



- the relative youth appeal of various flavors can change over time, including in response to government action.
3. FDA’s categorization of certain flavors, particularly menthol and mint, as “lower risk” to youth may lead to the improper authorization of ENDS products that will cause substantial harm to public health.
  4. The Draft Guidance does not adequately consider the likelihood of sustained dual use of combusted cigarettes and e-cigarettes by adults, and does not at all consider the health effects of that sustained dual use.
  5. In categorizing certain flavors as “lower risk,” FDA has failed to account for the toxicity of certain ENDS flavors.
  6. We support FDA’s view that restrictions on advertising and promotion and sales access restrictions cannot sufficiently protect against youth usage of non-tobacco flavored ENDS products.
  7. We support FDA’s view that device access restrictions (DAR) built into ENDS devices may not be sufficient on their own to protect against youth use of products with flavors that FDA regards as particularly appealing to youth. However, we believe that DAR are also unlikely to provide sufficient protection against youth use of *any* non-tobacco flavored ENDS, including menthol, mint, and any other flavored products FDA considers “lower risk.” Marketing order applicants relying on DAR to mitigate youth risk from non-tobacco flavored products must provide robust scientific evidence demonstrating their effectiveness in preventing youth access.
  8. The Draft Guidance is based, at least in part, on FDA’s general finding that ENDS products with flavors other than tobacco may facilitate switching away from cigarettes or reducing cigarette consumption among adults who would otherwise continue smoking. However, there is no scientific consensus on such evidence and we do not believe the Draft Guidance presents sufficient evidence of such beneficial effects to justify providing an easier pathway to marketing authorization for certain flavors.

## **I. Statutory Background and FDA Premarket Review of ENDS**

Under the Tobacco Control Act, no “new” tobacco product (those not marketed before February 15, 2007) can be marketed without authorization from the FDA. In the case of ENDS products, such authorization is possible through a premarket review process in which the applicant company must show, among other things, that the marketing of the product would be “appropriate for the protection of the public health” (APPH).<sup>2</sup> In applying the APPH standard, FDA must consider “the risks and benefits to the population as a whole,”<sup>3</sup> taking into account both the “increased or decreased likelihood that existing users of tobacco products will stop

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<sup>2</sup> 21 U.S.C. §387j(c)(2)(A).

<sup>3</sup> 21 U.S.C. §387j(c)(4).

using such products” and the “increased or decreased likelihood that those who do not use tobacco products will start using such products.”<sup>4</sup>

As described in the Draft Guidance, for an ENDS product to be APPH, an applicant company has the burden to demonstrate “that the benefits, including those to adults who use combusted cigarettes, outweigh the risk, including those to youth, resulting in a net benefit to public health.” Draft Guidance at 7. In weighing the risks and benefits of ENDS products, with particular attention to the risk of initiation among youth—since “youth are considered a vulnerable population,” *id.*—FDA has implemented a consistent methodology that distinguishes between tobacco-flavored products and products with any other flavor. That methodology is reflected in the Technical Project Lead (TPL) Reviews that explain the rationale for FDA’s repeated denial of marketing orders for a wide variety of flavored products. It is based upon FDA’s finding that “flavored ENDS products pose a substantial risk to youth, and they pose a greater risk to youth than tobacco-flavored ENDS.” Draft Guidance at 4. “Flavors facilitate initiation among youth and promote established regular ENDS use.” *Id.*

FDA also found that “[a]lthough 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.” *Id.* “[A]n 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.” *Id.* In *FDA v. Wages and White Lion Investments, L.L.C.*, the Supreme Court unanimously determined that a “comparative efficacy” requirement, comparing tobacco-flavored ENDS to all other flavors, was consistent with the TCA. 604 U.S. 542, 578 (2025) (“[T]he TCA expressly contemplates comparisons of different tobacco products.”). In *Wages*, the Supreme Court also held that the denial of marketing authorization for failure to meet the comparative efficacy requirement was entirely consistent with industry guidance the agency had issued previously. *Id.* at 578-582.

FDA also has addressed the kind of scientific evidence that is required to establish the comparative efficacy of flavored products vs. tobacco-flavored products. In the Model TPL Review FDA has published on its website,<sup>5</sup> which is representative of the TPL Reviews accompanying the denial of marketing authorization for scores of flavored ENDS products, FDA indicated that “only the strongest types of evidence will be sufficiently reliable and robust – most likely product specific evidence from a randomized controlled trial (RCT) or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis.” Model TPL Review (2021), at 3. In its *Wages* ruling, the Supreme Court found that requiring this level of evidence was within the FDA’s “broad discretion to decide what sort of scientific evidence an applicant was required to submit” under the TCA. *Wages*, 604 U.S. at 571. The Court also held that denying marketing authorization for failure to provide such evidence was consistent with the previous premarket application guidance issued by FDA. *Id.* at 575.

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<sup>4</sup> 21 U.S.C. §387j(c)(4) (A) and (B).

<sup>5</sup> <https://www.fda.gov/media/152504/download>

In applying this methodology to flavored ENDS products, FDA repeatedly has issued Marketing Denial Orders (MDOs) finding that applicants failed to supply sufficiently reliable and robust scientific evidence showing a benefit to adults who smoke from flavors exceeding that provided by tobacco-flavored products and sufficient to outweigh the risk of initiation for young people. Although there was a period during which FDA regarded menthol-flavored ENDS products as raising “unique considerations,”<sup>6</sup> the Draft Guidance states that “[i]n 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.” Draft Guidance at 14.

As of the issuance of the Draft Guidance, FDA had authorized only two flavored ENDS brands, NJOY menthol and JUUL menthol. In both cases, FDA found that menthol products, like other flavors, constitute a “known and substantial risk to youth,” but authorized the marketing of the products after determining that in FDA’s view the applicant had supplied sufficiently reliable and robust evidence to establish the comparative efficacy of the menthol products over tobacco-flavored products in providing a benefit to adults who smoke in transitioning off combustible cigarettes or significantly reducing their cigarettes smoked.<sup>7</sup> The Draft Guidance summarizes FDA’s approach to flavored ENDS products up to the present time: “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.” Draft Guidance at 6. Thus, FDA acknowledges that, to this point, its evaluation of flavored ENDS products under the statutory public health standard has been based on the agency’s conclusion that *all flavors other than tobacco* pose a substantial risk to youth such that robust and reliable evidence is required to demonstrate that the flavor provides a benefit to adults who smoke beyond that provided by a comparable tobacco-flavored product.

## **II. The Draft Guidance: Proposed Changes in FDA’s Application of the Public Health Standard to Flavored ENDS Products**

### **A. The Draft Guidance Does Not and Should Not Weaken the Requirement that Marketing Authorization of a Flavored ENDS Product Requires Robust and Reliable Evidence of an Added Benefit to Adults Who Smoke Beyond that Conferred by Tobacco-Flavored Products and Sufficient to Outweigh the Risks to Non-users**

Before turning to the changes in premarket review of flavored ENDS products indicated by the Draft Guidance, it is important to recognize that the Draft Guidance is not proposing to

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<sup>6</sup> FDA News Release, FDA Denies Marketing Applications for About 55,000 Flavored ECigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health (Aug. 26, 2021), <https://www.fda.gov/news-events/press-announcements/fda-denies-marketingapplications-about-55000-flavored-e-cigarette-products-failing-provide-evidence>.

<sup>7</sup> See TPL for NJOY ACE menthol, at 34 (“... menthol-flavored ENDS pose a known and substantial risk to youth.”); TPL for NJOY ACE menthol, at 7 (NJOY study showed “robust and reliable evidence” that the menthol-flavored ACE product was associated with statistically significant and substantially higher rates of complete switching than the tobacco-flavored NJOY ACE ENDS.); TPL for JUUL menthol, at 43 (“... menthol-flavored ENDS pose a known and substantial risk to youth.”); TPL for JUUL menthol, at 36 (JUUL studies showed menthol products to be “moderately beneficial” to adults when compared to tobacco-flavored products).

alter the requirement that a premarket application include robust and reliable evidence that the flavored product confers an added benefit, relative to tobacco-flavored ENDS, in helping adults who smoke to stop smoking. Thus, according to the Draft Guidance, the approach unanimously affirmed by the Supreme Court in the *Wages* case “remains unchanged.” *Id.* at 12. We strongly support FDA’s continued requirement that applicants support their marketing applications for flavored ENDS products with the strongest kinds of scientific evidence, including RCTs, longitudinal cohort studies or similarly robust and reliable evidence showing a benefit to adults who smoke beyond that of a tobacco-flavored product.

## **B. The Draft Guidance Fails to Account for the Variability of Youth Flavor Preferences for ENDS Products Over Time**

The Draft Guidance indicates that FDA, for the first time, is proposing to distinguish between non-tobacco flavors in applying the public health standard to ENDS products and determining the level of added adult benefit that must be conferred by a flavored product.<sup>8</sup> “While, based on FDA’s experience to date, all flavoring in ENDS presents 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.” *Id.* Thus, “[s]ome flavors may be shown to have lower youth appeal . . . and may be APPH if the added benefit they provide compared to tobacco-flavored products is relatively small.” *Id.*

At various points in the Draft Guidance, FDA identifies examples of these “lower risk” flavors; they include coffees, teas and spices (*id.* at 12), and also menthol, mint and wintergreen (*id.* at 11 and 14). According to the Draft Guidance, “[w]here 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.” *Id.*

It is apparent that the Draft Guidance is determining the category of “lower risk” ENDS products by relying on youth flavor preferences at a specific point in time. In the Draft Guidance, FDA determined flavors like mint, menthol and spice to be of lower risk to youth than flavors like fruit and candy, based on data from the 2024 National Youth Tobacco Survey (NYTS). The Draft Guidance (at 14) notes that, “[i]n 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.” Notably, FDA omitted prevalence data for mint from its assessment. Mint-flavored products were used by 25.1% of youth e-cigarette users in 2024.<sup>9</sup>

Although the Draft Guidance relies on survey evidence to measure relative appeal of various flavors to youth, it does recognize 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, with the low prevalence of certain flavors perhaps “a function of other factors such as the way the survey was

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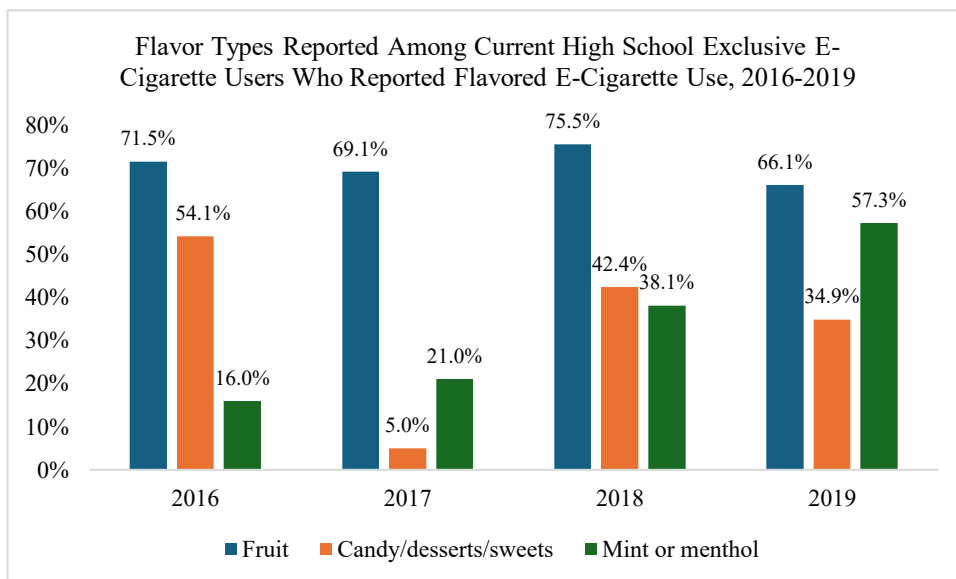
<sup>8</sup> Notably, the Draft Guidance also does not – as some other comments submitted to FDA allege – ban all flavored ENDS.

<sup>9</sup> Park-Lee, E., et al. (2024). “E-Cigarette and Nicotine Pouch Use Among Middle and High School Students — United States, 2024,” *MMWR* 73(35):774-778, <https://www.cdc.gov/mmwr/volumes/73/wr/pdfs/mm7335a3-H.pdf>.

conducted or more limited distribution of the product.” Draft Guidance at 13. The Draft Guidance also appropriately notes that the burden remains with the applicant to demonstrate that marketing the product will be APH. *Id.*

FDA’s assessment of the relative risks of each flavor category in the Draft Guidance does not appear to recognize that youth preferences for certain flavors have shifted over time, including in response to FDA regulatory actions. Youth preferences are likely to continue to shift if the availability of flavored e-cigarettes changes in response to enhanced enforcement against unauthorized flavored products or authorization of other flavored products. It is clear, however, that flavored e-cigarettes in all varieties continue to drive youth e-cigarette use, with nearly 90% of middle and high school e-cigarette users reporting that they use a flavored product.<sup>10</sup>

Mint- and menthol-flavored ENDS present a particularly significant illustration of shifting youth flavor preferences. With these flavors, youth preference has shifted over time in response to product availability from both changes in industry behavior as well as regulatory actions, most notably JUUL’s discontinuation of certain flavors and the FDA’s 2020 enforcement guidance that prioritized enforcement against cartridge-based ENDS in flavors other than menthol and tobacco. As shown below, use of mint and menthol flavors increased substantially between 2016 and 2019.<sup>11</sup>



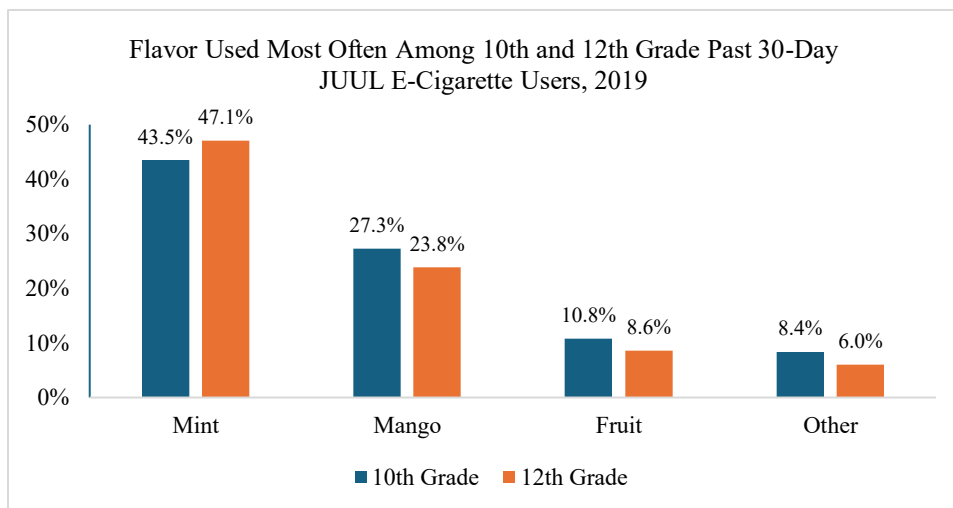
In 2018, JUUL pulled its fruit- and sweet-flavored products from retail stores and subsequently ended online sales of them in 2019. As the top-selling and most popular brand among youth ENDS users at the time, this market shift led to increases in the popularity of its remaining flavored products: mint and menthol. Use of mint- and menthol-flavored ENDS among high school exclusive e-cigarette users increased by 50% from 2018 to 2019 (from 38.1% to 57.3%), while use of fruit flavors fell.<sup>12</sup> This surge in use of mint- and menthol-flavored e-

<sup>10</sup> Food and Drug Administration. 2025 National Youth Tobacco Survey, March 4, 2026; <https://www.fda.gov/tobacco-products/youth-and-tobacco/national-youth-tobacco-survey-nyts>. Accessed: March 13, 2026.

<sup>11</sup> Cullen, K. A., et al. (2019). “E-cigarette Use Among Youth in the United States, 2019.” *JAMA* 2019; 322(21), 2095-2103.

<sup>12</sup> *Id.* See Supplemental Table 4.

cigarettes occurred during the height of the youth e-cigarette epidemic, when nearly 5.4 million youth were using e-cigarettes, including 27.5% of high school students.<sup>13</sup> As shown below, the 2019 Monitoring the Future Study also found that among 10<sup>th</sup> and 12<sup>th</sup> grade JUUL users, mint had become the most popular flavor, used by 43.5% of 10<sup>th</sup> grade JUUL users and 47.1% of 12<sup>th</sup> grade JUUL users.<sup>14</sup>



Flavored e-cigarette preferences among youth have continued to evolve in recent years, following the FDA’s 2020 enforcement guidance that prioritized enforcement against cartridge-based products but exempted menthol products and disposables in all flavors. This led to a sharp increase in the popularity of menthol-flavored cartridge-based e-cigarettes and disposable e-cigarettes, which are available in an endless variety of flavors. In 2020, 55.8% of high school flavored e-cigarette users reported using mint-flavored products, and 37% reported using menthol-flavored products.<sup>15</sup> The CDC and FDA that year reported that, “[a]lthough use of fruit flavored e-cigarettes was common among users in 2020, findings also suggest prominent menthol e-cigarette use, including among nearly one half of flavored prefilled pod or cartridge users and one quarter of flavored disposable product users.”<sup>16</sup>

Like shifts in youth e-cigarette flavor preference, there were also rapid shifts in device type preferences among youth, further demonstrating the mutable preferences of youth e-cigarette users. From 2019 to 2020, disposable e-cigarette use increased approximately 1,000% among high school e-cigarette users and approximately 400% among middle school e-cigarette users,<sup>17</sup> reflecting FDA’s exemption of disposables from its 2020 enforcement priorities. From 2020 to 2021, use of mint-flavored e-cigarettes among high school flavored e-cigarette users fell from 55.8% to 30.5%, following JUUL’s removal of its mint-flavored product and FDA’s

<sup>13</sup> Wang TW, et al. (2019). “Tobacco Product Use and Associated Factors Among Middle and High School Students —United States, 2019.” *MMWR*;68(No. SS-12):1–22. <https://www.cdc.gov/mmwr/volumes/68/ss/ss6812a1.htm>.

<sup>14</sup> Leventhal AM, et al. (2020). “Flavors of e-Cigarettes Used by Youths in the United States.” *JAMA*; 322(21):2132–2134.

<sup>15</sup> Wang, T.W., et al. (2020). “E-cigarette Use Among Middle and High School Students — United States, 2020,” *MMWR* 69(37):1310–1312. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e1.htm>.

<sup>16</sup> *Id.*

<sup>17</sup> *Id.*

February 2020 Enforcement guidance.<sup>18</sup> Despite declines in popularity in recent years, mint- and menthol-flavored e-cigarettes have continued to be among the top four flavor categories used by youth. Indeed, the week before the guidance was issued, FDA published the 2025 NYTS dataset, which shows that use of candy/desserts/other sweet flavors (29.2%, 95% CI [26.2%, 32.4%]) and mint flavors (27.4%, 95% CI [23.7%, 31.4%]) among middle and high school e-cigarette users are not significantly different.<sup>19</sup>

Youth shifts in the popularity of mint- and menthol-flavored e-cigarettes are also mirrored by e-cigarette sales data trends. For example, JUUL's removal of mint-flavored products was followed by a 59.4% increase in the market share of menthol-flavored e-cigarettes over four weeks, while the FDA's 2020 guidance was followed by a 42.7% increase in the market share of menthol-flavored e-cigarettes over four weeks and a 104.9% increase over eight weeks.<sup>20</sup> Examining a longer period, another study found that from September 2014 to August 2019, the percentage of prefilled cartridge e-cigarette sales that were mint increased from <0.1% to 47.6%. This was followed by a decline from August 2019 to May 2020 in the proportion of prefilled cartridge sales that were mint from 47.6% to 0.3%, coinciding with an increase in the proportion that were menthol from 10.7% to 61.8%.<sup>21</sup> Similar to the youth data, sales data demonstrate that flavor preferences are not fixed in time but are highly responsive to changes in industry behavior and regulatory policy that make certain flavors more or less available. The sales data also underscore the substitutability of menthol and mint flavors.

Given the mutability of flavor preferences, particularly among youth, the Draft Guidance may be creating a real risk that FDA will authorize particular flavors as "lower risk," based on a snapshot of flavor preferences at one point in time, only to have the authorized flavor increase in youth prevalence following FDA authorization, thus altering the risk/benefit analysis. Indeed, FDA has acknowledged this very risk. For example, referencing the FDA's 2020 enforcement guidance, the FDA's TPL Review for NJOY's ACE menthol pod product described how "the removal of one flavored product option prompted youth to migrate to another ENDS type that was available in the marketplace and offered the desired flavor options, underscoring the fundamental role of flavor in driving youth appeal and use of ENDS."<sup>22</sup> The TPL Review further noted that, "menthol-flavored ENDS (like the new products) could be particularly appealing to youth, and use of the new products by youth ENDS users might change, depending on the availability of other products on the market."<sup>23</sup> Similarly, the TPL Review for menthol JUULpods noted that, "[c]hanges in the availability of products affect patterns of youth use, such that the reduced availability of certain flavored ENDS products may lead to increased use of available flavored ENDS products."<sup>24</sup>

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<sup>18</sup> Park-Lee E, et al. (2021). "Notes from the Field: E-Cigarette Use Among Middle and High School Students — National Youth Tobacco Survey, United States, 2021." *MMWR*; 70 (39):1387–1389. <https://www.cdc.gov/mmwr/volumes/70/wr/mm7039a4.htm>.

<sup>19</sup> Food and Drug Administration. 2025 National Youth Tobacco Survey, March 4, 2026; <https://www.fda.gov/tobacco-products/youth-and-tobacco/national-youth-tobacco-survey-nyts>. Accessed: March 13, 2026.

<sup>20</sup> Diaz, M.C., et al. (2021). "Menthol e-cigarette sales rise following 2020 FDA guidance." *Tobacco Control* 30.6: 700-703.

<sup>21</sup> Ali FRM, et al. (2020). "E-cigarette Unit Sales, by Product and Flavor Type — United States, 2014–2020." *MMWR*;69(37):1313–1318. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e2.htm>.

<sup>22</sup> FDA, NJOY ACE POD Menthol Decision Summary (at 34), <https://www.accessdata.fda.gov/static/searchtobacco/2024/njoy-tpl-pm0000616-617.pdf>.

<sup>23</sup> *Id.*

<sup>24</sup> FDA, JUULpods Menthol Decision Summary (at 42), <https://www.accessdata.fda.gov/static/searchtobacco/7-10>.

Indeed, at least one federal appeals court has found it is FDA’s duty, in implementing premarket review, to consider changes in the marketplace due to FDA action authorizing certain products and enforcing the law against others. In upholding an MDO for menthol ENDS products in *Logic Technology Development LLC v. FDA*, 84 F.4th 537, 556 (3d Cir. 2023), the U.S. Court of Appeals for the Third Circuit wrote:

There is nothing improper under the APA [Administrative Procedure Act] about the Center prognosticating what will happen to children’s menthol use as other flavored ENDS exit the market. It made reasoned projections based on market responses to previous enforcement actions, and it did so pursuant to a statute that not only permits it to forecast, *but requires it to do so*.

(emphasis added). In contrast, the Draft Guidance fails to recognize the importance of accounting for the changes in flavor prevalence that will inevitably result from FDA’s proposal to begin distinguishing among flavors based on prevalence data at one point in time. By allowing some flavored products to be authorized if the applicant shows they provide only marginal benefits to people who smoke compared to tobacco-flavored products, the Draft Guidance opens the door to the authorization of flavored ENDS products that threaten young people with a substantial risk of addiction and other health harms. This is a fundamental flaw in the Draft Guidance.

### **C. The Categorization of Menthol and Mint as Posing “Lower Risk” to Youth Lays the Foundation for Authorization of ENDS Products that Will Cause Substantial Harm to Public Health**

That FDA apparently now views menthol as a “lower risk” ENDS flavor not only ignores the evidence described above, it also ignores the history of menthol in tobacco products, particularly the tobacco industry’s decades-long manipulation of menthol’s obvious appeal to youth. The FDA’s proposed rule to prohibit menthol cigarettes made a strong case that the “menthol in cigarettes increases smoking initiation,”<sup>25</sup> and facilitates “experimentation and regular use, particularly among younger smokers.”<sup>26</sup> These findings directly bear on FDA’s consideration of marketing applications for menthol e-cigarettes because—whether found in cigarettes or e-cigarettes—the flavor and sensory effects produced by menthol make tobacco products easier to inhale and more attractive to new users.

FDA also found that the interaction of menthol and nicotine in the brain enhances nicotine addiction, particularly among young people, stating that, “menthol, like nicotine, binds to nicotinic receptors in the brain...and menthol alone can increase the number of nicotinic receptors in the brain.”<sup>27</sup> An increase in nicotinic receptors is associated with the development of nicotine addiction.<sup>28</sup> FDA also noted that the combination of these chemicals is particularly damaging to young people: “The combined effects of nicotine and menthol in the developing brain make youth who smoke menthol cigarettes particularly vulnerable to the effects of menthol on nicotine dependence.” The end result is that “menthol facilitates repeated experimentation and

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<sup>25</sup> 87 Fed. Reg. 26,463.

<sup>26</sup> *Id.*

<sup>27</sup> *Id.* at 26,457.

<sup>28</sup> *Id.* at 26,468.

progression to regular smoking among youth and young adults.”<sup>29</sup> FDA also has recognized that menthol in ENDS products has a similar intensifying impact on addiction. Indeed, in Congressional testimony in 2021, then Acting FDA Commissioner Dr. Janet Woodcock noted the pharmacologic properties of menthol that “make it harder to stop either vaping or smoking” and agreed with the statement that menthol “heightens the addictive properties of e-cigarettes.”<sup>30</sup>

In FDA’s review of e-cigarette pre-market tobacco product applications, the Agency to date has consistently highlighted the risks and appeal of menthol e-cigarettes to youth, noting that “menthol-flavored ENDS pose a known and substantial risk to youth,” and that, “[t]here is substantial evidence that flavors in tobacco products, like menthol flavors in the new products, have significant appeal to youth and are associated with high likelihood of youth initiation and subsequent progression to regular use of such products when compared with tobacco-flavored ENDS. The literature demonstrates that the risk of menthol-flavored ENDS is higher than tobacco-flavored ENDS and indicates that youth are using menthol-flavored products more than tobacco-flavored products.”<sup>31</sup>

Thus, FDA has repeatedly acknowledged that menthol flavoring—whether in cigarettes or e-cigarettes—poses substantial risks to youth. Given FDA’s conclusions that menthol increases initiation of tobacco products, leads to more regular use of tobacco products, makes it harder to stop using such products, makes these products more appealing to youth, and leads to greater youth usage, it is difficult to understand FDA’s classification of menthol ENDS products as “lower risk” and therefore eligible for marketing authorization “even if the added benefit they provide compared to tobacco-flavored products is relatively small.” Draft Guidance at 14.

As menthol is derived from the mint plant, mint- and menthol-flavored e-cigarettes can have similar chemical profiles. To the extent that e-cigarettes labeled as mint, wintergreen, chill or ice also contain menthol, these same public health considerations apply. FDA should consider not just the name of the product, but the chemical constituents in evaluating their risk to youth. For example, while JUUL’s mint-flavored e-cigarette is not currently on the market, research found that it contained similar levels of menthol as JUUL’s menthol-flavored pods.<sup>32</sup> As such, the historically high rates of youth use of mint-flavored products reflect use of a product with high levels of menthol. In addition to the risks posed by the menthol flavoring additives in mint-flavored e-cigarettes, the previously documented youth use data clearly show that mint-flavored e-cigarettes have high youth appeal. In 2020, when youth preference for mint-flavored e-cigarettes was at its highest, over half (55.8%) of high school users of flavored e-cigarettes reported using mint-flavored products, far surpassing preference for candy/dessert/other sweet-flavored e-cigarettes (36.4%).<sup>33</sup> The latest data from the 2025 NYTS shows that use of candy/desserts/other sweet flavors (29.2%, 95% CI [26.2%, 32.4%]) and mint flavors (27.4%,

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<sup>29</sup> *Id.* at 26,465.

<sup>30</sup> Testimony of Dr. Janet Woodcock, Acting Commissioner, Food and Drug Administration, *An Epidemic Continues: Youth Vaping in America*, Hearing before the Subcommittee on Economic and Consumer Policy of the House Committee on Oversight and Reform (June 23, 2021), at 13.

<sup>31</sup> FDA, JUULpods Menthol TPL Review at 38, 43, <https://www.accessdata.fda.gov/static/searchtobacco/7-10>.

<sup>32</sup> Omaiye, E. E., (2022). “Flavour chemicals, synthetic coolants and pulegone in popular mint-flavoured and menthol-flavoured e-cigarettes.” *Tobacco Control*, 31(e1), e3-e9. Erythropel, H. C., et al., (2019). “Flavorant–solvent reaction products and menthol in JUUL e-cigarettes and aerosol.” *American Journal of Preventive Medicine*, 57(3), 425-427.

<sup>33</sup> Wang, T.W., et al. (2020). “E-cigarette Use Among Middle and High School Students — United States, 2020,” *MMWR* 69(37):1310–1312. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e1.htm>.

95% CI [23.7%, 31.4%]) among middle and high school e-cigarette users are not significantly different.<sup>34</sup> As such, youth use data does not substantiate FDA’s conclusion that mint-flavored e-cigarettes pose a lower risk to youth than flavors like candy, desserts or other sweets.

The FDA should similarly recognize the significant risks to youth of e-cigarettes containing synthetic coolants, which can mimic the cooling properties of menthol and may be marketed as mint, menthol, wintergreen, ice or chill flavors. Both menthol and synthetic cooling agents impart a cooling sensation by activating the same receptor—a transient receptor on the primary trigeminal neurons called TRP melastatin 8 (TRPM8).<sup>35</sup> The 2024 Surgeon General’s report concluded that:

Natural and synthetic cooling agents that have been found in some tobacco products (a) act on different parts of the oral cavity and the respiratory system to enhance the experience of smoking or use of other tobacco products and (b) can mimic the pharmacological and somatosensory effects of menthol but may not have a distinguishing taste or odor. Cooling agents, even those without a taste or odor, have the potential to increase the appeal of tobacco products, facilitate their use, and contribute to tobacco-related health disparities. Comprehensive flavor policies that account for these agents will better protect public health.<sup>36</sup>

E-cigarettes with synthetic coolants have become popular in recent years. Synthetic agents, including WS-3, WS-5, and WS-23, have been identified in e-cigarettes marketed as mint, menthol, wintergreen, ice, freeze or cool flavors. A review of these e-cigarette products concluded that:

[S]ynthetic coolants as compared to menthol have comparable or stronger pharmacological activity at TRPM8, cause less irritation, and might elicit stronger cooling and counterirritant effects. We speculate that these properties may lead to diminished sensory irritation and nicotine aversion, which could potentiate appeal of the user experience, promote deeper aerosol inhalation, and, in turn, encourage more frequent e-cigarette use.<sup>37</sup>

Some e-cigarettes also combine a mint, menthol or synthetic cooling flavor with the fruit, sweet and candy flavors that FDA has already established pose a high risk to young people, potentially compounding the risk to youth. For example, such products include flavors like blueberry ice, watermelon ice, and frozen grape. A review of these hybrid-flavored products noted that, “[i]f ice-fruit/dessert hybrid flavours elicit both cooling and sweet perceptions, these flavours might be particularly appealing,” and further warned that, “[t]he toxicological implications of inhaling multiple flavour chemicals simultaneously, either in presence or absence of menthol or synthetic

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<sup>34</sup> Food and Drug Administration. 2025 National Youth Tobacco Survey, March 4, 2026; <https://www.fda.gov/tobacco-products/youth-and-tobacco/national-youth-tobacco-survey-nyts>. Accessed: March 13, 2026.

<sup>35</sup> McKemy DD, et al. (2002). “Identification of a cold receptor reveals a general role for TRP channels in thermosensation.” *Nature*, 416:52-58. HHS, *Eliminating Tobacco-Related Disease and Death: Addressing Disparities: A Report of the Surgeon General (p.301)*, 2024, <https://www.hhs.gov/sites/default/files/2024-sgr-tobacco-related-health-disparities-full-report.pdf>.

<sup>36</sup> HHS, *Eliminating Tobacco-Related Disease and Death: Addressing Disparities: A Report of the Surgeon General (p.8)*, 2024, <https://www.hhs.gov/sites/default/files/2024-sgr-tobacco-related-health-disparities-full-report.pdf>.

<sup>37</sup> Leventhal, AM., et al. (2023). "Ice flavours and non-menthol synthetic cooling agents in e-cigarette products: A review." *Tobacco Control*, 32(6), 769-777

coolants, is poorly understood.”<sup>38</sup> The 2024 NYTS found that over half of youth e-cigarette users have used products with flavor names that include the word “ice” or “iced.”<sup>39</sup> FDA should also be cognizant of e-cigarettes with concept flavor names that may disguise such ice-hybrid flavors. For example, one study identified a flavor named “Ice Dragon” that was described as “Fruity blueberry & dragon fruit base with a fresh minty chill.”<sup>40</sup> Another study documented that Bidi Vapor had renamed its Icy Mango product to “Marigold” and its Mint Freeze product to “Arctic.”<sup>41</sup>

#### **D. The Draft Guidance Does Not Adequately Consider the Likelihood of Sustained Dual Use of Combusted Cigarettes and E-Cigarettes and the Negative Health Consequences of Sustained Dual Use**

The Draft Guidance is focused on the potential of flavors to aid in complete switching to e-cigarettes or substantial reductions in cigarettes smoked, but fails to adequately consider the likelihood of sustained dual use of combusted cigarettes and e-cigarettes by adults and does not at all consider the health effects of that sustained dual use. Dual use is not an effective way to safeguard health. Dual use of both e-cigarettes and cigarettes has not been proven to meaningfully reduce one’s risk of tobacco-related diseases. In fact, dual use may result in greater exposure to toxins and worse respiratory health outcomes than using either product alone.<sup>42</sup> Dual use, even with cutting back the number of cigarettes smoked, still elevates a person’s health risks for conditions like cardiovascular disease.<sup>43</sup> According to the National Academies of Sciences, Engineering, and Medicine (NASEM) report, “there is no available evidence whether or not long-term e-cigarette use among smokers (dual use) changes morbidity or mortality compared with those who only smoke combustible tobacco cigarettes.”<sup>44</sup> More than one-quarter (26.7%) of adults using e-cigarettes still smoke combusted cigarettes.<sup>45</sup>

#### **E. The Draft Guidance Fails to Account for the Toxicity of Flavored E-Cigarettes**

In assessing the relative risks of various non-tobacco flavors in e-cigarettes, in addition to the risks of youth initiation and dependence, FDA should consider the toxicity of flavored e-

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<sup>38</sup> *Id.*

<sup>39</sup> Park-Lee, E., et al. (2024). “E-Cigarette and Nicotine Pouch Use Among Middle and High School Students — United States, 2024,” *MMWR* 73(35):774-778, <https://www.cdc.gov/mmwr/volumes/73/wr/pdfs/mm7335a3-H.pdf>.

<sup>40</sup> Leventhal, AM., et al. (2023). “Ice flavours and non-menthol synthetic cooling agents in e-cigarette products: A review.” *Tobacco Control*, 32(6), 769-777

<sup>41</sup> Ramamurthi D., et al. (2023). “Flavour spectrum of the Puff family of disposable e-cigarettes,” *Tobacco Control* 32:e71-e77.

<sup>42</sup> CDC, Health Effects of Vaping, <https://www.cdc.gov/tobacco/e-cigarettes/health-effects.html>

<sup>43</sup> Tverdal, A and Bjartveit, K, “Health Consequences of Smoking 1-4 Cigarettes per Day,” *Tobacco control* 14(5), 2005.

Hackshaw, A, et al., “Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports,” *BMJ* 360:j5855, <http://doi.org/10.1136/bmj.j5855>, 2018. Hackshaw, A, et al., “Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports,” *BMJ* 360:j5855, <http://doi.org/10.1136/bmj.j5855>, 2018. HHS, *The Health Consequences of Smoking: A Report of the Surgeon General*, CDC, OSH, 2004. HHS, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, CDC, OSH, 2010. HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*, CDC, OSH, 2012, <https://www.ncbi.nlm.nih.gov/books/NBK99237/>. HHS, *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*, CDC, OSH, 2014, Schane, RE, Ling, PM, & Glantz, SA, “Health Effects of Light and Intermittent Smoking: A Review,” *Circulation* 121(3):1518-1522, 2010. Tverdal, A & Bjartveit, K, “Health consequences of reduced daily cigarette consumption,” *Tobacco Control* 15:472-480, 2006.

<sup>44</sup> Nat’l Acad. of Sci., Eng’g & Med., *Public Health Consequences of E-Cigarettes* 10 (2018), <https://perma.cc/AZZ8-LKXW>

<sup>45</sup> CDC, “Tobacco Product Use Among Adults – United States, 2022 – 2022 National Health Interview Survey (NHIS) Highlights,” September 10, 2024. <https://www.cdc.gov/tobacco/media/pdfs/2024/09/cdc-osh-ncis-data-report-508.pdf>.

cigarettes in determining whether a flavored product is appropriate for the protection of the public health. The Draft Guidance does not appear to account for the toxicity factor.

For example, mint- and menthol-flavored e-cigarettes can contain potentially dangerous levels of pulegone, a Type 2B carcinogen according to the International Agency for Research on Cancer.<sup>46</sup> One study found that pulegone levels in tested mint- and menthol-flavored e-cigarettes were “higher than the FDA considers unacceptable for intake of synthetic pulegone in food, and higher than in smokers of combustible menthol cigarettes.”<sup>47</sup> Another study found that pulegone levels measured in tested mint JUUL and PuffBar products “were high enough to present a cancer risk.”<sup>48</sup>

As noted, e-cigarettes marketed as mint, menthol, ice or chill have also been found to use synthetic cooling agents, including WS-3 and WS-23, to impart a cooling taste and sensation. These chemicals have been found in high levels in some e-cigarettes and, in addition to reducing irritation or harshness and promoting increased inhalation by users, can cause cytotoxic and other toxicological effects.<sup>49</sup> Results from one study “strongly suggest that E-cigarette users are exposed to synthetic coolant amounts which would be considered unsafe when consumed in food, raising concerns for health risks upon chronic exposure.”<sup>50</sup> Further, the common practice of combining “ice” with fruit or other flavor chemicals could have additive toxicological effects on e-cigarette users.<sup>51</sup>

FDA’s consideration of spice flavors as lower risk to youth raises concerns given the wealth of research indicating increased risk from cinnamon flavoring in e-liquids. Studies of cinnamon-flavored e-liquids have found various forms of cinnamaldehydes, which are cytotoxic and damaging to human cells in the bones and lungs, and embryonic cells.<sup>52</sup>

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<sup>46</sup> Omaiye, E. E., Luo, W., McWhirter, K. J., Pankow, J. F., & Talbot, P. (2020). Electronic Cigarette Refill Fluids Sold Worldwide: Flavor Chemical Composition, Toxicity, and Hazard Analysis. *Chemical research in toxicology*, 33(12), 2972–2987. <https://doi.org/10.1021/acs.chemrestox.0c00266>.

<sup>47</sup> Jabba, S. V., & Jordt, S. E. (2019). Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. *JAMA internal medicine*, 179(12), 1721–1723. <https://doi.org/10.1001/jamainternmed.2019.3649>.

<sup>48</sup> Omaiye, E. E., Luo, W., McWhirter, K. J., Pankow, J. F., & Talbot, P. (2022). Flavour chemicals, synthetic coolants and pulegone in popular mint-flavoured and menthol-flavoured e-cigarettes. *Tobacco control*, 31(e1), e3–e9. <https://doi.org/10.1136/tobaccocontrol-2021-056582>.

<sup>49</sup> Omaiye, E. E., Luo, W., McWhirter, K. J., Pankow, J. F., & Talbot, P. (2022). Flavour chemicals, synthetic coolants and pulegone in popular mint-flavoured and menthol-flavoured e-cigarettes. *Tobacco control*, 31(e1), e3–e9. <https://doi.org/10.1136/tobaccocontrol-2021-056582>. Leventhal, A. M., Tackett, A. P., Whitted, L., Jordt, S. E., & Jabba, S. V. (2023). Ice flavours and non-menthol synthetic cooling agents in e-cigarette products: a review. *Tobacco control*, 32(6), 769–777. <https://doi.org/10.1136/tobaccocontrol-2021-057073>. Tackett, A. P., Han, D. H., Peraza, N., Whaley, R. C., Mason, T., Cahn, R., Hong, K., Pang, R., Monterosso, J., Page, M. K., Goniewicz, M. L., & Leventhal, A. M. (2025). Effects of 'Ice' flavoured e-cigarettes with synthetic cooling agent WS-23 or menthol on user-reported appeal and sensory attributes. *Tobacco control*, 34(2), 175–182. <https://doi.org/10.1136/tc-2023-058125>.

<sup>50</sup> Jabba, S. V., Erythropel, H. C., Torres, D. G., Delgado, L. A., Woodrow, J. G., Anastas, P. T., Zimmerman, J. B., & Jordt, S. E. (2022). Synthetic Cooling Agents in US-marketed E-cigarette Refill Liquids and Popular Disposable E-cigarettes: Chemical Analysis and Risk Assessment. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, 24(7), 1037–1046. <https://doi.org/10.1093/ntr/ntac046>

<sup>51</sup> Leventhal, A. M., Tackett, A. P., Whitted, L., Jordt, S. E., & Jabba, S. V. (2023). Ice flavours and non-menthol synthetic cooling agents in e-cigarette products: a review. *Tobacco control*, 32(6), 769–777. <https://doi.org/10.1136/tobaccocontrol-2021-057073>.

<sup>52</sup> Behar, R. Z., Davis, B., Wang, Y., Bahl, V., Lin, S., & Talbot, P. (2014). Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicology in vitro : an international journal published in association with BIBRA*, 28(2), 198–208. <https://doi.org/10.1016/j.tiv.2013.10.006>. Wavreil, F. D. M., & Hegglund, S. J. (2019). Cinnamon-flavored electronic

Additional studies have generally found that flavored e-liquids contain various chemicals with known cytotoxic or carcinogenic potential,<sup>53</sup> can differentially affect cell processes,<sup>54</sup> and increase the production of carbonyl compounds like formaldehyde,<sup>55</sup> compared to unflavored e-liquids, affecting various organ systems.<sup>56</sup> While the effects of inhaling flavor chemicals rather than ingesting them have not been fully studied, research suggests that the impact of inhaling could be greater than ingestion.<sup>57</sup> The expected repeated inhalation of e-cigarettes may compound the toxicological effects of these flavor chemicals.

Flavor additives can not only contain harmful chemicals but, as we have seen with menthol, they also can change the addictiveness and appeal of e-cigarettes. Flavor chemicals have been found to alter the pH of e-liquids, to some degree,<sup>58</sup> in a way that could impact nicotine absorption.<sup>59</sup> While this is a primary concern for youth and other nicotine-naïve populations, it is also problematic if the flavor chemicals prolong or increase nicotine addiction among people who are trying to quit using e-cigarettes.

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- cigarette liquids and aerosols induce oxidative stress in human osteoblast-like MG-63 cells. *Toxicology reports*, 7, 23–29. <https://doi.org/10.1016/j.toxrep.2019.11.019>. Behar, R. Z., Luo, W., Lin, S. C., Wang, Y., Valle, J., Pankow, J. F., & Talbot, P. (2016). Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tobacco control*, 25(Suppl 2), ii94–ii102. <https://doi.org/10.1136/tobaccocontrol-2016-053224>. Lee, W, Ong, S, Zhou, Y. et al. Modeling Cardiovascular Risks of E-Cigarettes With Human-Induced Pluripotent Stem Cell–Derived Endothelial Cells. *JACC*. 2019 Jun, 73 (21) 2722–2737. <https://doi.org/10.1016/j.jacc.2019.03.476>. Clapp, P. W., Lavrich, K. S., van Heusden, C. A., Lazarowski, E. R., Carson, J. L., & Jaspers, I. (2019). Cinnamaldehyde in flavored e-cigarette liquids temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. *American journal of physiology. Lung cellular and molecular physiology*, 316(3), L470–L486. <https://doi.org/10.1152/ajplung.00304.2018>. Goniewicz, M, *Toxicants in E-Cigarette Refill Solutions and Vapor*, Presentation at the FDA “Electronic Cigarettes and the Public Health: A Public Workshop,” December 10, 2014, citing Bahl, V., Lin, S., Xu, N., Davis, B., Wang, Y. H., & Talbot, P. (2012). Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reproductive toxicology (Elmsford, N.Y.)*, 34(4), 529–537. <https://doi.org/10.1016/j.reprotox.2012.08.001>. 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. [https://www.ncbi.nlm.nih.gov/books/NBK538680/pdf/Bookshelf\\_NBK538680.pdf](https://www.ncbi.nlm.nih.gov/books/NBK538680/pdf/Bookshelf_NBK538680.pdf).
- <sup>53</sup> Omaiye, E. E., Luo, W., McWhirter, K. J., Pankow, J. F., & Talbot, P. (2020). Electronic Cigarette Refill Fluids Sold Worldwide: Flavor Chemical Composition, Toxicity, and Hazard Analysis. *Chemical research in toxicology*, 33(12), 2972–2987. <https://doi.org/10.1021/acs.chemrestox.0c00266>.
- <sup>54</sup> Tellez, C. S., Grimes, M. J., Juri, D. E., Do, K., Willink, R., Dye, W. W., Wu, G., Picchi, M. A., & Belinsky, S. A. (2023). Flavored E-cigarette product aerosols induce transformation of human bronchial epithelial cells. *Lung cancer (Amsterdam, Netherlands)*, 179, 107180. <https://doi.org/10.1016/j.lungcan.2023.107180>.
- <sup>55</sup> Fazeli, E., Martinez, B., Son, Y., & Khlystov, A. (2026). Flavoring Compound Chemical Class and Vaping Conditions Determine Toxic Carbonyl Emissions from E-Cigarettes. *Chemical research in toxicology*, 39(3), 329–338. <https://doi.org/10.1021/acs.chemrestox.5c00404>.
- <sup>56</sup> Sachdeva, J., Karunanathan, A., Shi, J., Dai, W., Kleinman, M. T., Herman, D., & Kloner, R. A. (2023). Flavoring Agents in E-cigarette Liquids: A Comprehensive Analysis of Multiple Health Risks. *Cureus*, 15(11), e48995. <https://doi.org/10.7759/cureus.48995>.
- <sup>57</sup> Jabba, S. V., & Jordt, S. E. (2019). Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. *JAMA internal medicine*, 179(12), 1721–1723. <https://doi.org/10.1001/jamainternmed.2019.3649>.
- <sup>58</sup> Lisko, J. G., Tran, H., Stanfill, S. B., Blount, B. C., & Watson, C. H. (2015). Chemical Composition and Evaluation of Nicotine, Tobacco Alkaloids, pH, and Selected Flavors in E-Cigarette Cartridges and Refill Solutions. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, 17(10), 1270–1278. <https://doi.org/10.1093/ntr/ntu279>.
- <sup>59</sup> St Helen, G., Dempsey, D. A., Havel, C. M., Jacob, P., 3rd, & Benowitz, N. L. (2017). Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug and alcohol dependence*, 178, 391–398. <https://doi.org/10.1016/j.drugalcdep.2017.05.042>.

There is already an established evidence base showing that some flavorings used in e-cigarette products can contribute to the presence of toxins or carcinogens when aerosolized.<sup>60</sup> Cherry-flavored products have been shown to contain high levels of benzaldehyde, which can cause eye pain, conjunctiva redness, burning sensations in the nose and throat, coughing and breathing difficulty.<sup>61</sup>

FDA should not regard specific flavors as low risk without taking into account their harmful effects on users.

#### **F. For All Flavored ENDS Products, FDA Should Impose a High Evidentiary Burden to Show that Device Access Restrictions Would Sufficiently Protect Against Use by Youth to Meet the APPH Standard**

In issuing MDOs for flavored ENDS products, FDA has considered whether marketing restrictions (i.e., advertising and promotion restrictions intended to limit youth exposure to and appeal of tobacco product marketing) or sales access restrictions intended to restrict youth access to tobacco products (e.g. restricting sales to face-to-face transactions, in adult-only facilities or on websites requiring robust age and identity verification) would be sufficient to mitigate youth use of flavored products. According to the TPL Review for NJOY menthol products, “FDA’s experience shows that advertising and promotion restrictions and sales access restrictions cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH.”<sup>62</sup> Rather, for flavored products, “only the most stringent mitigation measures have such potential” and only “device access restrictions” (DAR) have the potential “for that kind of impact.”<sup>63</sup> DAR are systems built into the ENDS device itself that are designed to prevent underage use through user age verification and identification required to unlock or use the product.<sup>64</sup> FDA’s assessment has been different for tobacco-flavored products; because the risk of youth initiation and use is lower with tobacco-flavored ENDS than flavored ENDS, “[r]estrictions on advertising and promotion and sales access for tobacco-flavored ENDS could mitigate that more limited risk and impact the overall net benefit assessment.”<sup>65</sup>

The Draft Guidance continues to reflect FDA’s view that advertising and promotion restrictions, as well as youth access restrictions, are inadequate to mitigate the risk of flavored ENDS to youth. Draft Guidance at 16. FDA notes that advertising and promotion restrictions “are intended to curb youth appeal, but do not directly prevent youth use.” *Id.* It points out that youth access restrictions are undermined by evasion through e-commerce, weak enforcement,

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<sup>60</sup> Klager, S., Vallarino, J., MacNaughton, P., Christiani, D. C., Lu, Q., & Allen, J. G. (2017). Flavoring Chemicals and Aldehydes in E-Cigarette Emissions. *Environmental science & technology*, 51(18), 10806–10813. <https://doi.org/10.1021/acs.est.7b02205>. Barrington-Trimis, J. L., Samet, J. M., & McConnell, R. (2014). Flavorings in electronic cigarettes: an unrecognized respiratory health hazard?. *JAMA*, 312(23), 2493–2494. <https://doi.org/10.1001/jama.2014.14830>.

<sup>61</sup> Goniewicz, M., *Toxicants in E-Cigarette Refill Solutions and Vapor*, Presentation at the FDA “Electronic Cigarettes and the Public Health: A Public Workshop,” December 10, 2014. Kosmider, L., Sobczak, A., Prokopowicz, A., Kurek, J., Zaciera, M., Knysak, J., Smith, D., & Goniewicz, M. L. (2016). Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. *Thorax*, 71(4), 376–377. <https://doi.org/10.1136/thoraxjnl-2015-207895>.

<sup>62</sup> TPL Review, NJOY ACE products, at 6.

<sup>63</sup> *Id.*

<sup>64</sup> The NJOY menthol PMTAs did not propose the use of a DAR. *Id.* at 7.

<sup>65</sup> *Id.* at 6.

limited penalties and the fact that most youth acquire ENDS products through friends and acquaintances – sources outside regulated commerce. *Id.*

The Draft Guidance appears to reflect an increased level of skepticism by FDA about whether the mitigation potential of DAR is sufficient in itself to reduce the magnitude of adult benefit needed to meet the APPH standard, at least with respect to products with flavors FDA regards as particularly appealing to youth and in light of the untested operation of DAR. According to the Draft Guidance:

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. . . 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).

Draft Guidance at 17.

Thus, whereas FDA has viewed DAR as the only mitigation measure identified, to date, with the potential to effectively prevent youth usage of flavored products sufficient to alter the risk/benefit calculus, the Draft Guidance makes it clear that a marketing order applicant bears a particularly heavy burden to demonstrate that a DAR alone would suffice to protect young people, at least as used on ENDS with particularly youth-appealing flavors. Again, FDA here appears to make a distinction between various non-tobacco flavors, implicitly suggesting that DAR could be sufficient to mitigate youth usage of flavors that it deems less appealing to youth, like menthol, mint, coffee, spice, etc. Given FDA’s acknowledgment, in the Draft Guidance, of the “current lack of real world experience” with DAR on tobacco products, it would be prudent for the agency to impose an especially high evidentiary burden on any applicant seeking to rely solely on a DAR to mitigate youth use of an ENDS product with *any* non-tobacco flavor, including mint and menthol, not simply for fruit, candy and dessert-flavored products. As explained previously, adjusting the risk/benefit analysis, according to the relative prevalence of youth usage of various flavors at a particular point in time, does not account for the variability of youth preferences, particularly in response to changes in government policy and product availability.

#### **G. The Draft Guidance Does Not Present Sufficient Evidence of the Beneficial Effects of Flavors in ENDS to Justify an Easier Pathway to Marketing Authorization**

Although premarket review of flavored e-cigarettes is based on the risk/benefit calculus of the specific flavored product under review, it appears that FDA’s new “graduated risk” approach set out in the Draft Guidance is based, at least in part, on the agency’s general finding

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 cigarettes and reducing cigarette consumption among adults who would otherwise continue smoking. Draft Guidance at 5. The Draft Guidance cites “emerging evidence” suggesting that adults who smoke transitioning to e-cigarettes prefer non-tobacco flavors, while acknowledging that the extent of any potential benefit depends on the specific characteristics of the products and how they affect users. *Id.* However, a number of the studies cited (*id.* at 5, fn. 6) were not designed to demonstrate if flavored e-cigarettes facilitated complete switching. For example, one study compared flavored e-cigarette use with non-use of e-cigarettes, making flavor type irrelevant to the study’s findings.<sup>66</sup> Similarly, another study was limited by its descriptive design, which did not allow for causal inferences.<sup>67</sup>

While some research indicates higher switching rates for flavored ENDS products compared to tobacco, the totality of the evidence regarding the role of flavored e-cigarette use and switching or overall smoking cessation outcomes is inconclusive due to the inadequate evidence base and the methodological limitations of existing literature. The majority of studies that evaluate the role of flavors are either cross-sectional surveys, which cannot establish a causal link between flavor use and switching or cessation outcomes, or studies that assess only consumer preferences. FDA has previously noted the limitations of this research in its model TPL Review of PMTAs for e-cigarette products.<sup>68</sup> A recent systematic review and meta-analysis, investigating the role of e-liquid flavors for complete switching, concluded that, “there is no clear association between the use of e-cigarette flavours and smoking cessation...”<sup>69</sup> Moreover, a 2023 systematic review sought to evaluate the impact of using different e-cigarette flavors on complete switching but overall found that the available studies were low-quality and ultimately the findings were inconclusive.<sup>70</sup> The review’s authors noted that, “there is presently not enough evidence to determine whether flavored ENDS are superior to tobacco-flavored ENDS for smoking cessation...”

The new “graduated risk” approach detailed in the Draft Guidance is based on the premise that there is value in having multiple flavor options available to adults who smoke given the heterogeneity of adult preferences. Draft Guidance at 13. However, a preference for flavors does not demonstrate that flavors actually increase complete switching among adults or that flavors are needed to stop cigarette smoking. As noted in the Draft Guidance, one 2023 study found that reported preference for non-tobacco flavors showed no significant association with longer periods of abstinence.<sup>71</sup> Further, a 2018 systematic review of consumer preferences for e-

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<sup>66</sup> Mok Y, et al. Associations between e-cigarette use and e-cigarette flavors with cigarette smoking quit attempts and quit success: evidence from a US large, nationally representative 2018–2019 survey. *Nicotine and Tobacco Research*. 2023 Mar 1;25(3):541-52.

<sup>67</sup> Chang JT, 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 and Tobacco Research*. 2023 Mar 1;25(3):596-601.

<sup>68</sup> Model TPL Review at 12.

<sup>69</sup> Lindson N, et al. An update of a systematic review and meta-analyses exploring flavours in intervention studies of e-cigarettes for smoking cessation. *Addiction*. 2025 Apr;120(4):770-8.

<sup>70</sup> Liber AC, et al. The role of flavored electronic nicotine delivery systems in smoking cessation: A systematic review. *Drug and Alcohol Dependence Reports*. 2023 Jun 1;7:100143.

<sup>71</sup> Bold K, et al. E-cigarette use patterns, flavors, and device characteristics associated with quitting smoking among a US sample of adults using e-cigarettes in a smoking cessation attempt. *Nicotine and Tobacco Research*. 2023 May 1;25(5):954-61.

cigarette characteristics, including flavors, found the evidence as to whether flavored e-cigarettes can assist with switching was “inconclusive.”<sup>72</sup>

Likewise, while adults who smoke menthol cigarettes may prefer similarly flavored e-cigarettes, studies do not show that menthol-flavored e-cigarettes improve switching outcomes compared to tobacco-flavored e-cigarettes for adults who smoke menthol cigarettes. One longitudinal analysis of 2016 and 2018 International Tobacco Control Four Country Smoking and Vaping (ITC 4CV) Surveys did not find a significant difference in quitting outcomes between the use of menthol- or mint-flavored e-cigarettes and tobacco or unflavored e-cigarettes.<sup>73</sup> A study conducted by FDA researchers (Rostron et al.) using cross-sectional data found that adults who smoke menthol cigarettes who also used e-cigarettes were more likely to use or “preferred” menthol/mint-flavored e-cigarettes and less likely to use tobacco-flavored e-cigarettes than adults who smoke non-menthol cigarettes who also used e-cigarettes, as were adults who smoke menthol cigarettes who had switched to e-cigarettes.<sup>74</sup> However, exclusive use of menthol/mint-flavored e-cigarettes among adults who smoke menthol cigarettes was much less common. At most, this study shows that adults who smoke menthol cigarettes show a greater preference for menthol and mint e-cigarettes than adults who smoke non-menthol cigarettes. This is far from establishing that adults who smoke menthol cigarettes who switched would not have done so had such e-cigarette flavors not been available.

Nearly ten percent (9.3%) of adult e-cigarette users use tobacco-flavored e-cigarettes, making it clear that these products are an acceptable and viable choice for adults who wish to use e-cigarettes.<sup>75</sup> As of September 7, 2025, tobacco-flavored e-cigarettes comprised 20.3% of total e-cigarette sales.<sup>76</sup> A recent study of consumer-level longitudinal purchase data found that U.S. adult e-cigarette users tend to purchase tobacco flavors over fruit or menthol flavors.<sup>77</sup> The authors note that “according to our results, banning fruit or menthol flavors might not affect much adult demand.”

### **III. Conclusion**

We commend FDA for seeking to provide industry, and the public, with additional clarity about the agency’s implementation of premarket review of flavored ENDS products. We support FDA’s view, reflected in the Draft Guidance, that flavored ENDS products pose a serious risk of addiction and other health harms to the nation’s youth, that marketing and sales access restrictions cannot sufficiently protect against youth usage of non-tobacco flavored ENDS

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<sup>72</sup> Zare S, et al. A systematic review of consumer preference for e-cigarette attributes: flavor, nicotine strength, and type. *PloS one*. 2018 Mar 15;13(3):e0194145.

<sup>73</sup> Li L, et al. How does the use of flavored nicotine vaping products relate to progression toward quitting smoking? Findings from the 2016 and 2018 ITC 4CV surveys. *Nicotine and Tobacco Research*. 2021 Sep 1;23(9):1490-7.

<sup>74</sup> Rostron BL, et al. Ends flavor preference by menthol cigarette smoking status among US adults, 2018–2019. *International Journal of Environmental Research and Public Health*. 2021 Jan;18(1):240.

<sup>75</sup> National Cancer Institute. Tobacco Use Supplement to the Current Population Survey (TUS-CPS): Data brief—select estimates from September 2022 data collection [Internet]. Bethesda (MD): U.S. Department of Health and Human Services; 2024 Apr [cited 2026 Mar 23]. Available from: <https://cancercontrol.cancer.gov/sites/default/files/2024-02/TUSDataBriefFinal-508.pdf>

<sup>76</sup> CDC Foundation, “Monitoring U.S. E-Cigarette Sales: National Trends,” <https://tobacomonitoring.org/>. Data from Circana, which includes e-cigarette sales data from convenience stores, gas stations and other retail store chains. Sales from the internet and tobacco-specialty stores, including vape shops, are not included

<sup>77</sup> Zare S, et al. Consumer preferences for e-cigarette flavor, nicotine strength, and type: evidence from Nielsen scanner data. *Nicotine and Tobacco Research*. 2021 May 1;23(5):823-8.

products, and that DAR alone may not be sufficient to prevent youth usage of products with flavors FDA regards as particularly youth-appealing (although we believe FDA’s conclusion regarding DAR should be extended to *any* non-tobacco-flavored ENDS). However, our organizations are concerned that the Draft Guidance proposes to distinguish between flavors according to their relative risk to youth and to base those distinctions on a snapshot of youth flavor prevalence at a particular point in time. The Draft Guidance thus fails to recognize the well-established history of significant variations in youth flavor preferences over time, often caused by regulatory decisions themselves. Because FDA is proposing to rely on this snapshot to potentially authorize certain “low risk” flavors, based on a relatively small countervailing benefit to adults who smoke cigarettes, this fundamental flaw in the Draft Guidance threatens to open the regulatory door to a wider array of FDA-authorized flavored products that will be appealing and accessible to youth, without sufficient countervailing health benefits to adults who smoke. We therefore urge FDA to reconsider this aspect of the Draft Guidance as currently written.

Respectfully submitted,

Academy of General Dentistry	American College of Chest Physicians
Action on Smoking and Health	American College of Obstetricians & Gynecologists
African American Tobacco Control Leadership Council	American College of Physicians
AME Church Social Action Commission	American Dental Association
American Academy of Family Physicians	American Heart Association
American Academy of Otolaryngology– Head and Neck Surgery	American Indian Cancer Foundation
American Academy of Pediatrics	American Lung Association
American Association for Cancer Research (AACR)	American Medical Women's Association
American Association for Dental, Oral, and Craniofacial Research	American Psychiatric Association
American Association for Respiratory Care	American Public Health Association
American Association of Psychiatric Pharmacists	American Society of Addiction Medicine
American Cancer Society Cancer Action Network	Americans for Nonsmokers Rights
American College of Cardiology	Association of Black Cardiologists
	Association of Black Women Physicians
	Association of State and Territorial Health Officials (ASTHO)
	Big Cities Health Coalition

Breathe Southern California	National Coalition for LGBTQ Health
CADCA	National Council for Mental Wellbeing
Campaign for Tobacco-Free Kids	National Hispanic Medical Association (NHMA)
Coalition of National Health Education Organizations	National Medical Association
Community Education Group	National Network of Public Health Institutes
COPD Foundation	National Tongan American Society
Counter Tools	NCNW
DC Tobacco Free Coalition	Parents Against Vaping
Family, Career and Community Leaders of America, Inc. (FCCLA)	Prevent Cancer Foundation
First Focus on Children	Preventive Cardiovascular Nurses Association
Hope Cancer Resources	Rescue Agency
Mocha Moms Inc	Respiratory Health Association
MomsRising	Right 2 Breathe
NAACP	SAGSAW (Save a Girl - Save a World)
National Association of Elementary School Principals	Society for Cardiovascular Angiography and Interventions
National Association of Hispanic Nurses	Society for Public Health Education
National Association of Pediatric Nurse Practitioners	The Cancer Network
National Association of School Nurses	The Center for Black Health & Equity
National Association of Secondary School Principals	Tobacco Free Portfolios
National Association of Social Workers	Trust for America's Health
National Black Nurses Association, Inc	Truth Initiative
National Center for Health Research	WomenHeart