menthol-flavored ENDS products, FDA has not identified any ENDS product with a flavor that is highly appealing to youth for which the applicant presented a magnitude of evidence of public health benefit sufficient to overcome the risk to youth.[15]

As part of FDA's PMTA ENDS evaluation, FDA assesses the likelihood of initiation by non-users and cessation of users across a range of tobacco use behaviors associated with the new tobacco product (e.g., initiation among never-users and former users; complete switching from combusted cigarettes; complete cessation of combusted tobacco; dual use; relapse among former smokers; and continued abstinence). FDA also evaluates the likelihood that vulnerable

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[11] 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, including relative to those of other tobacco products on the market. If an applicant does not include information that is needed for FDA to fully assess the risks and benefits of the product, the applicant has failed to carry its statutory burden of demonstrating that the product's benefits outweigh the risks.

[12] 21 U.S.C. 387j(c)(5)(A).

[13] 21 U.S.C. 387j(c)(5)(B).

[14] Park-Lee, E., A. Jamal, H. Cowan, et al. "Notes from the Field: E-Cigarette and Nicotine Pouch Use Among Middle and High School Students—United States, 2024."*Morbidity and Mortality Weekly Report* 73 (2024): 774–778. Available at https://doi.org/10.15585/mmwr.mm7335a3.

[15] FDA's "Searchable Tobacco Products Database" at https://www.accessdata.fda.gov/scripts/searchtobacco/ contains information on tobacco products that have been authorized by FDA for marketing.

populations—including youth, young adults, and other at-risk groups—may initiate use of the product.

In FDA's PMTA ENDS assessment, FDA considers available information, which might include published literature, applicant-initiated studies, and other scientific evidence evaluating the effects of ENDS products on relevant behavioral outcomes (including initiation, switching, cessation, dual use, relapse, decreased use and sustained abstinence) among current tobacco users and initiation among non-users. This evidence might include randomized controlled trials as well as observational studies examining real-world use patterns, perceptions, and behavioral outcomes.[16] Where studies involve products that are the same as or sufficiently similar to the applicant's product, applicants should provide a scientific rationale supporting the relevance and applicability of those comparisons. FDA also evaluates broader scientific information, including but not limited to peer-reviewed literature and product-specific observational and experimental data, addressing the aforementioned outcomes.

A. Escalating Role of Flavored ENDS in Youth Use and Initiation

Current youth e-cigarette use increased dramatically between 2017 and 2019, with high school e-cigarette use rising from 11.7% in 2017 to 27.5% in 2019, and overall use among middle and high school students more than doubling during this period, according to the National Youth Tobacco Survey (NYTS).[17,18] In 2017, FDA responded to a marked increase in complaints about ENDS products. FDA initiated an investigation of these complaints, the majority of which pertained to minors' access to and use of these products.

Flavored ENDS products played a major role in this surge, as most youth users reported using fruit flavors, [19,20] and more than three-quarters said they would not use e-cigarettes if flavored

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[16] See examples of FDA's study expectations in other FDA guidances, including U.S. Food & Drug Administration, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS): Guidance for Industry* (Center for Tobacco Products, Mar. 2023), available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

[17] Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al. "Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students – United States, 2011-2018." *Morbidity and Mortality Weekly Report* 67, no. 45 (2018): 1276–1277. Available at https://doi.org/10.15585/mmwr.mm6745a5. The NYTS defines e-cigarettes as "E-cigarettes are battery powered devices that usually contain a nicotine-based liquid that is vaporized and inhaled."

[18] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, et al. "E-Cigarette Use Among Youth in the United States, 2019." *JAMA* 322, no. 21 (2019): 2095–2103. Available at https://doi.org/10.1001/jama.2019.18387.

[19] *Id.*

[20] Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al. "Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students – United States, 2011-2018." *Morbidity and Mortality Weekly Report* 67, no. 45 (2018): 1276–1277. Available at https://doi.org/10.15585/mmwr.mm6745a5.

options were unavailable. [21] FDA was, and is, concerned about the extraordinary popularity of flavored ENDS products with youth. Research has long shown that flavors increase youth appeal of tobacco products, including ENDS.[22]

While reports of youth use of ENDS products have significantly declined since 2019 (to 5.9% among middle and high school students combined in 2024),[23] 87.6% of youth who currently used ENDS in 2024 reported using flavored products, among which fruit (62.8%) and candy, desserts, or other sweets (33.3%) flavors were the most common.[24] National surveillance and longitudinal studies confirm that flavors persist as a determinant of both initiation and persistence of youth vaping[25] and can thus contribute to adverse health outcomes. Repeated e-cigarette use among youth (≥5 days per month) has been associated with statistically significantly higher rates of bronchitic symptoms and shortness of breath compared with never users,[26] and youth ENDS use

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[21] Harrell, M.B., A. Loukas, C.D. Jackson, et al. "Flavored Tobacco Product Use among Youth and Young Adults: What if Flavors Didn't Exist?" *Tobacco Regulatory Science* 3, no. 2 (2017): 168–173. Available at https://doi.org/10.18001/TRS.3.2.4

[22] *E.g.,* Carpenter, C.M., et al. "New Cigarette Brands with Flavors that Appeal to Youth: Tobacco Marketing Strategies." Health Affairs 24, no. 6 (2005): 1601–1610. Available at https://doi.org/10.1377/hlthaff.24.6.1601; Pepper, J.K., K.M. Ribisl, and N.T. Brewer. "Adolescents' Interest in Trying Flavoured E-Cigarettes." *Tobacco Control* 25 (2016): ii62–ii66. Available at https://doi.org/10.1136/tobaccocontrol-2016-053174; Camenga, D.R., M. Morean, G. Kong, et al. "Appeal and Use of Customizable E-Cigarette Product Features in Adolescents." *Tobacco Regulatory Science* 4, no. 2 (2018): 51–60. DOI: 10.18001/TRS.4.2.5. Available at https://research.ebsco.com/c/xt5u2o/viewer/pdf/o274hxut4j?route=details; Harrell, M.B., S.R. Weaver, A. Loukas, et al. "Flavored E-Cigarette Use: Characterizing Youth, Young Adult, and Adult Users." *Preventive Medicine Reports* 5 (2017): 33–40. Available at https://doi.org/10.1016/j.pmedr.2016.11.001.

[23] Park-Lee, E., A. Jamal, H. Cowan, et al. "Notes from the Field: E-Cigarette and Nicotine Pouch Use Among Middle and High School Students—United States, 2024."*Morbidity and Mortality Weekly Report* 73 (2024): 774–778. Available at https://doi.org/10.15585/mmwr.mm7335a3. FDA recognizes that various factors can contribute to youth use patterns.

[24] CDC. "Notes from the Field: E-Cigarette and Nicotine Pouch Use Among Middle and High School Students — United States, 2024." *CDC.gov*. Accessed February 19, 2026. Available at https://www.cdc.gov/mmwr/volumes/73/wr/mm7335a3.htm?cid=mm7335a3w.

[25] U.S. Department of Health and Human Services. *E-Cigarette 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, 2016. Available at https://www.ncbi.nlm.nih.gov/books/NBK538680/; Leventhal, A.M., N.I. Goldenson, J. Cho, et al. "Flavored E-Cigarette Use and Progression of Vaping in Adolescents." *Pediatrics* 144, no. 5 (2019). Available at https://doi.org/10.1542/peds.2019-0789; Audrain-McGovern, J., D. Rodriguez, S. Pianin, and E. Alexander. "Initial E-Cigarette Flavoring and Nicotine Exposure and E-Cigarette Uptake Among Adolescents." *Drug and Alcohol Dependence* 202 (2019): 149–155. Available at https://doi.org/10.1016/j.drugalcdep.2019.04.037.

[26] Chaffee, B.W., J. Barrington-Trimis, F. Liu, et al. "E-Cigarette Use and Adverse Respiratory Symptoms among Adolescents and Young Adults in the United States." *Preventive Medicine* 153 (2021): 106766. Available at https://doi.org/10.1016/j.ypmed.2021.106766; Mukerjee, R., Hirschtick, J.L., et al. ENDS, cigarettes, and respiratory illness: Longitudinal associations among U.S. Youth. *Am J Prev Med* 66, no. 5 (2023): 789-796. Available at https://doi.org/10.1016/j.amepre.2023.12.005

has been linked to nicotine dependence, and nicotine exposure is associated with adverse effects on adolescent brain development. [27] [28]

Youth who preferred fruit flavors were approximately twice as likely to report ENDS as their first product, compared to those with other flavor preferences, while those who preferred menthol/mint/wintergreen flavor were half as likely to have tried ENDS first compared to those with other flavor preferences.[29] Youth who used non-traditional flavors (e.g., fruit and candy) had nearly four-fold higher adjusted odds of continued vaping six months later compared with those using only traditional (tobacco, menthol or mint, or flavorless) flavors.[30]

B. Graduated Risk-Proportionate Evaluation

Flavored ENDS pose a known and substantial risk to youth, which is greater than the risk of tobacco-flavored ENDS. Accordingly, FDA in general conducts a targeted review of applications for non-tobacco-flavored ENDS to determine if they have the types of robust and reliable

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[27] Boykan, R., Goniewicz, ML., et al. Evidence of Nicotine Dependence in Adolescents Who Use Juul and Similar Pod Devices. I*nt J Environ Res Public Health* 16, no. 12 (2019). Available at https://doi.org/10.3390/ijerph16122135; Case, K.R., Mantey, D.S., et al. E-cigarette- specific symptoms of nicotine dependence among Texas adolescents. *Addict Behav.* 84 (2018): 57-61. Available at https://doi.org/10.1016/j.addbeh.2018.03.032; McKelvey, K., Baiocchi, M., et al. Adolescents' and Young Adults' Use and Perceptions of Pod-Based Electronic Cigarettes. *JAMA Netw Open* 1, no. 6 (2018): e183535. Available at https://doi.org/10.1001/jamanetworkopen.2018.3535; Morean, M.E., Krishnan-Sarin, S., et al. Assessing nicotine dependence in adolescent E-cigarette users: The 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for electronic cigarettes. *Drug Alcohol Depend* 188 (2018b): 60-63. Available at https://doi.org/10.1016/j.drugalcdep.2018.03.029; Vogel, E.A., Prochaska, J.J., et al. Measuring e-cigarette addiction among adolescents. *Tob Control* 29, no. 3 (2020b): 258-262. Available at https://doi.org/10.1136/tobaccocontrol-2018-054900.

[28] McDonald, C.G., Eppolito, A.K., et al. Evidence for elevated nicotine-induced structural plasticity in nucleus accumbens of adolescent rats. *Brain Res* 1151 (2007): 211-218. Available at https://doi.org/10.1016/j.brainres.2007.03.019; McDonald, C.G., Dailey, V.K., et al. Periadolescent nicotine administration produces enduring changes in dendritic morphology of medium spiny neurons from nucleus accumbens. *Neurosci Lett* 385, no 2 (2005): 163-167. Available at https://doi.org/10.1016/j.neulet.2005.05.041; Ehlinger DG, Bergstrom HC, Burke JC, et al. Adolescent nicotine-induced dendrite remodeling in the nucleus accumbens is rapid, persistent, and D1-dopamine receptor dependent. *Brain Struct Funct* 122, no 1 (2016): 133-145. Available at https://doi.org/10.1007/s00429-014-0897-3; Happer JP, Courtney KE, Baca RE, et al. Nicotine use during late adolescence and young adulthood is associated with changes in hippocampal volume and memory performance. *Front Neurosci* 18 (2024): 1436951. Available at https://doi.org/10.3389/fnins.2024.1436951; Chaarani B, Kan KJ, Mackey S, et al. Low smoking exposure, the adolescent brain, and the modulating role of CHRNA5 polymorphisms. *Biol Psychiatry Cogn Neurosci Neuroimaging* 4, no 8 (2019): 672-679. Available at https://doi.org/10.1016/j.bpsc.2019.02.006..

[29] Groom, A.L., T.T. Vu, A. Kesh, et al. "Correlates of Youth Vaping Flavor Preferences." *Preventive Medicine Reports* 18 (2020): 101094. Available at https://doi.org/10.1016/j.pmedr.2020.101094.

[30] Leventhal, A.M., N.I. Goldenson, J. Cho, et al. "Flavored E-Cigarette Use and Progression of Vaping in Adolescents." *Pediatrics* 144, no. 5 (2019): e20190789. Available at https://doi.org/10.1542/peds.2019-0789.

evidence that could establish that the flavored ENDS has an added benefit relative to tobacco-flavored ENDS in facilitating adults who use combusted cigarettes to completely switch or significantly reduce their combusted cigarette use. This approach has been affirmed by the Supreme Court in *FDA* v. *Wages and White Lion* and remains unchanged.[31] This guidance addresses the next step in FDA's review, specifically regarding the level of added adult benefit necessary to demonstrate APPH.

While, based on FDA's experience to date, all flavoring in ENDS present a heightened risk to youth relative to tobacco-flavored ENDS, FDA recognizes that flavored ENDS products may present materially different youth initiation and use risks depending on flavor characteristics. Accordingly, FDA will consider evidence regarding the level of youth risk of initiation and use a particular flavor poses when weighing risks and benefits. However, we note that, where high risk to youth of certain flavors is well-known and established, such as it currently is for flavors such as fruit and candy/dessert/other sweet, under this sliding scale the evidentiary burden remains high.

Where applicants submit product-specific evidence demonstrating complete switching or significant reduction in combusted cigarette use among adults and other evidence regarding potential benefits relative to tobacco-flavored ENDS, FDA will consider such evidence in proportion to the relative youth risk posed by the product's flavor characteristics. Some flavors may be shown to have lower youth appeal, perhaps such as coffees, teas, or spices, such that they may pose a lower risk of appeal to youth and may be APPH if the added benefit they provide compared to tobacco-flavored products is relatively small.

FDA considers the full range of potential public health risks and benefits to the population as a whole in its APPH determination, including product-specific risks such as exposure to harmful or potentially harmful constituents (HPHCs).

FDA acknowledges that available data do not capture every discrete flavor descriptor or formulation. FDA may nevertheless consider as part of its APPH assessment publicly available information regarding population-level trends, preference data, initiation/cessation patterns, switching, and other relevant scientific evidence to make reasoned distinctions among flavor categories for purposes of APPH determinations. The applicant can also provide product-specific information regarding the likely extent of youth initiation and use. We note, however, that many products that do not appear to be used (or are used very little) by youth in surveys may nevertheless be appealing to youth, and the fact that a product does not appear to be widely used

[31] See *FDA v. Wages & White Lion Invs*., 604 U.S. 542 (2025) (finding that FDA's decisions denying marketing authorization to flavored ENDS were sufficiently consistent with the APPH standard, with the agency's guidance regarding the scientific evidence needed to support a premarket tobacco application, and with the need to compare proposed products to other products).

by youth may be a function of other factors such as the way the survey was conducted or more limited distribution of the product. Ultimately, it is the applicant's burden to show the product is APPH. If FDA does not have sufficient information regarding the product's potential risks and benefits, including the potential risks to youth, the applicant has not met its burden to show the product is APPH.[32]

1. Potential Benefit of Flavors for Adult Smokers in Switching Behavior or Significant Reduction in Tobacco Use

FDA recognizes that flavored ENDS products may provide public health benefits for adult smokers by offering alternatives to combusted cigarettes and potentially increasing the likelihood of complete switching, thereby substantially reducing harm caused by combusted tobacco products. Adult smokers attempting to quit combusted cigarettes have reported that flavor is an important factor in their decision to try ENDS products and in maintaining complete switching.[33] The heterogeneity of adult preferences underscores the potential value of multiple flavor options to increase the likelihood that individual adult smokers will find products that meet their needs and preferences. The effect of adults' stated preference is uncertain, however. A recent study of adults found that a reported preference for using non-tobacco flavors showed no significant association with longer smoking abstinence duration.[34]

The Agency acknowledges that flavored ENDS products afford options that may appeal to certain preferences held by adult smokers; for example, scientific literature supports that menthol-flavored cigarette smokers show a preference for menthol-flavored ENDS relative to tobacco-flavored ENDS. FDA is therefore open to evidence that a particular product may increase the likelihood that adult smokers will switch to that product and sustain complete abstinence from combusted cigarettes because it adds to the flavor options available to adult smokers.[35]

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[32] 21 U.S.C. 387j(c)(2)(A).

[33] Evans, A. T., Henderson, K. C, et al. What Motivates Smokers to Switch to ENDS? A Qualitative Study of Perceptions and Use. *Int. J. Environ. Res. Public Health* 17, no. 23 (2020): 8865. Available at https://doi.org/10.3390/ijerph17238865.

[34] Bold, K., S. O'Malley, S. Krishnan-Sarin, and M. Morean. "E-Cigarette Use Patterns, Flavors, and Device Characteristics Associated With Quitting Smoking Among a U.S. Sample of Adults Using E-Cigarettes in a Smoking Cessation Attempt." *Nicotine & Tobacco Research* 25, no. 5 (2023): 954–961. Available at https://doi.org/10.1093/ntr/ntac276.

[35] Joseph M, Morean ME, Wu R, Krishnan-Sarin S, O'Malley SS, Bold KW. Examining E-cigarette Flavor Use and Preference by Menthol Cigarette Status and Quit Duration Among U.S. Adults Using E-cigarettes in a Smoking Cessation Attempt. *Nicotine & Tobacco Research* 27. No. 9 (2025) 1657-1661. Available at https://doi.org/10.1093/ntr/ntaf059.

ENDS flavors for which there may be reliable scientific evidence demonstrating comparatively lower youth appeal and use—such as menthol, mint, and novel flavors (e.g., spice[36])—may present a lower risk of youth initiation and use relative to flavors where there is reliable scientific evidence demonstrating greater youth appeal, such as fruit and candy/dessert/other sweet flavored products.

Consistent with FDA's risk-based approach to evaluating whether marketing a product meets the APPH standard, the extent of evidence needed to demonstrate sufficient adult benefit may vary based on the relative magnitude of youth risks posed by the product's flavor characteristics. For example, available evidence demonstrates that menthol-flavored ENDS may present a materially different youth appeal and use profile than fruit- or candy-flavored products. In 2024, the most commonly used ENDS flavor type among youth was fruit (62.8%) followed by candy, dessert, and other sweets (33.3%). Menthol and tobacco were lower at 15.1% and 8.5% respectively. [37]

In 2022, FDA determined in the course of adjudicating a menthol-flavored ENDS application that applicants should provide the same types of robust studies that could demonstrate an additional adult benefit compared to tobacco-flavored ENDS that are required for other flavored ENDS products. That approach remains the same; this guidance focuses on the next step in FDA's review, specifically regarding the level of benefit that must be established to demonstrate that a menthol or other flavored ENDS is APPH. The use of menthol-flavored ENDS among youth e-cigarette users has significantly decreased since 2022 (down from 26.6% to 15.1% according to 2024 NYTS data).[38]Consistent with the graduated approach in this guidance, applications for menthol-flavored ENDS products may be able to demonstrate APPH even if the added benefit they provide compared to tobacco-flavored products is relatively small.

FDA has issued marketing granted orders (MGOs) for menthol-flavored ENDS products where applicants demonstrated that marketing such products satisfied the APPH standard. Thus, there is precedent that menthol-flavored ENDS can satisfy the APPH standard when supported by sufficient scientific evidence. Where the totality of evidence demonstrates comparatively lower youth initiation risk, FDA may consider a correspondingly lower magnitude of incremental adult benefit necessary to support an APPH determination relative to flavors with higher youth appeal.

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[36] Park-Lee, E., A. Jamal, H. Cowan, et al. "Notes from the Field: E-Cigarette and Nicotine Pouch Use Among Middle and High School Students—United States, 2024." *Morbidity and Mortality Weekly Report* 73 (2024): 774–778. Available at https://doi.org/10.15585/mmwr.mm7335a3; FDA notes 6.4% of youth current e-cigarette users reported spice flavor used in ENDS products in 2024.

[37] *Id.*

[38] Cooper, M., E. Park-Lee, C. Ren, et al. "Notes from the Field: E-Cigarette Use Among Middle and High School Students - United States, 2022." *Morbidity and Mortality Weekly Report* 71, no. 40 (2022): 1283–1285. Available at https://doi.org/10.15585/mmwr.mm7140a3; Park-Lee, E., A. Jamal, H. Cowan, et al. "Notes from the Field: E-Cigarette and Nicotine Pouch Use Among Middle and High School Students—United States, 2024." *Morbidity and Mortality Weekly Report* 73 (2024): 774–778. Available at https://doi.org/10.15585/mmwr.mm7335a3.

However, the applicant retains the burden of demonstrating, based on the totality of valid scientific evidence, that marketing the product would be APPH.

2. Potential Study Approaches to Assessing Youth Appeal for Flavored ENDS

FDA recommends that applicants provide scientifically valid evidence characterizing the relative appeal of their proposed flavored ENDS among youth, young adults, and adults, as appropriate.[39] The Agency intends to consider input and emerging data regarding appropriate methodologies for such characterization and may issue future guidance, as appropriate, to clarify evidentiary expectations. Sensory perception and consumer response studies—leveraging common and validated methods (e.g., blinded sensory panel assessments)—may provide useful information regarding the relative appeal and sensory characteristics of ENDS flavor formulations without requiring product use.[40] Done correctly, such an approach could be used to assess youth appeal for ENDS flavors. The sample sizes for such studies may be relatively modest.[41] Where applicants choose to conduct such studies, final sample sizes should be justified with a power calculation.

FDA recommends that such studies include benchmark flavors that include tobacco, fruit, candy, and other common flavors to provide context for interpreting relative appeal. This approach eliminates direct exposure from vaping while still capturing sensory responses to the actual chemical compounds used in e-cigarettes.

The Agency also encourages applicants that wish to submit other innovative, scientifically rigorous studies to demonstrate that their flavored ENDS products have lower youth appeal and provide a net public health benefit to request a meeting with FDA to discuss their study design plans.[42]

C. Novel Device Access Technology

Before determining that permitting the marketing of a new tobacco product would be APPH, FDA also considers the potential impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and use of tobacco products.

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[39] Where appropriate and consistent with ethical and regulatory considerations, applicants may include study populations consisting of young adults (e.g., ages 18 to 21) as a proxy for assessing youth-relevant sensory responses, particularly where recruitment of youth populations presents practical or ethical challenges.

[40] Pullicin, A.J., H. Kim, M.C. Brinkman, et al. "Impacts of Nicotine and Flavoring on the Sensory Perception of E-Cigarette Aerosol." *Nicotine and Tobacco Research* 22, no. 5 (2020): 806–813. Available at https://doi.org/10.1093/ntr/ntz058.

[41] Applicants should provide a scientific rationale for the selected study populations, study design, and sample size, including power calculations where applicable.

[42] For information on meetings with FDA, please see the Guidance for Industry and Investigators, "Meetings with Industry and Investigators on the Research and Development of Tobacco Products" at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

Current marketing restrictions include, not exhaustively, advertising and promotion restrictions intended to limit youth exposure to and appeal of tobacco product marketing (e.g., measures such as limiting advertising to platforms that are predominantly used by adults and using advertising content and methods that are not known to resonate with youth, or even eliminating advertising in certain media channels altogether) and sales access restrictions intended to restrict youth access to tobacco products (e.g., measures such as selling products only in face-to-face interactions, in adult-only facilities, or via websites that require robust age and identity verification).

However, because the advertising and promotion restrictions described above are intended to curb youth appeal but do not directly prevent youth use, they may not in themselves provide enough assurance of a sufficient reduction in youth use to mitigate the substantial risk that flavored ENDS pose to youth. Similarly, present state law heterogeneity and regulatory loopholes have undermined youth access restrictions; motivated youth and sellers can easily get around restrictions through e-commerce exclusions, weak enforcement, alternative delivery methods that circumvent postal rules, and limited penalties.[43,44,45] National surveillance indicates that most youth ENDS acquisition occurs through social sources—friends, acquaintances, and informal peer resale networks—pathways entirely outside regulated digital commerce. For instance, most online ENDS vendors rely on age self-certification[46], which underage users can and do readily exploit.[47,48]

FDA also considers whether the ENDS incorporate technological measures designed to prevent access and use by individuals younger than the federal minimum legal age of sale (21 years of

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[43] Leas, E.C., T. Mejorado, R. Harati, et al. "E-Commerce Licensing Loopholes: A Case Study of Online Shopping for Tobacco Products Following a Statewide Sales Restriction on Flavoured Tobacco in California." *Tobacco Control* 34, no. 4 (2025): 523–526. Available at https://doi.org/10.1136/tc-2023-058269.

[44] Gottlieb, M.A. "To End Youth Vaping as an On-Ramp to Addiction, Close Legal Loopholes and Rigorously Enforce the Law." *American Journal of Public Health* 113, no. 5 (2023): 472–473. Available at https://doi.org/10.2105/AJPH.2023.307271.

[45] Azagba, S., T. Ebling, and A. Korkmaz. "Social Media and E-Cigarette Use: The Mediating Role of Mental Health Conditions." *Journal of Affective Disorders* 344 (2024): 528–534. Available at https://doi.org/10.1016/j.jad.2023.10.053.

[46] Bertrand, A., M.C. Diaz, E.C. Hair, and B.A. Schillo. "Easy Access: Identification Verification and Shipping Methods Used by Online Vape Shops." *Tobacco Control* 34, no. 2 (2025): 259–262. Available at https://doi.org/10.1136/tc-2023-058303.

[47] Harati, R.M., S.E. Ellis, N. Satybaldiyeva, et al. "Online Retailer Nonadherence to Age Verification, Shipping, and Flavor Restrictions on E-Cigarettes." *JAMA* 332, no. 24 (2024): 2113–2114. Available at https://doi.org/10.1001/jama.2024.21597.

[48] Gaiha, S.M., L.K. Lempert, C. Lin, and B. Halpern-Felsher. "E-Cigarette Access and Age Verification among Adolescents, Young Adults, and Adults." *Addictive Behaviors* 161 (2025): 108193. Available at https://doi.org/10.1016/j.addbeh.2024.108193.

age). Such technological safeguards are referred to as device access restrictions (DAR). DAR are intended to be systems including software or technology that are part of the use of the ENDS device and provide sustained prevention of underage use of a tobacco product by requiring user age verification and identification to unlock and/or use the product. For example, an ENDS could employ age-gating technologies that require user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product or geo-fencing technologies (e.g., technologies that make it impossible to operate a tobacco product in a particular location such as a school or playground). FDA evaluates DAR in making the APPH determination. [49]

Given the added risk posed by youth appealing flavors and the current lack of real world experience regarding use of DAR to prevent or sufficiently mitigate the risk of youth use, an applicant whose high youth appealing flavored ENDS purports to rely solely on DAR technology to address risk to youth carries an especially high burden to demonstrate adequate mitigation of such risk based on valid and reliable evidence from robust scientific investigations. In its assessment of whether a product meets the APPH standard for marketing authorization, FDA evaluates the potential for youth initiation and use, especially in the context of youth-appealing flavored ENDS like fruit and candy/dessert/other sweet flavored. As such, DARs submitted for ENDS products with those types of youth-appealing flavors, without adequate and substantial evidence demonstrating sufficient mitigation of youth risk, are insufficient to overcome the heightened concerns associated with these flavor categories.

Accordingly, FDA's current thinking is that while such technologies may be a component of a comprehensive youth prevention strategy, they might not, standing alone, satisfy the especially high evidentiary burden to demonstrate adequate risk mitigation of youth use and initiation associated with high youth appealing flavored ENDS (e.g., fruit and candy/dessert/other sweet).

FDA's evaluation of flavored ENDS products under the APPH standard is grounded in a risk-proportionate, product-specific evaluation that weighs the potential benefits to adult smokers against the risks of non-user (e.g., youth) initiation and use. Given the well-established and substantial youth appeal associated with certain flavor categories, particularly fruit and candy/dessert/other sweet flavors that appeal to youth, applicants bear a heightened evidentiary burden to demonstrate that marketing such products would result in a net benefit to the population as a whole.

[49] This would generally include software design, functionality, risk analysis, operation, and maintenance practices, as well as studies on the DAR including human factors studies demonstrating the ability of the DAR to allow those 21 and over to access the device while preventing access for those under 21 years-of-age.