**FDA's draft guidance on the considerations related to youth risk of flavored electronic nicotine delivery systems (ENDS) premarket applications should not be finalized because it fails to protect youth or present an accurate estimate of the tradeoff between increased youth e-cigarette use vs theoretical benefits to adult smokers**

Docket No. FDA-2026-D-1817
"Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications – Considerations Related to Youth Risk; Draft Guidance for Industry"

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The Food and Drug Administration (FDA) issued a Draft Guidance for Industry on March 9, 2026 describing its current thinking on considering premarket tobacco product applications (PMTAs) for flavored electronic nicotine delivery systems (ENDS, which includes e-cigarettes and heated tobacco products). In particular, it aims to clarify its current approach and evidentiary considerations relevant to weighing the purported benefits of flavored ENDS to adult smokers who might stop smoking against the known risks posed by flavored tobacco products to youth. To date, FDA has authorized the marketing only of so-called "unflavored," "tobacco-flavored," and "menthol-flavored" e-cigarettes, but has not authorized the marketing of fruit, candy, dessert, or other sweet-flavored ENDS products.[1] Additionally, FDA initially granted marketing authorization in 2020 and renewed marketing authorization in 2023 and 2024[2] for Philip Morris's IQOS heated tobacco device and six flavors of IQOS Marlboro cigarettes, including: Blue Menthol HeatSticks, Green Menthol HeatSticks, Fresh Menthol HeatSticks, Bronze HeatSticks ("with notes of cocoa and dried fruit"[3]), Amber HeatSticks, and Sienna Heatsticks. On April 17, 2026, FDA renewed its

[1] Food and Drug Administration, E-Cigarettes, "Vapes" and Other Electronic Nicotine Delivery Systems (ENDS) Authorized by the FDA (current as of 03/13/2026). Available: https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/e-cigarettes-vapes-and-other-electronic-nicotine-delivery-systems-ends-authorized-fda#:~:text=Table_title:%20E%2DCigarettes%2C%20%E2%80%9CVapes%E2%80%9D%20and%20Other%20Electronic%20Nicotine,%7C%20:%20Vuse%20Alto%20Power%20Unit%20%7C

[2] Food and Drug Administration, Searchable Tobacco Products Database. https://www.accessdata.fda.gov/scripts/searchtobacco/

[3] IQOS website. Iqos.com

authorization of IQOS as a modified risk tobacco product (MRTP),[4] permitting IQOS -- including its Marlboro Green Menthol, Marlboro Blue Menthol, and Marlboro Amber flavored HeatSticks -- to be marketed with claims that "switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."

The following comment mostly presents evidence on e-cigarettes, the most widely-used form of ENDS among both youth and adults, and most widely available in the United States, but they are also relevant to heated tobacco products.

Although the Draft Guidance correctly acknowledges the "major role" that flavored e-cigarettes played in increasing youth use of ENDS between 2017 and 2019 and the significant risk that *some* flavored ENDS products continue to pose to youth, ***FDA incorrectly downplays the impact on youth of all flavored nicotine products (including, especially, menthol and mint flavors).*** And with FDA's 2020, 2023, and 2025 PMTA and MRTP authorizations of menthol- and other flavored IQOS heated tobacco products and increased availability of IQOS heated tobacco products in the US, flavored ENDS products could pose even greater risks to youth. FDA states that the amount of evidence an applicant must present to demonstrate an added benefit to smokers for a "flavored" ENDS product compared to a "tobacco-flavored" ENDS "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." (Draft Guidance, p. 4, emphasis added.) The Draft Guidance suggests that FDA would be open to authorizing e-cigarettes in flavors such as mint, menthol, coffee, teas, and spices that, FDA states, *without evidence,* would appeal less to kids.

In addition, although the guidance explicitly recognizes a tradeoff between youth and adult e-cigarette use, ***FDA fails to clearly explain how to quantify this tradeoff – i.e., what and how much evidence an applicant must present to demonstrate adult benefits outweigh youth risks.*** Failing to provide such guidance leaves the door wide open to industry manipulation of these estimates.

Further, ***FDA does not consider that flavored e-cigarettes present health harms to adult users as well as to youth users.***

The Draft Guidance also proposes allowing "novel device access technologies" using Bluetooth connections between e-cigarettes and other ENDS devices that would allow two-way communication between the ENDS and external agents as a way to hypothetically reduce youth use. ***These processes have not been shown to work, pose serious privacy issues, and leave the door wide open for companies to remotely tune the devices to maximize addiction based on individual users' inhaling topography. This technology should be prohibited.***

As described in more detail below, FDA's Draft Guidance fails to adequately address the following issues:

1. All flavored and so-called "unflavored" or "tobacco-flavored" ENDS products pose important risks to youth and adults.

[4] Food and Drug Administration, Modified Risk Granted Orders – Exposure Modification. April 17, 2026. https://www.fda.gov/media/192033/download?attachment

2. There is insufficient evidence that certain flavored tobacco products demonstrate adult benefits that outweigh youth risks, and the FDA has not explained what additional evidence would demonstrate purported benefits.
3. FDA should prohibit "novel device access technologies" that have not been proven to prevent or deter youth access to flavored ENDS products.

**1. All flavored and so-called "unflavored" or "tobacco-flavored" ENDS products pose important risks to youth and adults.**

Flavors are used in almost all e-cigarettes and other ENDS products (such as Marlboro HeatSticks cigarettes used with IQOS heated tobacco products) under varying names which makes it practically impossible for FDA to identify specific flavors that "appeal less to youth" but are popular with adults. As discussed in more detail below, even so-called "unflavored" and "tobacco-flavored" ENDS products contain flavor chemicals.

FDA correctly acknowledges the overwhelming evidence that flavored ENDS, pose a substantial risk to youth, including voluminous literature showing that flavors, particularly in e-cigarettes, facilitate initiation among youth[5,6] and promote continued e-cigarette use.[7, 8, 9] Nearly 90% of adolescent and young adult e-cigarette users prefer flavored e-liquids (e.g., fruit and mint), and flavors are frequently cited as a primary reason for initiation.[10, 11] Flavors enhance the palatability of e-cigarettes, making them more appealing to inexperienced users and lowering the threshold for experimentation.[12, 13] Mint-, menthol-, cooling-, fruit-, candy-, and other sweet-flavored e-cigarettes play a significant role in driving youth initiation and continued use of e-cigarettes.[14] Mint, menthol, cooling ingredients, and other tobacco flavors can reduce harshness and improve taste.[15] Moreover,

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[5] Gentzke AS, Wang TW, Cornelius M, et al. Tobacco product use and associated factors among middle and high school students—National Youth Tobacco Survey, United States, 2021. *MMWR Surveill Summ.* 2022;71(No. SS-5):1–29.
[6] Villanti AC, Johnson AL, Glasser AM, et al. Association of flavored tobacco use with tobacco initiation and subsequent use among US youth and adults, 2013-2015. *JAMA Netw Open*. 2019;2(10):e1913804.
[7] Centers for Disease Control and Prevention. Why Youth Vape. October 17, 2024. https://www.cdc.gov/tobacco/e-cigarettes/why-youth-vape.html
[8] Gaiha SM, Lempert LK, McKelvey K, Halpern-Felsher B. E-Cigarette devices, brands, and flavors attract youth: informing FDA's policies and priorities to close critical gaps. Addictive Behaviors. 2022 Mar 1;126:107179.
[9] Villanti AC, Johnson AL, Ambrose BK, et al. Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013- 2014). Am J Prev Med 2017;53:139–51.
[10] 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(35):774-778. doi:10.15585/mmwr.mm7335a3PubMedGoogle ScholarCrossref
[11] Leventhal AM, Dai H. Prevalence of flavored e-cigarette use among subpopulations of adults in the United States. J Natl Cancer Inst. 2021;113(4):418-424. doi:10.1093/jnci/djaa118PubMedGoogle ScholarCrossref
[12] Meernik C, Baker HM, Kowitt SD, Ranney LM, Goldstein AO. Impact of non-menthol flavours in e-cigarettes on perceptions and use: an updated systematic review. BMJ Open. 2019;9(10):e031598. doi:10.1136/bmjopen-2019-031598PubMedGoogle ScholarCrossref
[13] Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. Tob Control. 2016;25(suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174PubMedGoogle ScholarCrossref
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[15] Carstens E, Carstens MI. Sensory effects of nicotine and tobacco. Nicotine Tob Res. 2022;24(3):306–315. doi:10.1093/ntr/ntab086

flavored tobacco products are perceived by youth as less harmful or safe. State and local flavored tobacco bans are associated with reduced e-cigarette initiation and use.[16, 17, 18, 19]

In April 2026 the CDC Foundation's Monitoring Tobacco Project released a new Data Snapshot[20] on the use of flavored e-cigarettes among youth and young adults that underscored the fact that flavored e-cigarettes are a major driver of youth e-cigarette use. Analyzing data collected from August to December 2025, the Data Snapshot explores three measures of flavor use among youth and young adults: 1) First flavor used; 2) Flavors ever used; and 3) flavors currently used (past 30 days). The analysis found that nearly all (92.5%) of youth and young adults who have ever used e-cigarettes started with a flavored product. While fruit was the most commonly reported first flavor used (59.8% of youth and 48.2% of young adults), fruit, candy, desserts and other sweets (including chocolate), and mint and menthol are the most common e-cigarette flavors ever used among youth and young adults. Nearly all (94.6%) of youth and young adults who report current e-cigarette use indicate that have used non-tobacco-flavored e-cigarettes in the past 30 days. Barrington-Trimis et al also found that adolescents' use of a sweet or cooling flavored ENDS at first use was associated with having a positive first vaping experience, which in turn was associated with greater likelihood of continued use.[21]

Use of menthol and "ice-fruit" flavors (combining fruit flavors with coolants) increased among youth between 2020-2023.[22] The 2025 National Youth Tobacco Survey (NYTS) released in March 2026 reported that among US middle and high school students who currently use e-cigarettes, in addition to the 59.3% who report using fruit flavors, 31.7% report using "candy, desserts, or other sweets" (which likely includes vanilla), 29.5% report using mint, 15.5% use menthol, 11.6% use "non-alcoholic drink" flavors (which includes teas and coffees, some of which may have alternatively been categorized as desserts or other sweets), and 6.8% used spice flavors.[23]

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[16] Lin M, Abdelfattah LI, Hanchate AD, Sutfin EL, Denlinger-Apte RL. State-Level Flavored E-Cigarette Bans and Initiation Rates Among Youths and Adults. *JAMA Netw Open.* 2026;9(1):e2551744. doi:10.1001/jamanetworkopen.2025.51744

[17] Cheng D, Lee B, Jeffers AM, et al. State E-Cigarette Flavor Restrictions and Tobacco Product Use in Youths and Adults. *JAMA Netw Open.* 2025;8(7):e2524184. doi:10.1001/jamanetworkopen.2025.24184

[18] Appolon G, Leas E, Pines HA, et al. Local Flavored Tobacco Bans and Youth Electronic Nicotine Delivery Systems Use. *JAMA Health Forum.* 2026;7(4):e260631. doi:10.1001/jamahealthforum.2026.0631

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[20] CDC Foundation. Monitoring Tobacco Product Use Among Youth and Young Adults in the United States. TEEN+ Data Snapshot, Issue 3. April 2026. https://urldefense.com/v3/__https://tobaccomonitoring.org/wp-content/uploads/2026/04/DataSnapshot_Issue03_ECigFlavors_v2.pdf__;!!LQC6Cpwp!p_4CxW8uTRSn49g3l3xsXqL9C6-aReu76J7OrqK2APNFfJjSrBLYtT1iA_LP_vTscJgL8s7_fLHbXn7zhwSCxRZS0eFUPRPZZN4$

[21] Barrington-Trimis JL, Stoolmiller M, Vogel EA, Harlow A, Tackett AP, Unger JB, McConnell R, Leventhal AM, Audrain-McGovern J, Sargent JD. Recall of Flavor at First E-cigarette Use and Its Association with E-cigarette Progression: The Mediating Effects of First Sensory Experience. The Journal of pediatrics. 2024 Dec 1;275:114246.

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[23] US Food and Drug Administration, National Youth Tobacco Survey (NYTS), 2025 Dataset, Questionnaire, and Methodology Report. Available: https://www.fda.gov/tobacco-products/youth-and-tobacco/national-youth-tobacco-survey-nyts

In addition, while not ENDS, among middle and high school nicotine pouch users, the highest percentage (59.6%) use mint, 24.3% use fruit, 18.1% use menthol, 9.6% use spice, 9.1% use nonalcoholic drinks (such as coffees and teas), and 8% use candy, desserts, or other sweets. For example, cinnamon and coffee are the fourth and fifth top selling flavors for nicotine pouches.[24] These recent data counter the FDA's unsupported claims about which flavors are "less appealing to youth" and remove all doubt that mint and menthol flavored tobacco products both appeal to youth and are among the most popular flavors among youth.

Tea, coffee, and spice flavors are also widely popular with youth. Industry resources tracking flavor trends substantiate the growing popularity of coffee,[25, 26] tea,[27] and spice flavors among youth.[28, 29] Tea flavors that suggest the e-cigarette is "natural" and/or imparts "wellness" (for example, herbal and green teas) are a growing trend.[30, 31] For example, in a study of use patterns, brands and ingredients among youth of so-called "wellness" e-cigarettes found that 18.3% of youth aged 18-20 and 12.3% of youth aged 13-17 used tea-flavored non-nicotine e-cigarettes.[32] As they reach their teens, children switch from "kiddy" flavors to flavors that are more "adult" or "grown up." Adolescents are especially attracted to coffee flavored products that will make them appear to be older or more mature.[33] Clearly, JUUL Labs recognized the potential appeal of coffee flavors to youth, as evidenced by 20,765 previously secret documents released through JUUL litigation settlements concerning the company's interest in coffee flavors.[34]

***FDA also failed to consider the "any port in a storm" reality.*** That is, if mint, menthol, coffee, tea, and spice flavors are the only flavors available, those are the flavors that kids will use. This was made abundantly clear when in 2018, FDA "prioritized enforcement" against some flavored e-

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[24] He Y, Zhang Z, Keller-Hamilton B, et alTrends of oral nicotine pouch prices and sales by product characteristics in the USA, 2021–2024Tobacco Control Published Online First: 12 June 2025. doi: 10.1136/tc-2024-059222

[25] Reinoso KL. Gen Z Coffee Trends: What's Fueling the Buzz in 2026. August 11, 2025. https://tastewise.io/blog/gen-z-coffee-trends

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[27] Veda SB. How New Generations are Embracing Tea: Part 3, What are they Drinking? May 13, 2025. https://www.worldteanews.com/tea-nerdery/how-new-generations-are-embracing-tea-part-3-what-are-they-drinking

[28] SupplySide Supplement Journal, Flavors for Kids, June 8, 2007. https://www.supplysidesj.com/business-resources/flavors-for-kids

[29] Kerry, Driving Flavour Innovation in 2026 with Taste Charts, 12 January 2026. https://www.kerry.com/insights/kerrydigest/2026/taste-charts-2026#:~:text=Salted%20lime%20and%20salted%20chocolate,playful%20nostalgia%20are%20being%20reimagined.

[30] Kerry, Driving Flavour Innovation in 2026 with Taste Charts, 12 January 2026. https://www.kerry.com/insights/kerrydigest/2026/taste-charts-2026#:~:text=Salted%20lime%20and%20salted%20chocolate,playful%20nostalgia%20are%20being%20reimagined.

[31] Gaiha SM, Lin C, Lempert LK, Halpern-Felsher B. Use patterns, flavors, brands, and ingredients of nonnicotine e-cigarettes among adolescents, young adults, and adults in the United States. JAMA Network Open. 2022 May 25;5(5):e2216194.

[32] Gaiha SM, Lin C, Lempert LK, Halpern-Felsher B. Use patterns, flavors, brands, and ingredients of nonnicotine e-cigarettes among adolescents, young adults, and adults in the United States. JAMA Network Open. 2022 May 25;5(5):e2216194.

[33] SupplySide Supplement Journal, Flavors for Kids, June 8, 2007. https://www.supplysidesj.com/business-resources/flavors-for-kids

[34]https://www.industrydocuments.ucsf.edu/tobacco/documents/?q=null%2Call%2Ccontains%2Ccollection%3A%22JUUL+Labs+Collection%22+coffee+flavor&db-set=documents&industry=tobacco&sort=relevance&pg=1&npp=100

cigarettes, so youth use of mint and menthol disposable e-cigarettes increased dramatically.[35, 36, 37] This fact contradicts FDA's assertion that mint "may present a lower risk of youth initiation and use." Under experimental conditions, adolescents shopping in stores where mint/menthol and sweet flavored products were removed had increased future intentions to use tobacco-flavored vaping products.[38]

At least 46 countries as of May 2025 ban the sale of all e-cigarettes, and at least 10 countries (including Bulgaria, China, Finland, Hungary, Latvia, Lithuania, Montenegro, the Netherlands, Slovenia, and Ukraine) ban all characterizing flavors (other than tobacco flavor) in e-cigarettes.[39] For example, the Netherlands banned flavored e-cigarettes and e-liquids after recognizing that sweet flavors make e-cigarettes more alluring to young people.[40, 41]

In addition to the role of flavors that contribute to youth initiation and continued use of e-cigarettes, all e-cigarette use causes cardiovascular diseases and serious respiratory conditions such as asthma and chronic obstructive pulmonary disease.[42, 43, 44, 45, 46] Further, the aerosols in e-cigarettes damage

[35] Borowiecki M, Kim Y, Emery S. A Patchy Prohibition: Product and Flavor Substitution After the Food and Drug Administration's Prioritized Enforcement Policy on Flavored E-cigarettes. Nicotine Tob Res. 2024;26(5):527-535. doi:10.1093/ntr/ntad212

[36] Gaiha SM, Lempert LK, McKelvey K, Halpern-Felsher B. E-Cigarette devices, brands, and flavors attract youth: informing FDA's policies and priorities to close critical gaps. Addictive Behaviors. 2022 Mar 1;126:107179.

[37] Bansal-Travers M, Rivard C, Delnevo CD, Gross A, Anesetti-Rothermel A, Merson B, Xiao H, Cheng YC, Creamer MR, Kimmel HL, Stanton CA. Flavor and Device Choices Among People Who Use ENDS: Results From the PATH Study. American journal of preventive medicine. 2025 Feb 1;68(2):236-44.

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[40] Government of the Netherlands. Government measures to discourage smoking. https://www.government.nl/topics/smoking/government-measures-to-discourage-smoking

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[42] John Erhabor, Zhiqi Yao, Erfan Tasdighi, Emelia J Benjamin, Aruni Bhatnagar, Michael J Blaha, E-cigarette Use and Incident Cardiometabolic Conditions in the All of Us Research Program, Nicotine & Tobacco Research, Volume 27, Issue 9, September 2025, Pages 1651–1656, https://doi.org/10.1093/ntr/ntaf067

[43] Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. NEJM Evid 2024;3:EVIDoa2300229.

[44] Glantz SA, Oliveira da Silva AL. Comparison of e-Cigarette and Cigarette Use and Dual Use Associations With Disease: Updated Systematic Review and Meta-Analysis. Public Health Rep. 2026 Feb 17:333549251403349. doi: 10.1177/00333549251403349. Epub ahead of print. PMID: 41702869; PMCID: PMC12916339.

[45] Hamann, S. L., Kungskulniti, N., Charoenca, N., Kasemsup, V., Ruangkanchanasetr, S., & Jongkhajornpong, P. (2023). Electronic Cigarette Harms: Aggregate Evidence Shows Damage to Biological Systems. International journal of environmental research and public health, 20(19), 6808. https://doi.org/10.3390/ijerph20196808

[46] Wang MP, Ho SY, Leung LT, et al. Electronic Cigarette Use and Respiratory Symptoms in Chinese Adolescents in Hong Kong. JAMA Pediatr 2016;170:89–91.

DNA and cause epigenetic changes, inflammation, and immune system changes that are linked to cancer.[47, 48, 49, 50, 51]

In particular, a comprehensive 2026 review of peer-reviewed literature since 2017 involving a qualitative carcinogenic risk assessment of nicotine-based e-cigarettes concluded that vaping is likely to cause lung and oral cancer.[52] It found that vaping exposes users to many different carcinogens, including volatile organic compounds, metals, polycyclic aromatic hydrocarbon. In addition, the flavoring chemicals in e-cigarettes and the solvents propylene glycol and vegetable glycerin also cause damage that increases cancer risk. The authors identified 10 key characteristics of carcinogens and found evidence that implicated e-cigarette aerosols in all ten. There are studies that show mice exposed to e-cigarette aerosol developed lung cancers and bladder hyperplasia. Putting all this evidence together was the basis for the authors' conclusion that vaping is likely to cause cancer. The review concludes with a "clear and authoritative assessment" that "e-cigarettes delivering nicotine are likely to be carcinogenic to humans who use them causing oral cancer and lung cancer," and this cancer burden is separate from cancer attributable to e-cigarette users who transition to smoking and dual use.[53]

While it is still too early to show a substantial epidemiological risk for cancer, FDA should not ignore the growing body of evidence that ENDS increase cancer risk and should consider this when balancing the public health risks and benefits of relaxing restrictions on flavors that would almost certainly lead to increased use.

- **All ENDS contain highly addictive nicotine**

All widely-used e-cigarettes and other ENDS contain nicotine, a highly addictive substance which disrupts brain development and therefore poses a serious health risk to young users in particular.[54]

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[47] Sahu R, Shah K, Malviya R, et al. E- Cigarettes and Associated Health Risks: An Update on Cancer Potential. Adv Respir Med 2023;91:516–31.
[48] Tommasi S, Blumenfeld H, Besaratinia A. Vaping Dose, Device Type, and E-Liquid Flavor are Determinants of DNA Damage in Electronic Cigarette Users. Nicotine Tob Res. 2023 May 22;25(6):1145-1154. doi: 10.1093/ntr/ntad003. PMID: 36780924; PMCID: PMC10202635.
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[52] Stewart BW, Marshall H, Bonevski B, Griffin HJ, Hopkins AM, Itchins M, Mazza CJ, Modi ND, Ryan M, Varlow M, Sitas F. The carcinogenicity of e-cigarettes: a qualitative risk assessment. Carcinogenesis. 2026;47: 1-14 doi: 10.1093/carcin/bgag015. PMID: 41910510.
[53] Stewart BW, Marshall H, Bonevski B, Griffin HJ, Hopkins AM, Itchins M, Mazza CJ, Modi ND, Ryan M, Varlow M, Sitas F. The carcinogenicity of e-cigarettes: a qualitative risk assessment. Carcinogenesis. 2026;47: 1-14 doi: 10.1093/carcin/bgag015. PMID: 41910510.
[54] Lushniak BD, Samet JM, Pechacek TF, et al. The health consequences of smoking—50 years of progress: a report of the surgeon general. 2014.

Prolonged exposure to nicotine during adolescence increases the risk of cognitive, attentional and mood disorders,[55] and serves as a gateway to cigarette smoking.[56, 57, 58] An umbrella review published in 2025 that included 56 reviews from 384 articles found a consistent significant association between vaping and smoking initiation, supporting a causal relationship, with pooled ORs of 1.50–26.01 (21 systematic reviews), most of which suggested that young people using e-cigarettes are about three times more likely than those not using them to initiate smoking.[59] This review also found consistent associations between e-cigarette use and subsequent smoking, marijuana use, alcohol use, asthma, cough, injuries and mental health outcomes. Another systematic review of e-cigarette use and subsequent smoking in youth nonetheless found, "data consistently showed direct associations between vaping at baseline and smoking initiation (28 studies) and smoking progression (5 studies).[60] In direct contradiction to the FDA's assumption that e-cigarettes (and other ENDS) benefit adults by promoting smoking cessation, this review did not find a consistent association between vaping and smoking cessation.

An April 2026 review in the *European Heart Journal* makes clear that ***all nicotine-containing products, whether combustible or not and including ENDS, pose cardiovascular threats***. In particular, use of nicotine products including e-cigarettes triggers persistent endothelial injury promotes cardiovascular disease, which ultimately manifests as hypertension, acute and chronic acute coronary syndromes, heart failure, stroke, and arrhythmia.[61]

- **Even so-called "unflavored" and "tobacco-flavored" ENDS contain flavors and present risks, especially to youth**

FDA's Draft Guidance suggests that ENDS PMTA applicants for products that are unflavored, tobacco-flavored, or menthol-flavored would need to show a decreased adult benefit to demonstrate a net benefit to public health because these products have less "youth appeal" than some other flavors and therefore pose a lower risk to youth. However, ***the risks to youth of menthol, unflavored, and tobacco-flavored vapes may be meaningfully underestimated by the FDA because many of these ENDS products use the same flavor extracts that are used in flavored ENDS and are just as appealing to youth.*** Therefore, FDA's approach is not supported by the scientific evidence.

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[55] Lushniak BD, Samet JM, Pechacek TF, et al. The health consequences of smoking—50 years of progress: a report of the surgeon general. 2014.

[56] Kaur J, Goel S, Shabil M, Gupta S, Rana RK, Rinkoo AV, Chauhan A. E-cigarette use and subsequent tobacco smoking initiation: an umbrella review with Bayesian model meta-analysis. Tob Control. 2026 Feb 26:tc-2025-059783. doi: 10.1136/tc-2025-059783. Epub ahead of print. PMID: 41748427.

[57] Chan GCK, Stjepanović D, Lim C, et al. Gateway or common liability? A systematic review and meta- analysis of studies of adolescent e- cigarette use and future smoking initiation. Addiction 2021;116:743–56.

[58] Khouja JN, Suddell SF, Peters SE, et al. Is e-cigarette use in non- smoking young adults associated with later smoking? A systematic review and meta- analysis. Tob Control 2021;30:8–15.

[59] Golder S, Hartwell G, Barnett LM, Nash SG, Petticrew M, Glover RE. Vaping and harm in young people: umbrella review. Tob Control. 2025 Aug 19:tc-2024-059219. doi: 10.1136/tc-2024-059219. Epub ahead of print. PMID: 40829950.

[60] Begh R, Conde M, Fanshawe TR, Kneale D, Shahab L, Zhu S, et al. Electronic cigarettes and subsequent cigarette smoking in young people: A systematic review. Addiction. 2025;120(6):1090–1111. https://doi.org/10.1111/add.16773

[61] Thomas Münzel, Filippo Crea, Sanjay Rajagopalan, Thomas Lüscher, Nicotine and the cardiovascular system: unmasking a global public health threat, *European Heart Journal*, Volume 47, Issue 15, 14 April 2026, Pages 1764–1781, https://doi.org/10.1093/eurheartj/ehaf1010

Of particular concern, e-cigarette products labeled "unflavored" or "tobacco-flavored" frequently contain toxic flavor additives including menthol, synthetic cooling agents, and other flavorants. These so-called "tobacco-flavored" e-cigarette liquids are manipulated by manufacturers to have tastes that appeal to youth as well as adults. For example, damascenone is in many tobacco-flavored products together with pyrazines. Further, the term "tobacco-flavored" for e-cigarettes is misleading, since none contain extracts from tobacco. Rather, they are typically candy or vanilla flavored but renamed as "tobacco-flavored." Several flavor chemicals, including ethyl maltol, vanillin, corylone, and other "confectionery-related" flavor chemicals, are abundant in some e-cigarette liquids (including for Puff Bar) labeled "tobacco-flavored," coinciding with and apparently attempting to circumvent FDA's restrictions on the sale of sweet and fruity-flavored e-cigarettes.[62]

Particularly concerning is the fact that coolants are found in all e-cigarettes (not only those that are called "mint" or "menthol") including "clear" (a concept flavor name that is often categorized as "unflavored"). Like mint and menthol, these cooling additives make nicotine more palatable and the products more appealing to youth. For example, in this 2025 study, the Flum Pebble Clear ("unflavored") device had the highest total flavor chemical concentration of any product studied (96.4 mg mL−1).[63] Many e-cigarettes contain non-menthol synthetic cooling agents such as WS-3 and WS-23 and/or are labeled with ice-hybrid flavors such as "Raspberry Ice."[64] A 2025 study of "clear" e-cigarettes (introduced to evade Massachusetts flavor ban) shows that all "clear" e-liquids contain synthetic cooling agents WS-23 and/or WS-3, 18 of 19 studied products contained menthol, and 12 of 19 contained other flavorants and undermined the efficacy of the flavor ban.[65]

A recent 2026 paper found that the Beta-damascone (BD) flavor compound used in tobacco-flavored e-cigarettes has the effect of increasing nicotine consumption and preference.[66] Beta-damascone is also used in Juul menthol e-cigarettes, as revealed in FDA's reviewer notes concerning Juul's submitted ingredient listings for flavor formulations and toxicological information.[67] This effect would increase the appeal, addictiveness, and continued use of so-called "tobacco-flavored" e-cigarettes among youth, as well as adults.

Many e-cigarettes that are not labeled "vanilla" flavored include the flavor chemical vanillin. Vanillin is used in most e-cigarettes and flavor liquids to not only impart a vanilla flavor, but also to achieve a flavor profile that is sweet, sugary, or spicy. "There appears to be no clear association

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[62] Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. Ethyl maltol, vanillin, corylone and other conventional confectionery-related flavour chemicals dominate in some e-cigarette liquids labelled 'tobacco' flavoured. Tob Control. 2022;31(Suppl 3):s238-s244.

[63] Robertson NE, Hunsaker HC, Yamamoto M, Cheung K, Poulin BA, Nguyen TB. E-liquid and aerosol characterization of popular disposable E-cigarettes. ACS omega. 2025 Jul 3;10(27):29615-27.

[64] Leventhal AM, Tackett AP, Whitted L, Jordt SE, Jabba SV. Ice flavours and non-menthol synthetic cooling agents in e-cigarette products: a review. Tob Control. 2023 Nov;32(6):769-777. doi: 10.1136/tobaccocontrol-2021-057073. Epub 2022 Apr 28. PMID: 35483721; PMCID: PMC9613790.

[65] Minetti ET, Erythropel HC, Keith R, Davis DR, Zimmerman JB, Krishnan-Sarin S, Hamburg NM. Cardiovascular Health Effects and Synthetic Cooling Agents in E-Cigarettes Labeled as "Clear" Marketed in Massachusetts After the Tobacco Product Flavoring Ban. Journal of the American Heart Association. 2025 Aug 19;14(16):e036106.

[66] Pawaskar K, Scott SM, Engel S, Mulloy SM, Lee AM. Flavor Compounds Found in Electronic Cigarette Liquids Differentially Enhance Voluntary Nicotine Consumption and Preference in Mice. Nicotine Tob Res. 2026 Mar 24;28(4):545-553. doi: 10.1093/ntr/ntaf106. PMID: 40378181; PMCID: PMC12507343.

[67] https://www.industrydocuments.ucsf.edu/docs/sfgw0353/

between a product's flavor description and the inclusion of vanillin, which indicates that vanillin is used as a flavor enhancer or to introduce additional sweetness."[68] In addition to vanilla-flavored e-cigarettes, vanillin is used to mask unpleasant flavors or odors.

- **The "Generally Recognized as Safe" (GRAS) designation does not apply to inhaled ENDS compounds**

***While some flavors (e.g., vanilla and cinnamon) that are flavor additives in food products have been "Generally Recognized as Safe" (GRAS) by the FDA for ingestion, this does not mean they are not safe when inhaled in e-cigarettes.*** GRAS is a provision within the definition of a food additive under 21 USC 321(s) and as such, the safety of foods designated as "GRAS" is based on oral consumption (i.e., eaten or ingested as a food), and cannot serve as an indicator of the toxicity or safety of e-cigarette ingredients when aerosolized an inhaled.

A 2024 review of the toxicity of ingredients in e-cigarettes, including those ingredients that have been determined to be GRAS when ingested in food, describes the potentially significant harms associated with inhalation or cell exposure when several substances listed as GRAS in food are used in e-cigarettes via proinflammatory effects as well as immune suppression, respiratory tract irritation, and cytotoxicity.[69] The 15 substances described in the Kassem paper are: acetaldehyde, acetoin, cinnamaldehyde, diacetyl, ethyl acetate, eugenol, tocopherol acetate, triacetin, linalool, benzaldehyde, carvone, decanal, ethyl butyrate, ethyl vanillin, limonene.[70]

The Flavor and Extract Manufacturers Association (FEMA) Expert Panel that recommends compounds for GRAS designation evaluates the safety of flavor ingredients only under their conditions of intended use in food and only for exposure through ingestion. ***FEMA does not evaluate flavor ingredients for use in tobacco products including e-cigarettes, other ENDS, or any products that result in exposures other than by ingestion.*** "Therefore, FEMA GRAS status for the use of a flavor ingredient in food does not provide regulatory authority to use the flavor ingredient in e-cigarettes, ENDS devices or other tobacco products in the U.S." [71] Further, FEMA referred to its "long-standing statement[72] that flavor ingredients are not evaluated by the FEMA Expert Panel for safety and GRAS status for any uses other than use in food (https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus- electronic-nicotine-delivery-systems). Therefore, use in ENDS and other tobacco products must have separate safety assessments to assure safety and establish regulatory authority to use flavors in such products."[73]

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[68] Robertson NE, Hunsaker HC, Yamamoto M, Cheung K, Poulin BA, Nguyen TB. E-liquid and aerosol characterization of popular disposable E-cigarettes. ACS omega. 2025 Jul 3;10(27):29615-27.

[69] Kassem, N.O.F.; Strongin, R.M.; Stroup, A.M.; Brinkman, M.C.; El-Hellani, A.; Erythropel, H.C.; Etemadi, A.; Exil, V.; Goniewicz, M.L.; Kassem, N.O.; et al. A Review of the Toxicity of Ingredients in e-Cigarettes, Including Those Ingredients Having the FDA's "Generally Recognized as Safe (GRAS)" Regulatory Status for Use in Food. Nicotine Tob. Res. 2024, 26, 1445–1454.

[70] Kassem, N.O.F.; Strongin, R.M.; Stroup, A.M.; Brinkman, M.C.; El-Hellani, A.; Erythropel, H.C.; Etemadi, A.; Exil, V.; Goniewicz, M.L.; Kassem, N.O.; et al. A Review of the Toxicity of Ingredients in e-Cigarettes, Including Those Ingredients Having the FDA's "Generally Recognized as Safe (GRAS)" Regulatory Status for Use in Food. Nicotine Tob. Res. 2024, 26, 1445–1454.

[71] https://www.regulations.gov/comment/FDA-2012-N-0143-0055

[72] https://www.femaflavor.org/sites/default/files/2018-05/FEMAGRAS%20Ecig%2004302018.pdf

[73] https://www.regulations.gov/comment/FDA-2012-N-0143-0055

The American Thoracic Society similarly noted that GRAS applies to ingested and stated: "We note that much of the tobacco, vaping and e-cigarette industry state that the flavoring ingredients used in tobacco products are GRAS. While it may be true these products are GRAS in the digestive tract, ***these products have not been tested in the respiratory system and their safety in the respiratory tract is unknown.*** This point has been made frequently by representatives of the flavoring industry.[74]

Vanillin and other flavor chemicals inhaled from e-cigarettes including furaneol, benzyl alcohol, ethyl maltol, ethyl vanillin, and corylone are significantly correlated with cytotoxicity. Pulegone and estragole levels are high enough in some e-cigarettes to present a risk for cancer.[75] A 2024 paper showed that the flavoring agent ethyl vanillin used in e-cigarettes can induce energy pathway dysfunction and cellular stress responses in a renal model.[76] Flavor agents such as delta-decalactone found in e-cigarettes may be linked to dysregulation of urinary biochemicals.[77]

Specific evidence contradicts FDA's statement in its draft guidance that "spice" flavors, which would include cinnamon- and vanilla-flavored e-cigarettes, may have lower youth appeal so therefore FDA would require less evidence of adult benefits. It is well established that cinnamaldehyde, an ingredient in cinnamon e-cigarettes, is dangerous for anyone to inhale.[78, 79] In addition to cinnamaldehyde, other flavor aldehydes including benzaldehyde, citral, ethylvanillin, and vanillin react with the e-liquid solvent propylene glycol (PG), are chemically unstable and convert to flavor aldehyde PG acetals that are inhaled by the user with toxicological effects.[80] Toxic aldehydes are produced by e-cigarettes with both flavored and "unflavored" e-liquids, but decomposition of flavoring compounds is the main source of the emitted toxic aldehydes, and thermal decomposition of flavoring compounds during vaping produces levels that exceed occupational safety standards.[81] This is concerning because FDA suggested in its draft guidance that "spice" flavors, which would include cinnamon- and vanilla-flavored e-cigarettes, may have lower youth appeal so therefore FDA would require less evidence of adult benefits. Mechanistic studies of cinnamaldehyde found this chemical impairs respiratory cell immune function,[82] and induces

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[74] https://www.regulations.gov/comment/FDA-2012-N-0143-0041

[75] Omaiye EE, Luo W, McWhirter KJ et al. Electronic cigarette refill fluids sold worldwide: flavor chemical composition, toxicity, and hazard analysis. Chem Res Toxicol 2020;33:2972–87.

[76] Cox AJ, Brown KC, Valentovic MA. The Flavoring Agent Ethyl Vanillin Induces Cellular Stress Responses in HK-2 Cells. Toxics. 2024;12(7):472. Published 2024 Jun 29.

[77] Hsiao Y-C, Matulewicz RS, Sherman SE et al. Untargeted metabolomics to characterize the urinary chemical landscape of E-cigarette users. Chem Res Toxicol 2023;36:630–42.

[78] Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL, Glish GL, Jaspers I. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. Am J Physiol Lung Cell Mol Physiol. 2017 Aug 1;313(2):L278-L292. doi: 10.1152/ajplung.00452.2016. Epub 2017 May 11. PMID: 28495856; PMCID: PMC5582929

[79] Behar RZ, Luo W, Lin SC, et al. Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tob Control*. Nov 2016;25(Suppl 2):ii94-ii102. doi:10.1136/tobaccocontrol-2016-053224

[80] Erythropel HC, Jabba SV, DeWinter TM, et al. Formation of flavorant-propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids. Nicotine Tob Res. 2019;21(9):1248-1258. doi:10.1093/ntr/nty192

[81] Khlystov A, Samburova V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. Environ Sci Technol. 2016;50(23):13080-13085. doi:10.1021/acs.est.6b05145

[82] Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL, Glish GL, Jaspers I. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. Am J Physiol Lung Cell Mol Physiol. 2017 Aug 1;313(2):L278-L292. doi: 10.1152/ajplung.00452.2016. Epub 2017 May 11. PMID: 28495856; PMCID: PMC5582929

mitochondrial dysfunction and cellular stress responses in kidney cells,[83] and produces formaldehyde and acetaldehyde when heated.[84] Studies of aerosolized flavors in e-cigarettes including cinnamaldehyde, vanillin, ethyl vanillin, maltol, and ethyl maltol, found negative effects on cardiac electrophysiology.[85] Another review of 26 studies of the health impact of e-cigarette flavorants found detrimental effects of flavoring agents on the heart, lung, brain and other organs.[86]

A 2025 study of the cardiovascular health effects of flavorants and synthetic cooling agents included in e-cigarettes labeled as "clear" found that the marketing of "clear" products with these additives resulted in health harms including a greater increase in blood pressure and heart rate.[87]

**2. FDA does not explain what specific evidence an applicant must present to demonstrate adult benefits outweigh youth risks**

The Draft Guidance suggests FDA will use a "sliding scale" approach to determine how much evidence an applicant must present to demonstrate that the purported benefit to adults outweighs the risk to youth. This means a PMTA for what FDA considers an especially youth-appealing flavor (like candy, sweets) would be required to demonstrate a greater adult switching benefit than flavors that FDA considers have lower youth appeal. ***However, the guidance does not provide any specifics of how much evidence would be sufficient or what an applicant must show.*** This is concerning because it suggests that a flavor that FDA or an applicant arbitrarily decides has "lower youth appeal" (such as mint, menthol, cooling-flavored, coffee, tea, or spice) may be held to a lower (but not defined) evidentiary standard.

The Draft Guidance explicitly recognizes a tradeoff between youth and adult e-cigarette use, something FDA has recognized for years. However, despite this implicit recognition, FDA has never made this tradeoff explicit. ***Proper implementation of the proposed guidance requires that FDA finally make this tradeoff explicit by: (1) providing its own estimate of how many youth are likely to become addicted to e-cigarettes for each adult who successfully uses e-cigarettes to stop smoking cigarettes; and (2) requiring that applicants for PMTAs for flavored e-cigarettes provide specific estimates for the products for which they are seeking authorization.***

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[83] Cox A, Brown KC, Bender C, Valentovic MA. The e-liquid flavoring cinnamaldehyde induces cellular stress responses in human proximal tubule (HK-2) kidney cells. Biomed Pharmacother. 2024 Jun;175:116666. doi:10.1016/j.biopha.2024.116666. Epub 2024 Apr 27. PMID: 38677246; PMCID:PMC11293278.

[84] Kuehl PJ, McDonald JD, Weber DT, Khlystov A, Nystoriak MA, Conklin DJ. Composition of aerosols from thermal degradation of flavors used in ENDS and tobacco products. Inhal Toxicol. 2022;34(11-12):319-328. doi:10.1080/08958378.2022.2103602. Epub 2022 Aug 1. PMID: 35913821; PMCID:PMC9830633.

[85] Abou-Assali O, Chidipi B, Chang M, Reiser M, Asswaytte R, Zhang Y, Long Duong VB, Szekeres C, Calcul L, Noujaim SF. Oxidative stress mediates cardiac electrophysiological injury in inhalation exposure to flavored vaping products. Heart Rhythm. 2026 Mar;23(3):751-765. doi: 10.1016/j.hrthm.2025.09.006. Epub 2025 Sep 8. PMID: 40930480.

[86] Sachdeva J, Karunananthan A, Shi J, Dai W, Kleinman MT, Herman D, Kloner RA. Flavoring Agents in E-cigarette Liquids: A Comprehensive Analysis of Multiple Health Risks. Cureus. 2023 Nov 18;15(11):e48995. doi: 10.7759/cureus.48995. PMID: 38111420; PMCID: PMC10726647.

[87] Minetti ET, Erythropel HC, Keith R, Davis DR, Zimmerman JB, Krishnan-Sarin S, Hamburg NM. Cardiovascular Health Effects and Synthetic Cooling Agents in E-Cigarettes Labeled as "Clear" Marketed in Massachusetts After the Tobacco Product Flavoring Ban. Journal of the American Heart Association. 2025 Aug 19;14(16):e036106.

For example, a paper published in 2018 by Soneji et al. when the youth e-cigarette epidemic was beginning to explode used a model to provide an estimate of this tradeoff.[88] The model estimated that the 2,070 additional long-term quitters would avoid 3,000 years of life lost (95% CI: -351,000 to 325,000). The model also estimated that an additional 168,000 never-cigarette smoking adolescents and young adults in 2014 (95% CI: 114,000 to 229,000) who had ever used e-cigarettes would initiate cigarette smoking in 2015 and eventually become daily cigarette smokers at age 35–39, compared to those who had never used e-cigarettes, and would lose 1,510,000 years of life (95% CI: 1,030,000 to 2,060,000). Thus, considering all population subgroups, the model estimated that e-cigarette use in 2014 would lead to 1,507,000 years of life lost (95% CI: 920,000 to 2,160,000) under the discredited assumption of a 95% relative harm reduction of e-cigarette use compared to cigarette smoking.[89]

***In other words, for every adult smoker who quits, over 80 kids will have become daily smokers.***

Clearly, this tradeoff does not promote public health, and FDA should not authorize any e-cigarette that could not demonstrate a better tradeoff between purported adult benefits and youth harms. What is more, even the unacceptable tradeoff described in this paper is an unrealistically optimistic estimate because:

- It assumes e-cigarettes are 95% safer than cigarettes, a claim published in April 2014[90] that was based on a flawed analysis and has been long discredited.[91, 92] Data based on actual associations of e-cigarettes and disease suggest that sole e-cigarette use is only slightly below cigs in terms of risk, maybe 10-20%.[93, 94]

[88] Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms of e-cigarette use in the United States. PLoS One. 2018;13(3):e0193328. Published 2018 Mar 14. doi:10.1371/journal.pone.0193328

[89] Eissenberg T, Bhatnagar A, Chapman S, Jordt SE, Shihadeh A, Soule EK. Invalidity of an Oft-Cited Estimate of the Relative Harms of Electronic Cigarettes. Am J Public Health. 2020 Feb;110(2):161-162. doi: 10.2105/AJPH.2019.305424. PMID: 31913680; PMCID: PMC6951374.

[90] Nutt DJ, Phillips LD, Balfour D et al. Estimating the harms of nicotine-containing products using the MCDA approach. Eur Addict Res. 2014;20(5):218–225. doi: 10.1159/000360220.

[91] Eissenberg, T., Bhatnagar, A., Chapman, S., Jordt, S. E., Shihadeh, A., & Soule, E. K. (2020). Invalidity of an Oft-Cited Estimate of the Relative Harms of Electronic Cigarettes. American journal of public health, 110(2), 161–162. https://doi.org/10.2105/AJPH.2019.305424

[92] Public Health Law Center, Dispelling the Myth of the "Safe" E-cigarette. September 21, 2015. https://www.publichealthlawcenter.org/commentary/150921/dispelling-myth-safe-e-cigarette

[93] Glantz SA, Oliveira da Silva AL. Comparison of e-Cigarette and Cigarette Use and Dual Use Associations With Disease: Updated Systematic Review and Meta-Analysis. Public Health Rep. 2026 Feb 17:333549251403349. doi: 10.1177/00333549251403349. Epub ahead of print. PMID: 41702869; PMCID: PMC12916339

[94] Glantz SA, Nguyen N, Oliveira da Silva AL. Population-based disease odds for e-cigarettes and dual use versus cigarettes. NEJM evidence. 2024 Feb 27;3(3):EVIDoa2300229.

- The estimate does not account for dual use, which is more dangerous than just smoking.[95, 96, 97]
- The estimate of the association between e-cigarette use and cessation is based on an early randomized controlled trial (RCT) of e-cigarettes for cessation,[98] and we now know that RCTs conducted in clinical settings with cessation counseling result in higher estimates of efficacy than real world studies and do not reflect real world effectiveness.[99] Rather, in population-based observational studies in real-world settings, e-cigarette use as an unsupervised consumer product has not be associated with smoking cessation among adults.[100, 101]

Based on the high-quality, real-world data that is now available, FDA needs to update the Soneji et al model[102] and establish a benchmark for measuring the tradeoff between benefits vs harms before judging future applications.

FDA states at page 17 of the Draft Guidance, "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." This call for a "risk-proportionate" assessment requires the kind of specific quantitative assessment we are calling for. In addition, FDA's assessment must be conducted using an externally validated model, epitomized by the Soneji model, not an ad hoc model developed by the applicant.

- **Flavored ENDS do not promote smoking cessation**

A key FDA assumption underlying the Draft Guidance is that flavored ENDS help adult smokers quit, and this factor should be weighed against the "substantial risk to youth" that flavored ENDS products pose. However, this assumption is invalidated by evidence that, as used in the real world, e-cigarettes do *not* increase smoking cessation. There is growing evidence that real world e-

[95] Hamoud J, Hanewinkel R, Andreas S, Ammous O, Saalfrank M, Sussman S, Unger JB, Pisinger C, Mathes T. A systematic review investigating the impact of dual use of e-cigarettes and conventional cigarettes on smoking cessation. ERJ Open Res. 2025 May 6;11(3):00902-2024. doi: 10.1183/23120541.00902-2024. PMID: 40337339; PMCID: PMC12053992.
[96] Glantz SA, Oliveira da Silva AL. Comparison of e-Cigarette and Cigarette Use and Dual Use Associations With Disease: Updated Systematic Review and Meta-Analysis. Public Health Rep. 2026 Feb 17:333549251403349. doi: 10.1177/00333549251403349. Epub ahead of print. PMID: 41702869; PMCID: PMC12916339
[97] Glantz SA, Nguyen N, Oliveira da Silva AL. Population-based disease odds for e-cigarettes and dual use versus cigarettes. NEJM evidence. 2024 Feb 27;3(3):EVIDoa2300229.
[98] Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: a randomised controlled trial. The Lancet. 2013 Nov 16;382(9905):1629-37.
[99] Arora M, Kulkarni MM, Ghosal S, et al. E-Cigarettes and the Nicotine Epidemic: Statement From the International Pediatric Association. Pediatrics. 2025;156(5):e2025072337. doi:10.1542/peds.2025-072337
[100] Wang RJ, Bhadriraju S, Glantz SA. E-cigarette use and adult cigarette smoking cessation: a meta-analysis. Am J Public Health. 2021;111(2):230–246. PubMed doi: 10.2105/AJPH.2020.305999
[101] Hedman L, Galanti MR, Ryk L, Gilljam H, Adermark L. Electronic cigarette use and smoking cessation in cohort studies and randomized trials: a systematic review and meta-analysis. Tob Prev Cessat. 2021;7:62. PubMed doi: 10.18332/tpc/142320
[102] Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms of e-cigarette use in the United States. PLoS One. 2018;13(3):e0193328. Published 2018 Mar 14. doi:10.1371/journal.pone.0193328

cigarette use is not associated with stopping smoking in the real world, in contrast to the results found in randomized controlled trials of e-cigarettes as a smoking cessation treatment.[103, 104]

In particular, claims made in PMTAs about the purported benefits of flavored e-cigarettes for adults are not supported by growing scientific evidence that flavored e-cigarettes do not increase smoking cessation among adult smokers. A 2024 study that classified e-cigarette flavors into tobacco only, menthol/mint only, other non-tobacco and non-menthol/mint flavors, and combinations of flavors, found no evidence that use of menthol/mint only or other flavors—including fruit, candy/dessert, and other sweet flavors popular among youth (vs. tobacco only)—is associated with stopping smoking. Moreover, use of multiple flavors is associated with a lower probability of stopping both smoking and vaping.[105]

Analyses using more granular flavor categories—tobacco only, menthol/mint only, fruit only, candy/dessert/other sweet only, other flavors only (excluding the preceding categories), and combination flavors (any mix of these)—further reinforce these findings. Across all categories, no specific flavor is associated with increased smoking cessation. Moreover, use of menthol/mint only, candy/dessert/other sweet only, and combination flavors is associated with a lower likelihood of stopping vaping.[106] These patterns are consistent with other studies that similarly find no evidence that flavored ENDS products promote cessation. These findings underscore the need for careful consideration when evaluating purported adult benefits.[107, 108, 109, 110, 111]

### 3. FDA should prohibit novel device access technologies that maximize addiction potential and appeal to youth and do not prevent or deter youth access

There is no evidence that "novel device" electronic age-verification technologies via Bluetooth connections between ENDS devices and the internet work. At the same time, this technology poses

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[103] Arora M, Kulkarni MM, Ghosal S, Sathyan A, Gupta M, Verma S, Farmer M, Hadjipanayis A, Klein JD, Winickoff J, Thacker N, Glantz SA. E-Cigarettes and the Nicotine Epidemic: Statement From the International Pediatric Association. Pediatrics. 2025 Nov 1;156(5):e2025072337. doi: 10.1542/peds.2025-072337. PMID: 41067726.

[104] Hedman L, Galanti MR, Ryk L, Gilljam H, Adermark L. Electronic cigarette use and smoking cessation in cohort studies and randomized trials: a systematic review and meta-analysis. Tob Prev Cessat. 2021;7:62. PubMed doi: 10.18332/tpc/142320

[105] Wang Y, Sung HY, Glantz SA, Max W. The Association Between E-Cigarette Characteristics and Stopping Smoking and Vaping Among Adult Dual Users of Cigarettes and E-Cigarettes. eScholarship, University of California; 2024. https://escholarship.org/uc/item/0js1n2t2

[106] Wang Y, Sung HY, Glantz SA, Max W. The Association Between E-Cigarette Characteristics and Stopping Smoking and Vaping Among Adult Dual Users of Cigarettes and E-Cigarettes. eScholarship, University of California; 2024. https://escholarship.org/uc/item/0js1n2t2

[107] Bold K, O'Malley S, Krishnan-Sarin S, Morean M. 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.* 2023;25(5):954-961.

[108] Harlow AF, Fetterman JL, Ross CS, et al. Association of device type, flavours and vaping behaviour with tobacco product transitions among adult electronic cigarette users in the USA. *Tob Control.* 2022;31(e1):e10-e17.

[109] Lindson N, Butler AR, Liber A, et al. An exploration of flavours in studies of e-cigarettes for smoking cessation: secondary analyses of a systematic review with meta-analyses. *Addiction.* 2023;118(4):634-645.

[110] Meernik C, Baker HM, Kowitt SD, Ranney LM, Goldstein AO. Impact of non-menthol flavours in e-cigarettes on perceptions and use: an updated systematic review. *BMJ open.* 2019;9(10):e031598.

[111] Liber AC, Knoll M, Cadham CJ, et al. The role of flavored electronic nicotine delivery systems in smoking cessation: A systematic review. *Drug and alcohol dependence reports.* 2023;7:100143.

serious risks of creating an opportunity for tobacco companies to personalize device parameters to increase addiction risk. Rather than promoting such technologies, FDA should prohibit any two-way communication with ENDS devices.

The FDA has not presented any evidence that such technologies work, the companies have not presented any evidence that they work, and there is no evidence in the literature that they work. What we do know is that kids find ways to evade age-gating technologies, and this fact has been highlighted in recent weeks in the context of social media companies trying to prevent under-aged kids from accessing their social media accounts. Age verification technologies are overcome by kids who use both sophisticated and simple strategies including using VPNs and AI-generated deepfakes and selfies.[112] A February 2026 investigation into physical cosmetic attacks on AI age estimation systems found that teenagers can easily fool AI technologies using simple, household-accessible cosmetic changes, such as employing a synthetic beard, grey hair, makeup, and simulated wrinkles can fool AI age estimators and cause them to classify minors as adults.[113] Also, facial recognition technology is known to be less accurate for women and people of color.[114]

***Of particular concern, age-verifying software often collects private information about youth that may be used for targeting marketing to kids and/or dynamically adjusting devices based on puffing topography to make the products even more addictive.*** For example, In May 2019, Juul's then chief executive Kevin Burns said that Juul would soon be testing new Bluetooth technology that would let users monitor on their smartphones how many puffs they are taking and will allow Juul to have "a much more intimate relationship" with customers and help "coach" them to manage their nicotine intake.[115] In addition, in a July 19, 2023, announcement about submitting its PMTA submission, Juul stated that its age-verification technology included not only "device-locking" to restrict underage access but also "real-time product information and usage insights…"[116] Despite Juul's announcement that suggests its Juul devices use device access restrictions, FDA stated, surprisingly, in its Technical Project Lead review of the PMTA that the "PMTAs do not propose device access restrictions."[117]

Bluetooth-enabled or other technologies have the potential to allow manufacturers to customize the dose, speed of delivery, and frequency of use of nicotine to maximize the additive potential for individual users.[118] For example, some devices (e.g., IQOS) have features that allow

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[112] https://restofworld.org/2026/social-media-age-verification-tools/

[113] Shen X, Duong T, An X, Zhao Z, Hu Z, Hu H, Wang Z, Guo F, Ren S. Can a Teenager Fool an AI? Evaluating Low-Cost Cosmetic Attacks on Age Estimation Systems. arXiv preprint arXiv:2602.19539. https://arxiv.org/abs/2602.19539 2026 Feb 23.

[114] Evershed N and Nicholas J. Social media ban trial data reveals racial bias in age checking software: just how inaccurate is it? 18 Sept 2025. https://www.theguardian.com/news/2025/sep/19/how-accurate-are-age-checks-for-australias-under-16s-social-media-ban-what-trial-data-reveals

[115] Gray A and Edgecliffe-Johnson, Financial Times, Juul tests puff-tracking app for growing army of vapers, May 10, 2019. https://www.ft.com/content/07eb3e20-72bf-11e9-bbfb-5c68069fbd15

[116] Juul Labs. A Technological Solution for Public-Health Problems: Juul Labs Submits the First PMTA for its Next-Generation Platform to Improve Adult-Smoker Switching and Restrict Underage Access. July 19, 2023. https://www.juullabs.com/next-generation-platform-pmta/

[117] US Food and Drug Administration. Technical Project Lead (TPL) Review of PMTAs for Juul. July 15, 2025. https://www.accessdata.fda.gov/static/searchtobacco/7-10-25/Juul-TPL-Rev-Multiple-STNs.pdf

[118] Lempert LK, Glantz SA, Heated tobacco product regulation under US law and the FCTC. Tob Control. 2018 Nov;27(suppl1): s118-s125. DOI 10.1136/tobaccocontrol-2018-054560.

the device to communicate with the manufacturer that would automatically remind consumers to use the device and to reorder nicotine liquids or pods. This technology featuring two-way communication raises significant privacy as well as health concerns. It has the potential to allow Juul and other e-cigarette and ENDS companies to manipulate nicotine delivery in a way that would increase abuse potential and maximize nicotine addiction (while at the same time also maximizing product sales). FDA should prohibit these kinds of technologies and two-way communications in e-cigarettes and other ENDS products such as heated tobacco products.

FDA's April 30, 2019, December 7, 2020, and January 26, 2023 granting of marketing orders[119] permitting Philip Morris International (PMI) to market its IQOS heated tobacco product in the United States and subsequent authorization on July 7, 2020 and renewal of that authorization on April 17, 2026[120] permitting Philip Morris to market IQOS as a modified risk tobacco are disconcerting because the IQOS devices contain Bluetooth technology that allows PMI to monitor consumers' puffing behavior and remind them to purchase more nicotine HeatSticks.[121] This kind of technology leaves the door wide open to create and maintain nicotine addiction in youth.

Also concerning is the use of biometric age-verification technology in e-cigarette cartridges. A March 2026 article in *Wired* discusses why this kind of technology is unlikely to solve the problems they are designed to address. Rather, age-verification technologies "tend to rely on collecting personal information from users in a way that can make privacy a problem, or they use chips on devices that store info and have the potential to be hacked." The technology designers claim that as a result of a process that translates ID information into anonymized tokens, the manufacturer does not communicate consumer personal private information. However, once a person clears the age-verification process and the e-cigarette is turned on, that person can share their e-cigarette with anyone nearby without verifying their age.[122] In addition to raising serious privacy concerns, collecting personal information and allowing two-way communication with the manufacturer provides the manufacturer with an opportunity to monitor smoking topography and adjust the device to maximize addiction. Even if privacy issues could be resolved, the opportunity to tune the device to maximize addictive potential for that particular user remains.

***This capability poses significant risks of addiction for adults, as well as youth, and makes it less likely that the user will cease using nicotine products.***

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[119] US Food and Drug Administration. Premarket Tobacco Product Marketing Granted Orders, current as of 03/28/2024. https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders

[120] US Food and Drug Administration. Modified Risk Granted Orders, current as of 04/17/2026. https://www.fda.gov/tobacco-products/advertising-and-promotion/modified-risk-granted-orders

[121] Lassetter T, Wilson D, et al. Reuters Investigates, Philip Morris device knows a lot about your smoking habit, May 15, 2018. https://www.reuters.com/investigates/special-report/tobacco-iqos-device/

[122] Ashworth B, "Your Vape Wants to Know How Old You Are." Wired, March 28, 2026. https://www.wired.com/story/your-vape-wants-to-know-how-old-you-are/

Moreover, encouraging the integration of e-cigarette devices facilitates the development of "smart vapes" that include games, music, and other youth-appealing features.[123] Further, while most youth believe that cigarettes will kill you, they consider their omnipresent phones essential and harmless, so it is plausible that such perceptions would extend to devices such as e-cigarettes and other ENDS connected to their phones (such as e-cigarettes).

For these reasons, FDA should not permit such "novel device technologies." Instead, FDA should prohibit any Bluetooth or other two-way communication between an e-cigarette (or any other ENDS system) and external devices or parties that might externally control device characteristics and affect nicotine delivery.

**Conclusion**

As FDA acknowledged in its Draft Guidance on the considerations related to youth risk of flavored electronic nicotine delivery systems (ENDS) premarket applications, there is overwhelming scientific evidence that flavored e-cigarettes played a major role in increasing youth initiation, continued use, and addiction to e-cigarettes. However, FDA incorrectly downplays the impact on youth of *all* flavored nicotine products, including menthol and mint flavored products, e-cigarettes that are not labeled as "menthol" or "mint" but containing synthetic cooling agents such as WS-23 and/or WS-3, cinnamon and other spicy flavors, and flavors perceived to be "adult" such as coffee and tea flavors.

FDA's Draft Guidance is flawed because it fails to adequately address the following issues:

1. All flavored and so-called "unflavored" or "tobacco-flavored" ENDS products pose important risks to youth and adults;
2. There is insufficient evidence that certain flavored tobacco products demonstrate adult benefits that outweigh youth risks, and the FDA has not explained what additional evidence would demonstrate purported benefits; and
3. FDA should not rely on novel device access technologies to prevent or deter youth access to flavored ENDS products.

Therefore, FDA's Draft Guidance is not appropriate for the protection of public health because it does not protect youth or adults and does not present an accurate estimate of the tradeoff between increased youth e-cigarette use vs theoretical benefits to adult smokers. ***FDA should not finalize this Draft Guidance.***

[123] Wong M, Talbot P. Pac-Man on a vape: electronic cigarettes that target youth as handheld multimedia and gaming devices. Tob Control. 2025 Dec 10;34(6):849-851. doi: 10.1136/tc-2024-058794. PMID: 38879183; PMCID: PMC11646284.