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Food and Drug Administration
Center for Tobacco Products
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Docket No. FDA-2026-D-1817-0036, "**Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications-Considerations Related to Youth Risk; Draft Guidance for Industry**"

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the world's first and largest scientific organization dedicated to cancer research focused on prevention of and cures for human cancers, we express our sincere appreciation for the opportunity to provide comments from our Tobacco Products and Cancer Subcommittee on the draft guidance "Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications-Considerations Related to Youth Risk; Draft Guidance for Industry."

AACR convened our Tobacco Products and Cancer subcommittee in 2009 alongside the enactment of the Family Smoking Prevention and Tobacco Control Act to foster scientific and policy initiatives that reduce the incidence of disease and mortality due to tobacco use (1). As experts on topics including nicotine addiction, smoking cessation, and lung and head and neck cancer screening and treatment, the members of this subcommittee are well positioned to provide additional considerations for incorporation into the draft guidance and to highlight areas where further clarification would improve its scientific grounding, interpretability, and implementation.

Flavored ENDS products are of particular concern to AACR because of their dual role as a primary driver of ENDS initiation and sustained use among youth and young adults, including those who are not cigarette users, while also being cited by adults who smoke as an important factor in switching away from combustible cigarettes. This duality underscores the need for a nuanced, evidence-based regulatory approach, particularly as many of the toxicologic and potentially carcinogenic effects of these products are unclear given the relative recency of their availability. As a result, AACR maintains its 2022 policy position that flavored products should not be marketed until a clear benefit in aiding adults who smoke combusted cigarettes to quit is sufficiently validated, including the proviso that use of flavored ENDS products does not result in an increase in youth initiation of ENDS (2). Potential carcinogenic effects of ENDS and flavored ENDS are important considerations in assessing safety of these products for youth and young adults (3).

In response to the FDA's Federal Register announcement, and in recognition of the significant knowledge within the FDA's Center for Tobacco Products (CTP), the AACR provides the following comment with suggestions for the draft guidance:

1. **Provide Parameters and Product Standards for Graduated Risk-Proportionate Product Evaluation**

AACR supports FDA's continued understanding, highlighted in this draft guidance, that flavored ENDS products pose a "substantial risk to youth, and they pose a greater risk to youth than tobacco-flavored ENDS." Consistent with this, we also support FDA's commitment to requiring that any applicant seeking to market a flavored ENDS product needs to show that its product confers added benefit compared to tobacco-flavored products in aiding adults quit smoking while outweighing the risk posed to youth.

This guidance proposes that there may be nuance among flavored ENDS products, with some having lower youth appeal than others. If such a product also provided significant benefits to adult smokers by encouraging complete switching to ENDS, we agree that a flavored product may be appropriate for the protection of the public health (APPH). As such, AACR acknowledges that a graduated risk-proportionate approach to regulating flavored ENDS products, as proposed in the guidance, may be appropriate when evaluating whether a flavored product is APPH. However, AACR does not support the idea suggested in the guidance that flavored products with lower youth appeal may be APPH if the added benefit they provide compared to tobacco-flavored products is relatively small. Potential marketing authorizations that trade a relatively small benefit for adults in exchange for a relatively small risk to youth in accordance with this statement may not represent a favorable trade-off. FDA

should support this statement with clear scientific backing that establishes how a small benefit to adults outweighs a small risk to youth.

We recommend this guidance outline regulatory-grade, science-backed breakpoints and definitions along the proposed sliding evidentiary scale. For example, there should be clear delineations of what a "relatively small" benefit for adults who smoke is, and what kind of studies may support such an evaluation. In support of FDA decision-making in placing products into "low" or "high" benefit/risk categories, AACR recommends strong epidemiological/observational studies as well as well-designed and adequately powered sensory perception panels in both youth and adult tobacco users are performed to address appeal and addictive potential across populations. Additionally, products seeking authorization should be subjected to randomized controlled trials to evaluate potential benefits for adult tobacco users, including complete product switching and other cessation-related endpoints. We highlight that public scientific studies have not yet conclusively shown that any flavored ENDS product, including the recently authorized menthol and fruit flavored products, provide a significant cessation benefit over non-flavored products (4). In addition, studies have reported that flavored products may contribute to higher odds of dual tobacco product use, dependent on demographics, and that dual use is associated with increased nicotine exposure and higher nicotine dependence as well as similar or worse health outcomes compared to those who use only cigarettes (5–9). Therefore, we disagree with the guidance's characterization of a simple reduction in cigarette use as a significant enough benefit for this product class to adults who smoke, as the level of reduction, among other factors, modifies the benefit. Importantly, "non-flavored" ENDS can foster reduced cigarette use and cessation; therefore, flavors should be subject to a high bar of evidence for consideration as APPH. Thus, while reduction alone is not sufficient evidence for a flavored product to be considered APPH, it may be for other types of products clearly unappealing to youth. Complete smoking cessation should be prioritized as the gold standard marker of benefit to adults who smoke.

2. **Provide Strong Plans for Continued Evaluation of the Youth Appeal of Flavored Products and Plans for Removal of Products Whose Risk-Profile Changes Over Time**

AACR recommends that FDA more explicitly consider that the relative youth appeal of various flavors can change over time. While at the current moment national surveys suggest that youth prefer to use fruit, candy, and dessert flavored products more so than some of the flavors indicated in this guidance as potentially lower risk (including menthol, mint, coffee, tea, and spice flavors), youth do use these flavors in significant numbers and these trends have previously shifted, especially for mint flavors that mimic candy. Indeed, it has been shown that when the currently preferred sweet and fruit flavored products are less available, such as after JUUL's removal of their fruit and sweet flavors from the market in 2018/2019, youth uptake of some of the flavors described as "lower risk" spiked (10,11). As such, there is concern that FDA may authorize a flavor that is perceived as "lower risk" at a given timepoint, only to have the risk/benefit of the product altered at a later date due to changes in use patterns. To combat this possibility, AACR recommends that FDA require applicants to provide robust, prospective plans for ongoing post-market surveillance of youth appeal and use patterns for flavored products, as well as clear criteria under which products may be reevaluated or removed from the market if their risk profile changes over time. Such plans should include commitments to regular analysis of national and regional youth survey data, monitoring of marketing practices and trends, and periodic reassessment of whether the product continues to meet the statutory standard of APPH. If a flavored product is authorized, then subsequently associated with a significant increase in youth use, this product should be removed from the marketplace.

Additionally, while these flavors are currently less used by youth, the selection of flavors highlighted as lower risk in the guidance should be further explained. For example, while the guidance notes that "in 2024, the most commonly used ENDS flavor type among youth was fruit (62.8%) followed by candy, dessert, and other sweets (33.3%). Menthol and tobacco were lower at 15.1% and 8.5% respectively," in the same report mint-flavored products were used by 25.1% of youth users (12). Additionally, some evidence shows that cooling flavors such as mint are associated with greater nicotine dependence among youth than flavors that do not contain cooling properties (13). While research has focused on cooling and sweet flavors, it may not be clear at this time whether additional flavors have similar effects. Given that identifying particular flavors in FDA guidance as potentially "lower risk" may facilitate increased product development and potentially downstream youth uptake, these selections should be more clearly supported.

3. **Address the Potential Role of Flavor Additives in Enhancing Carcinogenicity of ENDS.**

AACR appreciates FDA's recognition in the guidance that non-nicotine constituents of ENDS may present toxicological risks. However, the draft guidance does not sufficiently address a growing body of evidence

indicating that flavor additives may independently contribute to carcinogenic risk or enhance the carcinogenic potential of ENDS aerosols.

Laboratory studies show that certain flavoring constituents can induce oxidative stress, DNA strand breaks, mitochondrial dysfunction, inflammatory signaling, and epithelial barrier disruption, all contributors to oncogenesis (14,15). Specifically, flavored aerosols and vapor extracts can produce greater genotoxicity, cytotoxicity, and immune dysregulation, all characteristics potentially conducive to carcinogenesis, than unflavored equivalents under otherwise identical conditions (16,17). Importantly, these biological effects occur at exposure levels relevant to typical ENDS use. While long-term epidemiologic data are not yet available given the relative recency of ENDS products, systematic reviews of the mechanistic evidence raise concerns that flavors are not toxicologically inert additives and therefore may be active contributors to potential cancer risk that warrant further study (3,18,19).

This knowledge gap is particularly concerning given the central role that flavors play in youth initiation and sustained use. Moreover, youth populations may be biologically more susceptible to any carcinogenic properties of ENDS and flavor additives, undermining public health efforts to prevent tobacco-related cancer. Given this emerging science, AACR recommends that the final guidance explicitly address the need for robust toxicological and carcinogenicity evaluations of flavor additives proposed in premarket tobacco product applications, in both their heated and unheated forms. Specifically, FDA should consider requiring the chemical characterization of thermal degradation products of the proposed flavor formulations under realistic device operating conditions, *in vitro* genotoxicity and cytotoxicity testing of the flavored aerosols compared with unflavored controls, and the evaluation of potential synergistic effects between the proposed flavoring agents, nicotine, and other relevant constituents.

4. **Expand on Study Designs for Assessing Youth Appeal**

AACR supports FDA's inclusion of sensory perception and consumer response testing as part of the evidentiary framework for evaluating flavored ENDS products. However, AACR recommends FDA expand and clarify expectations for study design, population selection, and evidentiary thresholds to ensure that these assessments meaningfully capture youth appeal and addictive potential rather than relying on limited or underpowered studies.

Sensory perception panels can be a valuable tool for assessing product appeal, but studies must include sufficient sample sizes to detect even small differences in appeal across flavors and product characteristics, given that modest differences in appeal may translate into substantial differences in youth initiation at the population level. Applicants should be required to explicitly justify and report their sample size calculations, study participant demographics, statistical power assumptions, and effect size thresholds, and the evidentiary bar for demonstrating low youth appeal should be clearly defined. Furthermore, applicants should not rely solely on panel studies conducted in only youth or adults. Sensory perception experiments that involve exposure to the flavored product, and its aerosol, should be conducted in both adult tobacco users and in naïve youth or young adults under appropriate ethical and research safeguards. Pre-market testing in either population alone fails to address the core public health concern identified in the guidance. AACR also emphasizes that sensory panels alone do not interrogate the impact of flavors on addictiveness. Studies demonstrate that flavorants, particularly menthol, can increase the reinforcing properties of nicotine, and promote dependence and sustained use (20,21). Studies assessing this potentiality should be explicitly required for any flavored ENDS product seeking marketing authorization.

5. **Strengthen Language Surrounding Device Access Restrictions and Product Appropriateness for Public Health**

AACR supports FDA's recognition that Device Access Restrictions (DARs) may serve as one component of a comprehensive strategy to reduce youth access to flavored ENDS products. While many age-verification, age-gating, and authentication approaches may be easily circumvented by technologically adept youth, AACR recommends that FDA require applicants include at least one DAR. As indicated by FDA, these approaches are not sufficient to mitigate youth risk on their own, but may provide a valuable extra step that increases the difficulty of youth use. AACR recommends FDA strengthen the language in the guidance to clarify both the expectations for inclusion of DARs in premarket applications and the evidentiary standards required to demonstrate that such technologies meaningfully prevent youth use. AACR acknowledges that performing large epidemiologic or observational studies to verify the utility of any DAR is difficult at this time, since they entered the marketplace

only very recently. As such, observed abilities of the DAR to prevent youth access and post-marketing surveillance will be critical, and should be highlighted.

6. Create Clear Marketing and Labeling Rules for Flavored Products

As previously stated, AACR supports FDA's continued understanding that flavored ENDS products pose a "substantial risk to youth, and they pose a greater risk to youth than tobacco-flavored ENDS." Unfortunately, flavored ENDS products are especially present in ads targeted at youth, and flavors in particular have been shown to drive youth receptivity and engagement (22–24). To mitigate the risk of marketing tactics contributing to youth e-cigarette initiation, this guidance should include detailed considerations surrounding the "labelling and description of marketing plans" portion of premarket tobacco product applications for flavored ENDS products. In general, marketing plans should follow the guidance and rules of both the Tobacco Master Settlement Agreement and the Tobacco Control Act, both of which forbid tactics aimed at youth initiation of tobacco products (25,26). These requirements include, among other provisions, that the industry may not engage in celebrity endorsements of their products. Sponsors should also be required to conduct studies to assess the appeal of product packaging and labelling to youth and adults. While bright colored packaging and concept flavor names are often profiled as youth appealing, there is no standardized definition of youth-appealing marketing or packaging. To further the evaluation of such products, FDA should use any data submitted as part of this requirement to define such parameters.

Summary and Conclusion

AACR and AACR's Tobacco Products and Cancer subcommittee commend the FDA for developing this draft guidance that acknowledges the inherent tension between the potential for flavored e-cigarettes to facilitate smoking cessation among adults and the potential to spur youth initiation. We especially commend its focus on reducing youth initiation of flavored ENDS, as the role of flavored ENDS products in facilitating complete switching from cigarettes in adults and their long-term health risks remain unclear. Our recommendations, including further delineation of the graduated risk-proportionate approach, clearer study requirements across youth and adult populations, larger calls for the inclusion of DARs, clear rules for marketing of flavored products, and outlined mechanisms for post-market reassessment and product removal as risk profiles change, are intended to help ensure that products authorized for marketing meet the statutory APPH standard and reflect the best available scientific evidence. If the AACR can provide any additional information or assistance to the FDA, please do not hesitate to contact Brad Davidson, PhD, Regulatory Science and Policy Analyst, at brad.davidson@aacr.org.

Sincerely,

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