



Robyn Gougelet
VP Regulatory Affairs

May 11, 2026

Electronic Submission

Dockets Management Staff
(HFA-305) Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

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on Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications—Considerations Related to Youth Risk; Draft Guidance for Industry

1 Executive Summary

Juul Labs, Inc. (JLI) writes in response to the solicitation for comments in Docket No. FDA-2026-D-1817, “Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications — Considerations Related to Youth Risk - Draft Guidance for Industry” (Draft Guidance),¹ published in the March 11, 2026, edition of the *Federal Register*. JLI offers comments on the Draft Guidance and respectfully urges FDA to consider the recommendations below in the context of the broader state of the U.S. ENDS marketplace.

The U.S. ENDS marketplace today is defined by a profound imbalance: 45 ENDS authorized between 2021 and 2026 sit alongside tens of thousands of unauthorized products that make up roughly 80% of the market, or about \$11 billion in annual sales.² These illicit products are imported in violation of U.S. law and are sold openly at retail. The vast majority come in non-tobacco or -menthol (NTM) flavors. Current industry tracking estimates that 13.5 million Americans use flavored disposable ENDS.³

JLI appreciates the Agency’s May 8, 2026, assessment: “FDA is committed to combating illicit tobacco products in this country. The illicit market undermines the regulatory framework and

¹ 91 Fed. Reg. at 11980, “Flavored Electronic Nicotine Delivery Systems (ENDS) Premarket Applications— Considerations Related to Youth Risk; Draft Guidance for Industry,” dated March 11, 2026. *Available at*, <https://www.govinfo.gov/content/pkg/FR-2026-03-11/pdf/2026-04732.pdf>.

² JLI estimates based on tracked and untracked channels.

³ Altria Group. (2026). *Q4 2025 earnings presentation*. https://edge.sitecorecloud.io/altriacli9c5f-altriacli2f33-prod0b41-3d12/media/Project/Altria/Altria/Investors/events-and-presentations/2026/2025-Q4/Q4-2025-Earnings---Presentation.pdf?sc_lang=en

puts consumers at risk from products that haven't undergone any scientific review.”⁴ We believe the most effective way to address this risk is to transition from the current unregulated environment to a robust, authorized marketplace of products that consumers actually want to use to keep away from combustible cigarettes. This can be done while keeping stringent safeguards and leveraging postmarket surveillance to protect youth.

The 2025 NYTS results mark a milestone in tobacco control, showing that tobacco use rates have reached historic lows: youth past-30-day ENDS use was at a 10-year low (5.2%) and cigarette smoking at just 1.4%. The continued decline in ENDS use among youth — occurring at a time when illicit flavored products are widely available and marketed inappropriately — underscores the public health benefit regulated ENDS can provide for adults who smoke.

To establish a more comprehensive and viable framework to bring flavored ENDS under FDA’s regulatory auspices, the guidance would benefit from addressing the following key areas:

- Specify how a flavored ENDS PMTA can demonstrate the “outsize benefit” compared to tobacco-flavored ENDS that FDA suggests is required;
- Recognize the role of “reach” — the proportion of adults who smoke who adopt a product — in evaluating population benefit;
- Account for the substantial decline in youth ENDS use that has occurred even while 80% of the market is illicit, flavored products; and
- Address the public health risks posed by the unauthorized segment itself, including for youth.

In the comments that follow, JLI offers additional context on each of these points, along with recommendations the Agency might consider establishing a workable framework for flavored ENDS PMTAs.

- **Immediate-term:** As FDA continues weighing the virtue of authorizing flavored ENDS, the Agency should **prioritize authorizing more tobacco- and menthol-flavored ENDS** to immediately provide more authorized options for adults who smoke and to better counter the illicit market.
- **Short-term:** The PMTA pathway and alternative pathways, such as the supplemental PMTA (sPMTA) and exemption request pathways, must become predictable and achievable, including for flavored products. Leveraging these alternative pathways will accelerate the introduction of regulated ENDS with focused review, as the underlying PMTA has already been assessed to be appropriate for the protection of public health (APPH). FDA should make these pathways function as efficiently as the pathways to introduce new combustible products — including in characterizing flavors — to market.
- **Medium-term:** Providing adults who smoke or use ENDS with a sufficient range of authorized flavors will, over time, remove the economic incentives that sustain the current illicit market and support a fully regulated U.S. ENDS market — one in which people who use nicotine would use only the products that have been fully reviewed and

⁴ U.S. Food and Drug Administration. (2026). *FDA issues guidance on enforcement priorities for unauthorized ENDS and nicotine pouch products*. <https://www.fda.gov/tobacco-products/ctp-newsroom/fda-issues-guidance-enforcement-priorities-unauthorized-ends-and-nicotine-pouch-products>

authorized by FDA, with strict postmarket safeguards that allow either FDA or the manufacturer to take action if a product is no longer APPH, including in response to youth use signals.

1.1 Key Recommendations

Combating the Illicit Market (Section 2).

- *Authorize products that can displace the illicit market.* The 45 ENDS authorized to date — many of which are old, belong to the same ENDS system, or are not currently on the market — are insufficient to compete with the illicit segment. As Acting CTP Director Dr. Bret Koplow has stated, “the more products we can authorize, the less incentive there will be for retailers and distributors to participate in the illicit market”;⁵ FDA has also acknowledged that a 2025 authorization measurably reduced the illicit market’s share.⁶ FDA should authorize ENDS PMTAs efficiently and in a greater variety of flavors that adults prefer and use.
- *Incorporate real-world conditions.* FDA should incorporate the risks of unregulated illicit products into its APPH analysis. The Agency should consider current market dynamics, such as declining youth use and the surge in illicit market share, when calculating public health impacts.
- *Enforce strategically.* Provide clear, centralized guidance on which products can be marketed to assist state-level enforcement. While traditional methods like warning letters continue, there is potential to further leverage available CTP resources to support more comprehensive enforcement initiatives and provide a more visible deterrent to unauthorized actors.

Balancing Flavors’ Benefits and Risks (Section 3)

- *Incorporate reach into APPH analysis.* FDA should evolve its regulatory framework to weigh a product’s **reach**—its appeal and adoption rate among the smoking population—as heavily as its **effectiveness** in switching. We recommend that the Agency recognize the critical role of non-tobacco flavors in driving this reach, as diverse options help adults successfully transition away from combustible cigarettes.
- *Use population health impact modeling.* By shifting toward a holistic **population health impact** model, FDA can ensure that products providing a significant net benefit to society are not inadvertently excluded by overly narrow benchmarks.

Reducing Youth Use of ENDS through Targeted Interventions (Section 4).

- *Establish a comprehensive marketing standard* for all tobacco products, including consistent restrictions on advertising and promotion.
- *Establish a national age-verification standard at retail*, including ID scanning and/or facial age estimation at the point of sale.
- *Use postmarket surveillance to manage risk and refresh APPH status*; condition continued authorization on real-world performance, with rapid withdrawal authority where warranted.

⁵ Dr. Bret Koplow, October 2025 FDLI Tobacco and Nicotine Policy Conference, Q&A.

⁶ *Ibid*

- *Treat Device Access Restrictions (DAR) as a balancing or remedial mechanism*, not a default requirement, while FDA collects real-world data on DAR’s impact on adult use.

Make the PMTA Process Predictable and Efficient to Crowd Out Illegal Products (Section 5).

- *Prioritize Noncombustible Products.* Focus on the efficient authorization of scientifically substantiated smokefree nicotine products over combustible products to improve public health.
- *Increase Transparency and Clarity.* Provide clear checklists, templates, and a database detailing FDA's toxicological tiering of commonly used ingredients to reduce application bloat and uncertainty.
- *Streamline the Review Process.* Apply transferable knowledge across applications instead of conducting de novo reviews for similar products, with a goal of meeting the 180-day review mandate.
- *Enhance Collaboration and Technology.* Allow for more real-time communication with industry and explore the use of artificial intelligence (AI) to automate mundane review tasks

Defining APPH (Section 6)

- *Quantitatively define APPH.* Leverage dynamic population modeling, integrating the three statutory parameters (health risks, adoption by non-users, and switching by current users), and use population mortality as the definitive metric to assess whether a new product is APPH.

Open Additional Pathways for Modifications to APPH Products (Section 7).

- Adopt a 90-day target review cycle for sPMTAs covering modifications to authorized products.
- Open the Exemption Request (EX) pathway to ENDS for minor ingredient changes or device updates, using FDA’s 2018 Substantial Equivalence (SE) pathway action as guiding precedent.

2 The Status Quo and State of the Illicit Market

2.1 The Illicit Market Is Meeting Preferences of Adults Who Smoke and Driving Residual Youth Use

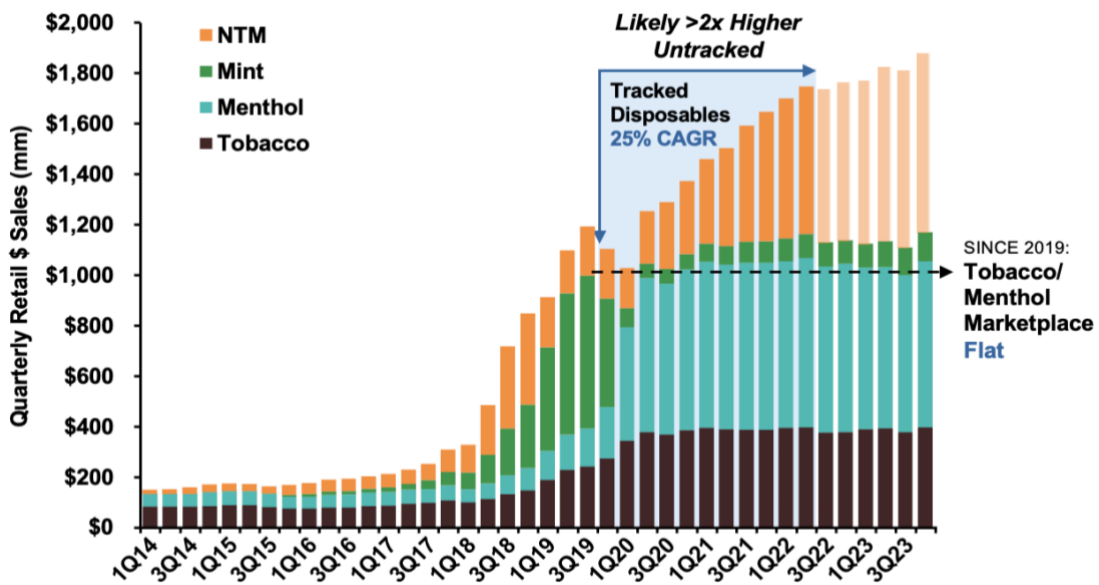
Adult consumer demand for ENDS (and flavored ENDS in particular) far outpaces authorized supply. The illicit segment has expanded to fill that gap, with illegal actors moving quickly to innovate and meet the demand of adult consumers who use flavored products to remain smoke-free. Most adults who use ENDS are not aware that the products they purchase in stores and inhale into their lungs are illegal, unregulated, and may carry additional risks above the risk of the products FDA has authorized.

Certain branding, product design elements, and marketing practices observed in the illicit segment are not appropriate for the tobacco category and risk increasing underage appeal. These products are often marketed to youth in appealing flavors such as bubblegum or using devices resembling toys and invoking cartoon characters.

The economic incentives to comply with the U.S. law and FDA’s regulatory authority remain limited, particularly when the probability of enforcement materially affecting business operations is low.

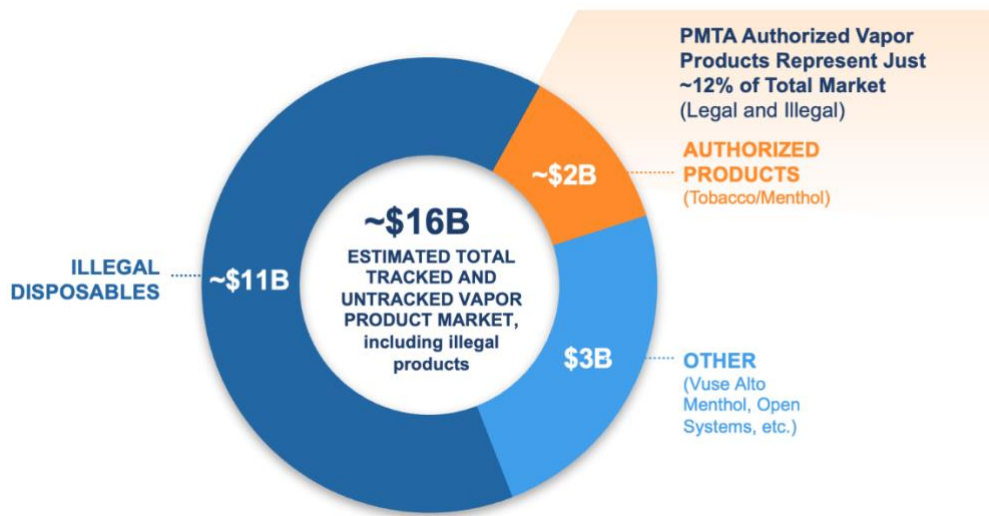
The growth of this segment has a simple implication: adults want to use flavored ENDS. Over the last seven years, the market for tobacco- and menthol-flavored ENDS has remained roughly flat, while all growth in ENDS use has come from NTM ENDS (Figure 1). Adults use flavored ENDS to move away from cigarettes; underage use of flavored ENDS has declined dramatically; and the illicit market is supplying demand for flavored ENDS regardless of whether FDA authorizes such products (Figure 2). Higher barriers to FDA authorization will continue driving people to the illicit market.

Figure 1. Tracked ENDS Consumable Retail \$ Sales (millions)⁷



⁷ JLI estimates constructed from all available data sources and longitudinal tracking of disposables

Figure 2. PMTA Authorized Vapor Products Are Not Meeting Consumer Demand



2.2 FDA Should Consider Additional Health Hazards that Illegal Products Pose in their APPH Determination

Authorized flavored ENDS present a potential public health benefit by appealing to the significant population of adult ENDS users who currently use illicit products. Manufacturers bypass U.S. regulatory requirements and cut corners on manufacturing quality and supply chain integrity, maximizing profits at the expense of public health.

When conducting its APPH analysis, FDA should account for consumers using these unauthorized products, which contain unknown ingredients and have not been subjected to rigorous hazard evaluation. While the specific health risks of these products are unknown, these products typically contain exceptionally high levels of flavor ingredients compared to authorized products. JLI's internal analysis of illicit ENDS products revealed total flavor ingredient levels between 4 and 8%. For context, JLI's authorized Virginia Tobacco e-liquid contains less than 0.4% flavor ingredients, 10 to 20 times less than the levels in illicit products.

The high levels of flavor ingredients included in illicit ENDS products may present health concerns for consumers, particularly as those ingredients have not been evaluated by the Agency. FDA has refined its assessment approach for ENDS products to include a quantitative calculation of the potential excess lifetime cancer risk (ELCR) for ENDS. While JLI does not always agree with FDA's genotoxicity tiering of specific ingredients,⁸ JLI does agree that FDA's ELCR approach can provide a useful means to compare potential cancer risk between ENDS products.

⁸ FDA suggested during the recent Roundtable on PMTA Submissions for ENDS that manufacturers could simplify review by using only ingredients classified as Tier 5 (unlikely to contribute to the carcinogenic risk of ENDS) according to FDA's June 2024 Memorandum. While FDA has helpfully provided its rubric for determining an ingredient's tier, the rubric involves the assessment of complex scientific information and expert judgement. As a

FDA applied its ELCR approach to JLI's Virginia Tobacco 5.0% e-liquid. In its TPL supporting authorization of this product, FDA calculated that the ELCR for Virginia Tobacco 5.0% was 368 per 100,000, almost entirely driven by ingredients that FDA determined could have potential cancer risk. As a reminder, the flavor ingredients in Virginia Tobacco comprise less than 0.4% of the formulation. If a product used this same flavor formulation at 8.0%, levels found in illicit ENDS products, then the resulting ELCR would increase 20-fold to 7,360. Using the rubric contained with FDA's ELCR memo, this would equate to a cancer risk that is almost 40% that of a combustible cigarette. Moreover, this calculation does not take into account toxic metals such as lead, nickel, and antimony that have been found in the aerosol of these products.⁹ These are likely present due to low quality construction and poor temperature regulation.¹⁰

FDA states in its ELCR memo that "the ELCRc of the new product under review should be evaluated along with the ELCRc range of the ENDS MGO [those ENDS products granted market authorization] marketplace" and that "Toxicology reviewers should report the new product ELCRc as a percent above or below the median of the ENDS MGO marketplace." FDA's focus on ELCRs of the small minority of ENDS products that have received authorization completely disregards 80 percent of the market, which leads to artificially low ELCRs.

FDA should incorporate the health risks of illicit products into its APPH analysis and authorize flavored ENDS products that have the potential to appeal to users of illicit ENDS products because switching adults who use illicit ENDS to FDA-authorized ENDS presents a public health benefit. Doing so will also create a robust authorized ENDS marketplace that will have broader appeal to adults who smoke and current users of illicit ENDS products alike.

2.3 The Importance of Federal Enforcement

The current guidance highlights how state-level legal heterogeneity and regulatory loopholes undermine youth access restrictions. While state efforts are vital, there is an opportunity to further utilize robust federal authorities granted to FDA to address these marketplace complexities. FDA has exclusive authority to authorize tobacco products for sale in the US. Any product that has not been authorized by FDA is adulterated and misbranded — providing the necessary statutory basis for nationwide removal.

As federal tobacco product regulation or enforcement has not fully addressed the unauthorized marketplace, a growing number of states have established their own product registries. They have done so without clear guidance from the Agency regarding which products are authorized, currently under an administrative or court stay, or are subject to other enforcement discretion.

result, there can be legitimate scientific disagreement as to the tier of specific ingredients based on the available evidence. Since the tiering rubric alone is not enough to understand FDA's position on the tier of specific ingredients, FDA should provide a database with FDA's tiering of all ingredients it evaluates during the review of ENDS PMTAs. Providing this database would allow manufacturers to develop products that have lower potential risk and that could move through the review process more efficiently.

⁹ Salazar, M. R., Saini, L., Nguyen, T. B., Pinkerton, K. E., Madl, A. K., Cole, A. M., & Poulin, B. A. (2025). Elevated toxic element emissions from popular disposable e-cigarettes: Sources, life cycle, and health risks. *ACS Central Science*, *11*(8), 1345–1354. <https://doi.org/10.1021/acscentsci.5c00641>

¹⁰ Talih, S., Salman, R., Soule, E. S., El-Hage, R., Karam, E., Karaoghlanian, N., El-Hellani, A., Saliba, N., & Shihadeh, A. (2021). Electrical features, liquid composition and toxicant emissions from 'pod-mod'-like disposable electronic cigarettes. *Tobacco Control*, *31*(5), 667–670. <https://doi.org/10.1136/tobaccocontrol-2020-056362>

The absence of clear, centralized direction leaves states vulnerable to bad actors who falsely claim to be in good standing with FDA.

To provide much-needed clarity for adult consumers, retailers, distributors, and law enforcement, FDA should update its Searchable Tobacco Product Database to clearly and accurately list all products that can be legally sold in U.S. storefronts. Based on the updated “Enforcement Priorities for Certain New Tobacco Products Marketed Without Premarket Authorization,” it seems the Agency is moving in this direction.

Beyond the storefront, FDA has significant authority over the global supply chain in coordination with U.S. Customs and Border Protection through Import Alerts, which allow federal agents to detain unauthorized shipments at the border. The Agency also wields significant financial and legal leverage; it can levy Civil Money Penalties and, in coordination with the Department of Justice, secure federal injunctions or deploy U.S. Marshals to execute multi-million-dollar inventory seizures.

States are not structurally equipped to police this globalized, illicit market because, unlike federal agencies, they cannot regulate international borders or interstate commerce. While a state can inspect local retail shelves—a whack-a-mole strategy at best—it cannot stop the massive influx of unauthorized disposable vapes arriving from overseas. These systemic gaps cannot be resolved by a patchwork of state laws; they require the federal government to exercise its unique power to secure the national supply chain.

Rather than viewing state-level enforcement as the primary variable in youth access, we suggest a framework that emphasizes federal leadership as the primary driver of market integrity. State and local governments—operating with more localized resources—have shown a strong commitment to addressing the unauthorized market. FDA can best support these efforts by providing the clear, centralized direction and supply-chain oversight that only a federal agency can provide.

3 The Evidence on Flavors

3.1 Flavored ENDS Can Help Adults Who Smoke Move Away from Smoking

Smoking remains the leading cause of preventable death in the United States, accounting for nearly one in five premature deaths and claiming approximately 480,000 lives annually. Nearly 7 in 10 smokers want to quit, and more than 50% try to quit each year. While smokers' best option to reduce the risks to their health is to quit all tobacco and nicotine products, the reality is that long-term success rates for quitting remain below 10%.

ENDS have demonstrated an ability to help smokers move away from smoking, and unlike cigarettes, do not expose the smoker to many highly toxic products of combustion. A growing body of evidence demonstrates that ENDS are effective in switching adults who smoke, including the latest systematic review and meta-analysis by the Cochrane Tobacco Addiction Group, which found “high-certainty evidence that [ENDS] with nicotine increase quit rates

compared to NRT [nicotine replacement therapy],”¹¹ among other meta-analyses.^{12, 13} Thus the effectiveness of ENDS for stopping smoking has been amply demonstrated in controlled clinical trials – and has also been demonstrated in real-world naturalistic observational studies^{14, 15} and in actual use studies.^{16, 17}

The Draft Guidance acknowledges the critical role flavored ENDS play in transitioning adults who smoke away from combustible cigarettes and explicitly states that these products can facilitate switching, increase quit attempts, and support sustained abstinence. To fully realize this potential, the final framework would benefit from additional technical clarity to ensure the PMTA process is predictable and actionable for applicants.

3.2 Flavors and Reach

While the FDA’s regulatory framework and Draft Guidance emphasize effectiveness—the rate at which individual users switch away from combustible cigarettes—the critical element of “reach” is largely neglected. Reach refers to the proportion of the target population – adults who smoke – that adopt a product and is equally as important as effectiveness in determining the population benefits of ENDS products. The importance of reach was highlighted by Abrams et al., who

¹¹ Lindson, N., Butler, A. R., McRobbie, H., Bullen, C., Hajek, P., Wu, A. D., Begh, R., Theodoulou, A., Notley, C., Rigotti, N. A., Turner, T., Livingstone-Banks, J., Morris, T., & Hartmann-Boyce, J. (2025). Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews*, (1).
<https://doi.org/10.1002/14651858.CD010216.pub9>

¹² Thomas, K. H., Dalili, M. N., López-López, J. A., Keeney, E., Phillippo, D., Munafò, M. R., Stevenson, M., Caldwell, D. M., & Welton, N. J. (2021). Smoking cessation medicines and e-cigarettes: A systematic review, network meta-analysis and cost-effectiveness analysis. *Health Technology Assessment*, 25(59), 1–224.
<https://doi.org/10.3310/hta25590>

¹³ Chan, G. C. K., Stjepanović, D., Lim, C., Sun, T., Shanmuga Anandan, A., Connor, J. P., Gartner, C., Hall, W. D., & Leung, J. (2021). A systematic review of randomized controlled trials and network meta-analysis of e-cigarettes for smoking cessation. *Addictive Behaviors*, 119, Article 106912. <https://doi.org/10.1016/j.addbeh.2021.106912>

¹⁴ Kim, S., Goldenson, N. I., Selya, A., & Shiffman, S. (2024). Switching away from smoking and reduction in cigarette consumption among U.S. adult purchasers of the JUUL system across 24 months including diverse subpopulations disproportionately affected by cigarette smoking. *Nicotine & Tobacco Research*, 26(9), 1183–1191.
<https://doi.org/10.1093/ntr/ntae072>

¹⁵ Kasza, K. A., Tang, Z., Benson, A. F., Creamer, M. R., Edwards, K. C., Sharma, E., Chang, J. T., Cheng, Y.-C., Clement, J., Cunningham, C., Ellison, C. D., Ergun, M. A., Greenberg, M., Oniyide, O., Tashakkori, N. A., Xiao, H., Stanton, C., Kimmel, H. L., Compton, W., & Hyland, A. (2026). Trends in cigarette discontinuation rates in the United States across 2014/15–2021 among adults who use electronic nicotine delivery systems (ENDS): Trends by ENDS flavor, ENDS device type, and age group from the PATH study. *Nicotine & Tobacco Research*, 28(4), 626–633. <https://doi.org/10.1093/ntr/ntaf213>

¹⁶ Goldenson, N. I., Shiffman, S., Sembower, M. A., Selya, A., Pype, S., & Black, R. A. (2025). Evaluating the effect of the JUUL2 system with 5 flavors on cigarette smoking and tobacco product use behaviors among adults who smoke cigarettes: 6-week actual use study. *Interactive Journal of Medical Research*, 14, e60620.
<https://doi.org/10.2196/60620>

¹⁷ Roulet, S., Kanitscheider, C., Magnani, P., & Kallischnigg, G. (2025). Evaluating use patterns of a closed electronic nicotine delivery system among adults in the United States who smoke cigarettes daily: 8-week actual use study. *JMIR Formative Research*, 9, e76019. <https://doi.org/10.2196/76019>

pointed out that products that are less harmful than smoking but fail to appeal to adults who smoke, will have very little population benefit.¹⁸

Consideration of reach as an element in APPH is particularly important to flavored ENDS because they have a fundamental role in reach by making ENDS products appealing to adults who smoke, especially those who want to distance themselves from flavors reminiscent of the harmful behavior – smoking – they are trying to shed. By making ENDS more attractive to adults who smoke and thus increasing adoption, appealing non-tobacco flavors can increase the number who switch away from smoking or materially reduce their cigarette consumption, to the benefit of population health.

The incremental reach of non-tobacco-flavored ENDS relative to tobacco-flavored ENDS was discussed in the Draft Guidance:

[A]dults who smoke attempting to quit combusted cigarettes have reported that flavor is an important factor in their decision to try ENDS products and in maintaining complete switching. The heterogeneity of adult preferences underscores the potential value of multiple flavor options to increase the likelihood that individual adults who smoke will find products that meet their needs and preferences.

However, neither the Draft Guidance nor the available documentation on marketing granted orders, have yet to take reach into account.

The importance of reach can be seen in hypothetical examples, including in [Table 1](#). Consider a hypothetical tobacco-flavored ENDS product that switches 20% of its users (effectiveness) but is only used by 10% of the adult smoker population (i.e., has 10% reach). This results in a total switch rate of 2% of the smoking population. This 20% switch rate becomes the regulatory benchmark that any flavored product must surpass to be deemed APPH under FDA's current approach. As described in the table below, if the Agency fails to consider reach, they may inadvertently deny products with a population benefit.

Table 1. Hypothetical Demonstration of Product Reach

Product	Effectiveness	Reach	Total Switched	Resulting Population Impact
Base case: Tobacco flavored ENDS	20%	10%	2.0%	Base-case reference for other products

¹⁸ Abrams, D. B., Glasser, A. M., Pearson, J. L., Villanti, A. C., Collins, L. K., & Niaura, R. S. (2018). Harm minimization and tobacco control: reframing societal views of nicotine use to rapidly save lives. Annual review of public health.

Product	Effectiveness	Reach	Total Switched	Resulting Population Impact
Product A: Mint/ menthol flavored ENDS	25%	10%	2.5%	The current standard would appropriately identify product A as incrementally benefiting adults who smoke. Despite this product having no greater reach than the tobacco example, the higher switch rates mean it would switch more smokers than tobacco.
Product B: Flavored ENDS with Device Access Controls	25%	5%	1.25%	The current standard would inappropriately identify product B as incrementally benefiting adults who smoke. Despite having a higher switch rate than tobacco, it would switch fewer adults who smoke due to its lower reach because of the technological barriers that device access restrictions provide.
Product C: Fruit A flavored ENDS	20%	20%	4.0%	The current standard would inappropriately identify product C as <i>not</i> incrementally benefiting adults who smoke, because switch rate was not increased – this despite that it would switch twice as many smokers as tobacco. The current standard would mistakenly deny this product because it considers only switch rates and not reach.
Product D: Fruit B flavored ENDS	15%	20%	3.0%	The current standard would inappropriately identify product D as <i>not</i> incrementally benefiting adults who smoke despite that it would switch 50% more smokers than tobacco. This example demonstrates that even products with <i>lower</i> switch rates than their reference (i.e., tobacco-flavored ENDS) can still be APPH if increased reach is considered.

FDA is aware of the importance of reach in considering how to help adults who smoke quit. Acting CTP Director Dr. Bret Koplow agreed with this sentiment during the Society for Research in Nicotine and Tobacco’s 2026 Annual Meeting. While remarking on the important considerations in the FDA’s decisions about marketing orders, Dr. Koplow spoke to the importance of reach or uptake, noting that “the most effective NRT won’t help adults quit if they

don't use it."¹⁹ Indeed, the regulatory history shows that FDA changed NRTs' status from prescription-only products to over-the-counter consumer products, not on the basis of incremental efficacy, but because of increased reach.²⁰

It is also important to consider that a new flavor need not be more appealing than existing or reference flavors in order to increase reach. Flavor preferences vary between people, so a new flavor may appeal to a segment of the population of adults who smoke who are not served by the existing or reference flavor. Such a flavor would have the potential to increase reach by bringing in an additional population of smokers, even if it is not, on the whole, preferred over the reference. This concept provides a framework for evaluating incremental reach of proposed flavor and highlights the need for a variety of flavors to maximize the reach into the adult smoker population.

The effect of non-tobacco flavors on ENDS reach is evident in research on flavor bans. Banning flavors in vaping products can lead to increases in smoking combustible cigarettes.^{21,22} Analyses of US states that have implemented complete ENDS bans and non-tobacco flavored ENDS bans demonstrate a consistent increase in cigarette sales, suggesting that many consumers chose to purchase readily available cigarettes when governments restrict the ENDS they prefer.^{23,24} As the UK's Royal College of Physicians warned, policies that reduce the palatability of e-cigarettes and inhibit innovation cause harm by perpetuating smoking:

if [a regulatory] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer-friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking.²⁵

FDA has indicated that it is aware that reach is a potential consideration in the evaluation of flavored ENDS products. However, FDA has suggested it is unsure of how to measure or estimate reach for new ENDS products during the review process. In fact, FDA is already assessing reach when it projects the risk youth will initiate on a particular new flavored ENDS

¹⁹ Dr. Bret Koplow, Special Session: 1 FDA's Comprehensive Approach to Regulating Tobacco Products: Updates from the Center for Tobacco Products, SRNT Annual Meeting 2026, Baltimore, Md. *Available at*, <https://srnt.org/srnt-2026-plenary-lectures/>

²⁰ Shiffman, S., & Sweeney, C. T. (2008). Ten years after the Rx-to-OTC switch of nicotine replacement therapy: What have we learned about the benefits and risks of non-prescription availability? *Health Policy*, 86(1), 17–26. <https://doi.org/10.1016/j.healthpol.2007.08.006>

²¹ Buckell, J., Marti, J., & Sindelar, J. L. (2019). Should flavours be banned in cigarettes and e-cigarettes? Evidence on adults who smoke and recent quitters from a discrete choice experiment. *Tobacco Control*, 28(2), 168–175. <https://doi.org/10.1136/tobaccocontrol-2017-054165>

²² Yang, Y., Lindblom, E. N., Salloum, R. G., & Ward, K. D. (2020). The impact of a comprehensive tobacco product flavor ban in San Francisco among young adults. *Addictive Behaviors Reports*, 11, Article 100273. <https://doi.org/10.1016/j.abrep.2020.100273>

²³ Xu, Y., Jiang, L., Prakash, S., & Chen, T. (2022). The impact of banning electronic nicotine delivery systems on combustible cigarette sales: Evidence from US state-level policies. *Value in Health*, 25(8), 1352–1359. <https://doi.org/10.1016/j.jval.2022.01.015>

²⁴ Chen, T., Jiang, L., & Prakash, S. (2023). Spatial spillover effects of state-level policies banning electronic nicotine delivery systems. *American Journal of Health Economics*, 9(4), 548–572. <https://doi.org/10.1086/726003>

²⁵ Royal College of Physicians. (2016). *Nicotine without smoke: Tobacco harm reduction*. <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0>

product. This analysis is nothing more than a forward projection of the likely rate of uptake among youth. As FDA already has the knowledge and experience to conduct an analysis of reach, it should do so among adults as well during its review of flavored ENDS PMTAs.

JLI believes there are multiple ways that reach can be estimated in a premarket environment. These methods include:

- a) **Examination of ENDS preferences in-market utilizing the economic concept of “revealed preferences”**—observing actual consumer behavior to determine what populations truly value. Data consistently indicates a robust preference for non-tobacco and non-menthol flavors among adults who smoke. Furthermore, because adolescent flavor profiles closely mirror those of adults, broadly identifying flavors that appeal exclusively to one group is likely impossible.

Besides examination of revealed preferences in-market, experimental methods are also available for examining flavors in a pre-market environment:

- b) **Tobacco Product Perception and Intention Studies.** There are established methods for assessing the likelihood of initiation among tobacco product nonusers, including underage individuals, specifically studies that evaluate perceptions and behavioral intentions following exposure to marketing and promotional materials, as outlined in the 2022 FDA Guidance titled, "Principles for Designing and Conducting Tobacco Product Perception and Intention Studies." These studies assess intent to use the product in appropriate on-target audiences (adults who smoke) and in off-target audiences (non-users of tobacco, including young adults as a proxy for youth). The studies are usually randomized experiments and could be designed to compare a proposed product, such as a flavored ENDS, with a control product, such as tobacco-flavored ENDS. JLI studies, for example, showed that a substantial proportion of adults who smoke who rejected a tobacco-flavored product were interested in a menthol-flavored product.^{26, 27} In a sense, these studies, which present respondents with images of the test and control products, reflect how a person may perceive and respond to a product at retail, where they see a package, including flavor designation, but have not yet tasted the actual flavor.
- c) **Product trial and evaluation studies.** These studies, which JLI has submitted as part of its pending application for JUUL2 products, are also randomized experimental studies, in which adults who smoke try the applicant product and a reference product, and provide data about use intentions. The studies can be designed as cross-over studies, such that a comparison of flavors is within-person. This methodology moves beyond theoretical flavor perception; it generates data based on actual usage, allowing for a precise within-person comparison of use intentions and flavor appeal.

²⁶ Shiffman, S., Kim, S., Sembower, M., Hannon, M., & Goldenson, N. (2026). US adults' complete switching away from cigarettes by menthol-and tobacco-flavored ENDS and by menthol cigarette preference: testing robustness to missing data. *Internal and Emergency Medicine*, 1-13.

²⁷ Selya, A., Kim, S., Shiffman, S., & Goldenson, N. I. (2025). Association of Use of Menthol- Versus Tobacco-Flavored ENDS with Switching Completely Away from Cigarettes and Differences by Menthol Cigarette Smoking. *Substance Use & Misuse*, 60(3), 311–318. <https://doi.org/10.1080/10826084.2024.2422963>

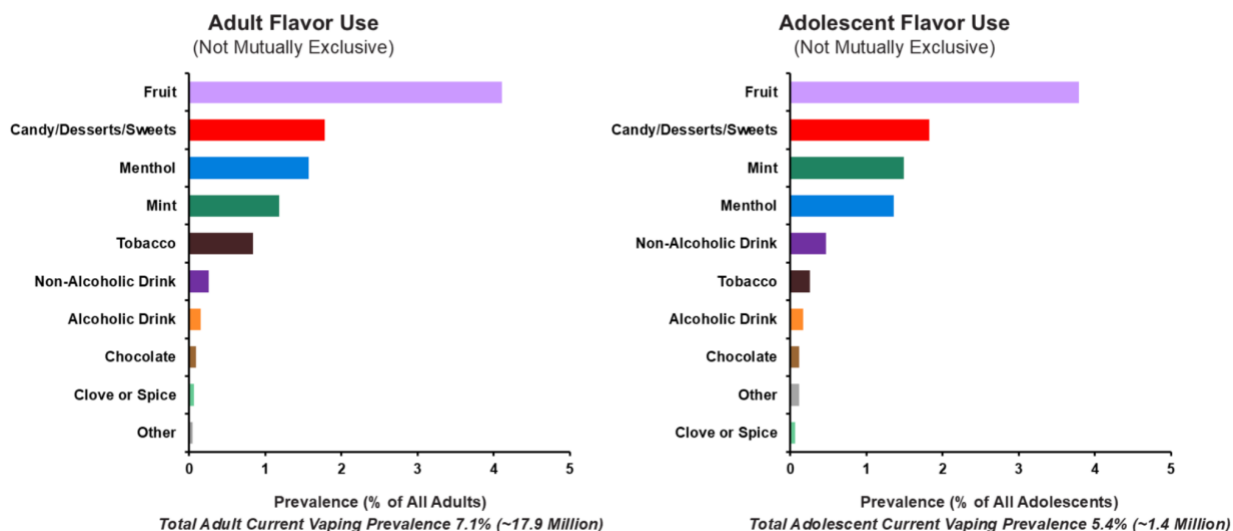
3.3 In-Market Assessment of Adult and Youth Flavor Preferences

The figure below shows the proportion of adult and adolescent ENDS-users, respectively, reporting the use of flavor classes, as captured in FDA’s PATH survey.

Both adults and adolescents prefer flavors other than tobacco. Both prefer menthol and mint flavors over tobacco. Overall, though there are some differences, particularly regarding tobacco flavored ENDS, adult and adolescent preferences are remarkably similar.

The similarity of adult and adolescent flavor preferences challenges the idea of identifying adult-only flavors, which FDA emphasized in its Draft Guidance. The Draft Guidance stated that, “[s]ome flavors may be shown to have lower youth appeal, perhaps such as coffees, teas, or spices, such that they may pose a lower risk of appeal to youth and may be APPH if the added benefit they provide compared to tobacco-flavored products is relatively small.” However, the PATH data show that these flavors have very little appeal to adults, so would lack the reach to adults who smoke necessary to achieve a strong public health benefit.

Figure 3. Distribution of flavors used by adults and adolescents in PATH Wave 7



In sum, reach among adults who smoke is a crucial element in evaluating an ENDS products’ population benefit and whether it is APPH. Moreover, there are multiple methods by which the reach of applicant ENDS products can be evaluated. FDA already uses in-market adoption as an index of likely use among adolescents. The logic is compelling that this could and should be applied to adults who smoke. Further, there are also experimental methods that are more product-specific and are already part of PMTA submissions that could be constructively applied to assess reach.

It is critical that FDA heavily consider the effect of flavors on reach to adults who smoke as part of its APPH calculus.

3.4 Flavors and Switching Efficacy

While flavors’ potential to increase reach is a key consideration in their impact on population health, switching effectiveness is, of course, also important. Ample evidence shows that flavors

can increase ENDS' ability to help smokers switch away from cigarette smoking. An analysis of an actual use study sponsored by JLI showed that those using menthol-flavored JUUL products were significantly more likely to achieve complete switching than those using tobacco-flavored JUUL ENDS.²⁸

The importance of flavors in encouraging switching is further supported by FDA's own longitudinal Population Assessment of Tobacco and Health Study (PATH) data, which found that adults who smoke who used non-tobacco-flavored ENDS were more than twice as likely to quit smoking at follow-up compared to those who used tobacco-flavored ENDS.²⁹ Furthermore, cross-sectional data suggests that flavor variety may prevent relapse, as the use of multiple flavors is more common among those who have successfully switched than among those who tried and later rejected ENDS.³⁰ Using cross-sectional data, Harrell et al. found that use of tobacco flavor at initiation was common among dual users of ENDS and combustible tobacco, whereas use of non-tobacco flavors was significantly more common among former smokers.³¹ Friedman and Xu found that adults who preferred non-tobacco flavors at baseline had more than two times the odds of stopping smoking at follow-up, after adjusting for other variables.³²

In a study conducted by Smith et al., of 427 adults who smoke, only five percent of participants chose to use tobacco ENDS exclusively. Those who used non-tobacco flavors were significantly more likely to reduce their cigarette consumption by at least 50%, researchers concluded that "non-tobacco e-cigarette flavors may be more appealing than tobacco flavors, and better promote uptake of e-cigarettes and cigarette smoking reduction."³³ Finally, adults using flavors may be less likely to later relapse to smoking. Jones et al. analyzed cross-sectional data from the Georgia State University Tobacco Products and Risk Perceptions Surveys.³⁴ Crucially, in this study, use of multiple ENDS flavors was more likely among adults who partially or completely switched compared to adults who tried but later rejected ENDS (current smokers, former ENDS users).

In sum, multiple studies point to the potential for flavored ENDS to increase ENDS' effectiveness in promoting complete switching away from smoking. But flavors' contributions

²⁸ Goldenson, N. I., Shiffman, S., Sembower, M. A., Selya, A., Pype, S., & Black, R. A. (2025). Evaluating the effect of the JUUL2 system with 5 flavors on cigarette smoking and tobacco product use behaviors among adults who smoke cigarettes: 6-week actual use study. *Interactive Journal of Medical Research*, *14*, e60620.

<https://doi.org/10.2196/60620>

²⁹ Friedman, A. S., & Xu, S. (2020). Associations of flavored e-cigarette uptake with subsequent smoking initiation and cessation. *JAMA network open*, *3*(6),

³⁰ Jones, D. M., Ashley, D. L., Weaver, S. R., & Eriksen, M. P. (2019). Flavored ends use among adults who have used cigarettes and ends, 2016-2017. *Tobacco regulatory science*, *5*(6), 518-531.

³¹ Harrell, M. B., Weaver, S. R., Loukas, A., Creamer, M., Marti, C. N., Jackson, C. D., ... & Eriksen, M. P. (2017). Flavored e-cigarette use: characterizing youth, young adult, and adult users. *Preventive medicine reports*, *5*, 33-40.

³² Friedman, A. S., & Xu, S. (2020). Associations of flavored e-cigarette uptake with subsequent smoking initiation and cessation. *JAMA network open*, *3*(6),

³³ Smith, T. T., Wahlquist, A. E., Wagener, T. L., Cummings, K. M., & Carpenter, M. J. (2025). The impact of non-tobacco e-cigarette flavoring on e-cigarette uptake, cigarette smoking reduction, and cessation: A secondary analysis of a nationwide clinical trial. *Addictive Behaviors*, *163*, Article 108240.

<https://doi.org/10.1016/j.addbeh.2024.108240>

³⁴ Jones, D. M., Ashley, D. L., Weaver, S. R., & Eriksen, M. P. (2019). Flavored ends use among adults who have used cigarettes and ends, 2016-2017. *Tobacco regulatory science*, *5*(6), 518-531.

should be more broadly construed to include their effect in increasing the reach of ENDS, which results in more adults who smoke switching, and thus in improving population health.

3.5 Balancing Flavors' Benefits and Risks: The Case for Population Modeling

Flavored ENDS can deliver considerable benefits to the population of adults who smoke, while also posing risks to underage tobacco-naïve individuals. The Family Smoking Prevention and Tobacco Control Act (TCA or the Act) imposes on FDA the challenging task of weighing these costs and benefits to decide whether a product submitted in a PMTA is appropriate for the protection of public health. The publicly available documents, including marketing granted orders, make clear that FDA is making these weighing judgments, but it is hard to discern *how* these decisions are being made, and thus neither these nor the Guidance give potential applicants clear direction how they might design a flavored product, an evidence portfolio, and a PMTA submission that would pass muster.

While such weighing judgments are complex, there is a method that FDA itself uses to assess and justify its own policy proposals, such as the nitrosamine³⁵ limits in oral tobacco products or the low-nicotine standard for cigarettes³⁶ – population health impact modeling. Such modeling explicitly considers the risks and benefits from a proposed tobacco product's market entry, producing a quantitative result in an objective metric that captures the core of APPH – the number of premature deaths averted (or increased) by the proposed marketing. With key empirically-estimated inputs – namely, the expected mortality risk of the product compared to cigarette smoking; the likely adoption by adults who smoke (reach); the expected switch rate among adopters (effectiveness); and, crucially, the likely adoption by non-tobacco users including youth – modeling can estimate the likelihood and the magnitude of benefits or harms. Especially with sensitivity analyses – because inputs necessarily are subject to some uncertainty – the model can also support the dichotomous decisions FDA is tasked to produce: will this product improve or worsen population health outcomes, compared to the status quo?

Although modeling itself is complex, the framework for regulation can be simple and explicit. Section 6.4 illustrates how such a framework would function and how it would provide a transparent and objective standard to these challenging decisions.

As such, modeling is well-suited to making sound decisions about flavored ENDS products, taking the current situation (including illicit flavored products) into account, and using empirical data to project a likely outcome. Models would explicitly include and incorporate the risks of uptake by youth, as well as the benefits to adults who smoke, both in reach and in switching effectiveness. The burden of collecting the necessary inputs continues to fall on the applicant, but, unlike the current situation, inputs would feed into a predictable, transparent framework that gives applicants a sense of what they need to achieve to have a product that can be authorized.

JLI urges FDA to make modeling more central in its consideration of flavored ENDS.

³⁵ Tobacco Product Standard for N-Nitrosornicotine Level in Finished Smokeless Tobacco Products, 82 Fed. Reg. 8004 (proposed Jan. 23, 2017) (to be codified at 21 C.F.R. pt. 1132).

³⁶ Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, 83 Fed. Reg. 11818 (proposed Mar. 16, 2018) (to be codified at 21 C.F.R. pt. 1130). <https://www.federalregister.gov/documents/2018/03/16/2018-05345/tobacco-product-standard-for-nicotine-level-of-combusted-cigarettes>

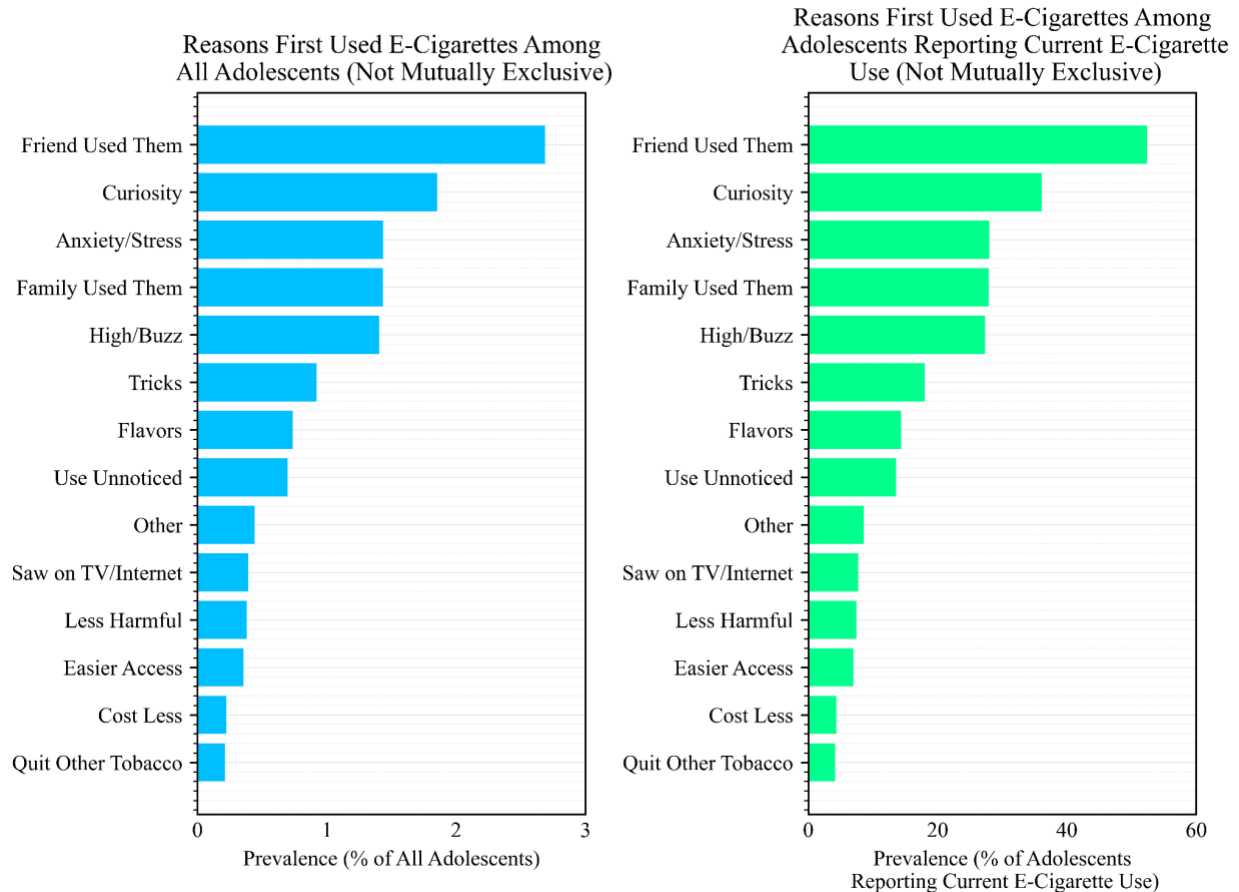
4 How to Reduce Youth Use of Flavored ENDS

FDA indicates that NTM flavors are the primary driver of youth use. This would imply that introduction of a variety of flavors would increase youth use — a pattern not seen in the current marketplace. Factors other than flavor play important roles in youth use; the initiation of tobacco product use is also driven by factors other than pharmacological or sensory effects associated with use of the product, including marketing, social factors, access, price, and perceptions of harm and/or useful effects of the product.

The Draft Guidance notes that “FDA also evaluates the likelihood that vulnerable populations—including youth... – may initiate use of the product.” The National Youth Tobacco Survey (NYTS) contains a question directly relevant to this assessment; The 2025 NYTS asked respondents who used e-cigarettes “Why did you first use an e-cigarette?” (Select all that apply, not mutually exclusive):

- Flavors (“They were available in flavors, such as menthol, mint, candy, fruit, or chocolate”) was only the **seventh** most commonly-endorsed response option, being reported by 0.7% of all adolescents and 14.4% of adolescents who currently used e-cigarettes (Figure 4). In other words, only one in seven adolescents who currently used e-cigarettes in 2025 reported flavors as a reason for their first use of e-cigarettes.
- In contrast, the most commonly-endorsed reasons for first use of e-cigarettes were: use by a friend (2.7% of all adolescents, 52.4% of adolescents reporting current e-cigarette use; Figure 4, curiosity (1.9% and 36.1%), anxiety/stress (1.4% and 28.0%), use by a family member (1.4% and 27.9%), and to get a high/buzz (1.4% and 27.4%).
- Indeed, just 0.02% of all adolescents and 0.4% of adolescents reporting current e-cigarette use selected flavors as their *only* reason for first use (with none of the other response options selected; these percentages are so low, that they are considered statistically unreliable in NYTS [CV>0.3]). In other words, only one in 250 adolescents who currently used e-cigarettes in 2025 reported flavors as the *only* reason for their first use of e-cigarettes.

Figure 4. Distribution of reasons for first use of e-cigarettes by adolescents in NYTS 2025



4.1 Overview of JLI’s Recommendations to Reduce Youth Use of ENDS

The latest NYTS survey results suggest that targeted interventions, including mass media campaigns like the Real Cost and reducing social sourcing through raising the legal age of purchase from 18 to 21 for all tobacco products, have been instrumental in preventing youth appeal of and access to tobacco products.

A comprehensive set of tools can continue to drive youth use down while still providing authorized flavored options for adults who smoke.

4.1.1 Marketing Restrictions

ENDS and other noncombusted tobacco products face fragmented marketing requirements determined on a case-by-case basis through marketing granted orders.

This patchwork approach creates an inconsistent and reactive system that lacks the clarity of a universal framework. A comprehensive, balanced standard is urgently needed to protect public health by encouraging adults who smoke to transition to less harmful alternatives and reducing underage appeal in tobacco products. A comprehensive marketing standard is essential to ensure robust public health protections and consistent accountability across all tobacco product

categories. Additionally, FDA could consider authorizing flavored ENDS with more restrictive marketing practices or retail channels than for tobacco- or menthol-flavored products.

4.1.2 Retail Standards

To further curb youth access, there are additional measures that can discourage youth use while providing compelling, flavored options to adults. In the 2019 NYTS, only 21.5% of middle and high school students who self-reported having used any tobacco in the past 30 days and who self-reported having made an attempt to buy any tobacco directly in the past 30 days, self-reported having been refused the sale of tobacco products because of their age. In 2025, this percentage was essentially unchanged at 19.7%.

While major retailers have made progress in implementing advanced age verification technology, FDA should develop a national standard for age verification for purchasing tobacco and nicotine products in all retail locations. This could include the use of novel technology at retail (through ID scanning and facial age estimation technology) that reduces purchasing friction for adults while making it more difficult for someone under the legal age of purchase. Under such a system, when any tobacco or nicotine product is scanned for purchase, the point-of-sale system will “block” the transaction until a valid, government-issued photo ID is scanned, or an age estimation is completed to verify the purchaser is of legal age. This point-of-sale integrated technology automatically controls transactions involving tobacco and nicotine products from beginning to end, ensuring that the retailer verifies every purchaser’s age and/or ID validity. This standards-based program can be easily integrated with both existing and new point-of-sale systems for retailers, vendors, and industry stakeholders.

4.1.3 Postmarket Surveillance

An MGO is not permanent: FDA retains authority to revoke marketing orders if surveillance reveals that a product's real-world harms (such as a spike in youth uptake) outweigh its benefits to adults. Rather than withholding authorizations primarily on projections of future youth use, the Agency can withdraw authorizations when warranted. This approach keeps FDA responsive to evolving evidence and supports public confidence that authorized products must consistently demonstrate they protect public health to remain on the market.

By better leveraging postmarket surveillance, FDA could be more decisive with authorizations, particularly for flavors like tobacco and menthol. Because the Draft Guidance asserts that tobacco and menthol may have comparatively lower youth appeal, much of the behavioral analysis regarding their impact can be conducted in a real-world, postmarket setting rather than a speculative one. To operationalize this shift, FDA should implement rigorous, category-wide monitoring and impose specific postmarket requirements as part of marketing orders to ensure that potential risks are identified and mitigated immediately (see section 6.4 for additional detail).

4.1.4 Device Access Restrictions

JLI is encouraged by the recent authorization of Glas, which has integrated Device Access Restrictions (DAR) technology requiring smartphone-linked ID verification and biometric activation and re-verification to unlock and use the device. As Dr. Koplow has said, this could be a “potential gamechanger” in reducing the risk of underage access. Used as a balancing mechanism, DAR can offset weaker switching evidence, supporting authorization of products

that might otherwise not be APPH. DAR could also serve as a remedial action: if postmarket surveillance identifies a measurable spike in youth uptake for an authorized product with DAR that was not required as part of an authorization, FDA could condition the continuation of that product's marketing order on the immediate implementation of DAR. But JLI believes DAR should not be required as a default for all flavored ENDS.

JLI encourages the Agency to contemplate the specific needs of ENDS utilizing DARs, which will need routine updates to firmware or accompanying mobile applications. These updates will require flexibility on the part of the Agency, as a premarket review of every firmware update will make these apps unusable. Additionally, Apple currently views manufacturer DAR apps, which are designed to enable stringent youth mitigation measures, as encouraging the use of tobacco or posing risk of physical harm and does not allow tobacco-related apps onto the App Store. We urge FDA to communicate the Agency's fully articulated DAR principles to Apple and other app stores to facilitate the inclusion of DAR apps across these platforms.

While DAR may provide a pathway to further restrict youth access, JLI urges FDA to collect real world data on the unintended consequences of widespread implementation of DAR, particularly if the Agency were to require routine age verification. If the path away from cigarettes is paved with technological frustrations, the likelihood of successful transition diminishes significantly, potentially leaving the most vulnerable populations anchored to combustible products.

Using a product that has DAR is expected to be an onerous process for adults who smoke — often older, lower socioeconomic status, and less technologically savvy. For these individuals, a device that requires frequent digital authentication, smartphone tethering, or complex biometric interfaces is not just a feature — it is an onerous process that functions as a barrier to entry. By locking an ENDS, a potential user may take away that the product is more dangerous than an unlocked product.

Currently, the most lethal nicotine delivery system — the combustible cigarette — remains the most accessible and easiest to use. It is entirely free from technological interference; the simple act of lighting a cigarette requires no age verification, no firmware updates, no app connectivity, and no authentication. By introducing sophisticated technological barriers to ENDS, FDA may inadvertently grant a competitive advantage to cigarettes and widely available illicit products. Other measures, such as comprehensive marketing and retail standards (described above), can ensure that youth risks are mitigated while not adversely impacting adults who smoke.

5 Challenges with the PMTA Process Perpetuate the Illegal Market

5.1 Challenges in the PMTA process

The PMTA process has been challenging for both FDA and manufacturers committed to following the law. But fixing it is feasible, and doing so is the surest way to promote a scientifically validated nicotine marketplace and instill consumer confidence for Americans who use nicotine. Doing so requires remedying the most significant barriers to successful PMTA pathways.

- **Deadly products are authorized faster than reduced harm products.** The Act explicitly requires FDA to complete PMTA reviews no later than 180 days after their receipt. While JLI recognizes that FDA has been inundated with PMTA applications for

ENDS, the pace of review has nonetheless been too slow. And, while FDA has authorized only 45 ENDS products, it issued 637 substantial equivalence orders and 1,246 exemption orders – most of these for combustible products – from FY2021 to FY2025.

- **PMTAs are not efficiently reviewed with compiled knowledge.** Instead of leveraging almost a decade of collected expertise in reviewing ENDS applications, each application is reviewed independently. Products within the categories of noncombustible products tend to be highly similar in their risk profile (e.g. ENDS or nicotine pouch products) and FDA could better leverage learnings across applications to focus on new and critical questions of public health.
- **Applicants face uncertainty regarding PMTA data requirements.** FDA’s lack of transparency around how they determine APPH creates uncertainty for applicants. Without clear communication of requirements from the Agency, applicants are left guessing how FDA weighs the risks and benefits of a new tobacco product. This leads to applicants submitting unnecessary data and extraneous review for FDA.
- **The Agency’s lack of transparency increases uncertainty.** Applicants are unclear about which studies and information are essential to include in applications. FDA has internal review guides and other resources to assist reviewers that could be made available to applicants, but FDA does not share these documents with applicants. The Agency should post review guides it uses to inform applicants’ future submissions. The FOIA process cannot be relied upon for timely information. As of May 2026, JLI still does not have an unredacted TPL for its 2020 applications, much less the underlying reviews or review guides relied upon for making a decision to authorize.

5.2 A framework for PMTA process reform

The PMTA process can be streamlined in a manner entirely consistent with the TCA. JLI’s proposed approach comports with the Least Burdensome Provisions adopted by some centers at FDA, which state, as a guiding principle, that “FDA intends to request the minimum information necessary to adequately address the regulatory question or issue at hand.”³⁷ By focusing on the statutory criteria for the review and authorization of PMTAs and requiring the minimum amount of information necessary to adequately understand potential health risks of new products, FDA could focus its resources on the most critical questions of public health, specifically:

- Is the candidate product less harmful than a combustible cigarette?
- Can the candidate product switch adults who smoke?
- Does the product present significant risk for youth initiation and, if so, what restrictions has the applicant proposed to reduce access and limit appeal by those underage?

³⁷ U.S. Food and Drug Administration. (2019, February 5). *The least burdensome provisions: Concept and principles: Guidance for industry and Food and Drug Administration staff* [Guidance document]. <https://www.fda.gov/media/73188/download>

FDA should commit to a rational and efficient process for reviewing applications and use its authority to authorize innovative alternatives to cigarettes.

The process should be grounded in the goal of authorizing scientifically substantiated, smokefree nicotine products that give Americans who smoke the widest array of compelling options to help them switch.

Furthermore, the review process should take place within the 180 days Congress mandates in the Act. Unfortunately, FDA has never met this statutorily mandated requirement. The following suggestions could help alleviate many of the issues with the current PMTA review process:

Increase Transparency & Clarity for PMTA Content and Review Standards

- **Provide industry with a list of how commonly used ingredients are tiered.** FDA suggested during the recent Roundtable on PMTA Submissions for ENDS that manufacturers could simplify review by using only ingredients classified as Tier 5 (unlikely to contribute to the carcinogenic risk of ENDS) according to FDA’s June 2024 Memorandum.³⁸ While FDA has helpfully provided its rubric for determining an ingredient’s tier, the rubric involves the assessment of complex scientific information and expert judgement. As a result, there can be legitimate scientific disagreement as to the tier of specific ingredients based on the available evidence. Since the tiering rubric alone is not enough to understand FDA’s position on the tier of specific ingredients, FDA should provide a database with FDA’s tiering of all ingredients it evaluates during the review of ENDS PMTAs. Providing this database would allow manufacturers to develop products that have lower potential risk and that could move through the review process more efficiently.
- **Provide a clear checklist for smokefree nicotine product applications.** Applicants submitting PMTAs are uncertain of how FDA determines a product is APPH; this leads to bloated PMTAs, which can include potentially unnecessary information, leading to review delays. FDA’s lack of transparency fosters this dynamic through vague and at times contradictory rules, guidance, conference presentations, and correspondence with industry. It also puts unnecessary strain on the review process. Clear checklists would allow industry to fund and conduct the science FDA needs to determine a product is APPH.
- **Create clear templates for industry.** Giving manufacturers clear guidance – including in the form of templates requiring specific information – ensures the applications themselves contain the exact information FDA wishes to receive in the exact form FDA wants to receive it. Less variation across applications makes reviews less burdensome and reduces bottlenecks because applicants and reviewers will all be on the same page.

³⁸ U.S. Food and Drug Administration. (2024). Genotoxicity hazard identification and carcinogenicity tiering of constituents in ENDS premarket tobacco product applications [Memorandum]. <https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/regulatory-science-policy-memoranda-about-fda-review-tobacco-product-applications>

Correct Review Priorities

- **Prioritize efficient review of responsibly marketed and compelling alternative nicotine products.** Combustible products are known to be deadly, yet in recent years, FDA has authorized more combustible products than smokefree nicotine products. Deprioritizing the review of combustible products would free up resources to more efficiently review smokefree products that have a positive impact on public health. This approach aligns with the Act’s standard of “appropriate for the protection of public health,” which does not require equal resources for all product categories and allows CTP to prioritize tobacco products with the greatest potential to reduce smoking-related disease and death.

Review Process Enhancements

- **Streamline the review process to eliminate needless inefficiency and duplication.** Rather than compiling knowledge and learnings from years of application review and applying the expertise to PMTAs, FDA considers each application *de novo*; each PMTA must build the world in which the product exists from scratch. This creates an inordinate amount of work for both applicants and FDA reviewers. Applying transferable learnings, information gathering, and analyses performed from one application to the next would eliminate the inefficiency FDA’s current application-by-application review approach creates. Providing PMTA reviewers with an up-to-date guide of FDA’s wealth of knowledge would create a more predictable “may pass go” flow that allows innovative, smokefree products to consistently enter the market.
- **Allow more collaboration with industry.** Industry science is often ahead of CTP’s knowledge base. During the application review process, CTP reviewers should be empowered to clarify questions with applicants to ensure questions that can be answered easily are not the source of delay or unnecessary rejections. FDA has stated that real-time communication with applicants during its nicotine pouch pilot program is critical to its efficient review of the PMTAs in the program. This type of communication should be extended across all applicants and product categories.

Other Proposals to Increase PMTA Review Efficiency

- **Use artificial intelligence (AI) to automate mundane tasks and to ensure consistency across applications.** Reviewers at many stages are tasked with ensuring consistency in the PMTA process. AI could help automate mundane review tasks and free up resources to focus on reviewing additional applications. This would also help reduce bottlenecks that result from fewer senior reviewers who have to review more applications. FDA should also explore utilizing AI to provide faster data for postmarket surveillance.
- **Shift CTP’s focus from pre-market behavioral data to postmarket surveillance to monitor how products affect the population as a whole.** For certain ENDS, particularly those—such as tobacco, menthol, mint, and spice—for which the FDA itself has suggested there “may be reliable scientific evidence demonstrating comparatively lower youth appeal and use,” much of the behavioral analysis can be conducted in a postmarket setting.

- **Establish a comprehensive marketing standard for all tobacco products.** As discussed in Section 4.1.1, providing a marketing standard for all new tobacco products also would allow FDA to streamline application review and ensure sufficient safeguards to mitigate against youth appeal.

6 How to Assess APPH

To support the public health goal of transitioning adult smokers from combustible cigarettes to lower-risk alternatives, it is essential to establish a PMTA review process that is efficient, predictable, and transparent. A functional regulatory pathway is vital not only for enabling scientifically validated products to reach the market but also for preventing the growth of an unregulated illicit market that can thrive when the formal process is delayed. By focusing on statutory APPH criteria—specifically relative harm, adult switching potential, and effective youth-access restrictions—the FDA can create a stable environment that benefits public health and ensures the market is defined by authorized, compliant products.

6.1 Product Design and Properties

An important aspect of an APPH determination is whether a candidate product is consistently manufactured in a way that does not produce excess risk from nonconforming or contaminated products. Candidate products should have validated manufacturing, disclosed and consistent ingredients, and technology that minimizes harmful or potentially harmful constituents (HPHCs) found in tobacco products. Additionally, candidate products should adhere to the forthcoming tobacco product manufacturing standards (TPMPs) and be subject to inspections of manufacturing facilities.

Congress also requires applicants to submit “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product.” The purpose of this information is to demonstrate that the manufacturer of the new ENDS products can consistently produce products that conform to product specifications. These manufacturing processes and controls provide FDA assurance that, once the new ENDS product is introduced into the market, it will be consistent with the product design evaluated by the Agency. Applicant-provided product studies, or reasonable bridging arguments, demonstrating stability of the new ENDS product also support consistency of the product design.

The proposed TPMP rule, once finalized and effective, will provide a much-needed high-level framework for tobacco manufacturers to comply in the manufacture, pre-production design validation, packing, and storage of finished and bulk tobacco products, and will help minimize the risk of tobacco products, beyond those inherent with their use. It will also help FDA efficiently evaluate consistency, safety, and compliance with regulatory requirements while reducing the need to request additional information.

6.2 Health Risk Evaluation

The Act requires applicants to submit “a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product.” The Act requires manufacturers to submit “testing and reporting of tobacco product constituents, ingredients, and additives, including smoke constituents, by brand and subbrand.” Together, these requirements provide FDA with a holistic view of product design and resulting emissions.

This data is sufficient for the Agency to determine if a new product’s health risks deviate significantly from existing market benchmarks or if a more intensive de novo evaluation is required.

FDA assesses the cancer risk of ENDS in a “within the market” approach with its ELCR approach, discussed above. Ultimately, this framework provides a reliable mechanism for the FDA to identify whether the cancer risks of a new ENDS product differ materially from products already available to consumers. Although methods for quantifying potential non-cancer health risks for ENDS are not available,³⁹ comparison of constituents and ingredients in the new ENDS product to existing ENDS products can also provide FDA evidence as to whether any non-cancer risks for a new ENDS product are likely to differ materially from other ENDS products on the market. For each of the 93 constituents on the HPHC list, FDA notes whether they are associated with cancer, respiratory diseases, cardiovascular diseases, reproductive or developmental diseases or addiction. FDA can then estimate the likely relative risk of major smoking related diseases between a new ENDS product, cigarettes, and existing ENDS products.

Similar analyses can be applied to ENDS ingredients. Most responsible ENDS manufacturers conduct a toxicological assessment of flavor ingredients added to their products.⁴⁰ This information is routinely supplied to FDA as part of a premarket application for a new ENDS product. FDA can then determine if flavor or other added ingredients in a new ENDS product are likely to contribute to non-cancer disease risk and compare the added ingredients and their use levels in a new ENDS product with the existing market. Furthermore, it is likely that there is significant commonality among ingredients used by ENDS manufacturers.

FDA should, at this point, have a compendium of toxicological data relating to almost all ingredients likely to appear in a new ENDS product. Toxicological analysis of ingredients may be particularly suitable to analysis by artificial intelligence as a means to further streamline the review process.⁴¹ FDA also could create a toxicological repository of commonly used e-liquid ingredients, allowing manufacturers to reference this compendium rather than generate new data.

Overall, FDA can reasonably estimate the cancer and non-cancer health risks of a new ENDS product based on the constituent and product formulation information that Congress mandated

³⁹ U.S. Food and Drug Administration. (2024). *Calculating excess lifetime cancer risk in ENDS premarket tobacco product applications* (Memorandum). <https://www.fda.gov/media/180610/download>

⁴⁰ Costigan, S., & Meredith, C. (2015). An approach to ingredient screening and toxicological risk assessment of flavours in e-liquids. *Regulatory Toxicology and Pharmacology*, 72(2), 361–369. <https://doi.org/10.1016/j.yrtph.2015.05.018>; Zhang, J., Chang, X., Holland, T. L., Hines, D. E., Karmaus, A. L., Bell, S., & Lee, K. M. (2022). Evaluation of inhalation exposures and potential health impacts of ingredient mixtures using in vitro to in vivo extrapolation. *Frontiers in Toxicology*, 3, Article 787756. <https://doi.org/10.3389/ftox.2021.787756>; Stevenson, M., Czekala, L., Simms, L., Tschierske, N., Larne, O., & Walele, T. (2019). The use of Genomic Allergen Rapid Detection (GARD) assays to predict the respiratory and skin sensitising potential of e-liquids. *Regulatory Toxicology and Pharmacology*, 103, 158–165. <https://doi.org/10.1016/j.yrtph.2019.01.001>

⁴¹ Hartung, T. (2023). Artificial intelligence as the new frontier in chemical risk assessment. *Frontiers in Artificial Intelligence*, 6, Article 1269932. <https://doi.org/10.3389/frai.2023.1269932>; Kleinstreuer, N., & Hartung, T. (2024). Artificial intelligence (AI)—it's the end of the tox as we know it (and I feel fine). *Archives of Toxicology*, 98(3), 735–754. <https://doi.org/10.1007/s00204-023-03666-2>; Lin, Z., & Chou, W. C. (2022). Machine learning and artificial intelligence in toxicological sciences. *Toxicological Sciences*, 189(1), 7–19. <https://doi.org/10.1093/toxsci/kfac075>

manufacturers provide the Agency. This information can be compared with ENDS products currently available in the market to determine if the new product differs materially from current market products. If the ENDS product falls reasonably within the range of current ENDS, existing public health conclusions about the likely health risks of ENDS can then be applied to the new ENDS product. FDA itself used an excess relative risk (ERR) of 0.15 (indicating a 15% increase in all-cause mortality risk; i.e., an 85% reduction in risk) for noncombustible products, including ENDS, in its model justifying its proposed rule limiting the nicotine content of combustible cigarettes.⁴²

The risk estimate (relative to cigarettes) for a new ENDS product can then be an input into an APPH analysis of the new ENDS product based on estimates of likely tobacco product user and non-user behavior resulting from market introduction of the new ENDS product.

6.3 Behavioral Impact: Assessing the Likelihood of Use

Congress recognized that whether a new, lower-risk tobacco product could benefit or harm “the population as a whole” depends not only on the health risks of that product, but also on who uses the product. A new, lower-risk product that is predominantly used (switched to) by current cigarette smokers but is initiated on by few non-tobacco users will obviously benefit “the population as a whole.” Conversely, if the same product is primarily used by those who are nicotine naive, it would harm public health even though it is lower risk compared to cigarettes. Therefore, the Tobacco Control Act requires manufacturers of a new product to provide data projecting the increased or decreased likelihood that:

1. “existing users of tobacco products will stop using such products”
2. “those who do not use tobacco products will start using such products”

The likely rate of adoption by adults who smoke, on the one hand, and by adult nonusers, on the other, can be estimated from behavioral studies that expose study respondents to information about the product, including its advertising and promotional materials, and assess their intent to try and to use the product.⁴³

It is reasonable to assess likelihood of use for a new tobacco product among both users and nonusers of tobacco based upon their response to marketing and labeling materials:

- First, these are the very materials that will appear in the market and be seen by the population as a whole when a new ENDS product is authorized.
- Second, responsible manufacturers will conduct research to verify that their marketing materials resonate with the adult smoker target audience for new ENDS products and do not resonate with the non-target population of non-tobacco users, information that will be provided to FDA as part of a new ENDS product application.

⁴² See, 87 Fed. Reg. at 26454, “Tobacco Product Standard for Menthol in Cigarettes,” dated May 4, 2022. Available at, <https://www.federalregister.gov/documents/2022/05/04/2022-08994/tobacco-product-standard-for-menthol-in-cigarettes#citation-12-p26480>.

⁴³ McCaffrey, S., Shiffman, S., Hannon, M. J., & Black, R. A. (2026). A randomized study evaluating the impact of ENDS advertising and promotional materials on use intentions among adults who smoke and non-tobacco users. *Journal of Consumer Policy*, 49(1), 1–18. <https://doi.org/10.1007/s10603-025-09608-y>

- Third, in the Act, Congress mandated that manufacturers submit “all consumer information and other labeling for such tobacco product, a representative sampling of advertisements for such tobacco product,”⁴⁴ indicating that Congress intended FDA to consider such information.

It is important to recognize that, for new tobacco product applications, Congress did not mandate that manufacturers provide a demonstration of long-term actual product use.⁴⁵ Congress reserved this requirement for Modified Risk Tobacco Product Applications in which manufacturers must provide “data and information on how consumers actually use the tobacco product.”⁴⁶ This suggests that Congress’ use of “likelihood” when describing the requirements for new tobacco product applications under § 910 was intentional and indicates that the evaluation should be based upon anticipated patterns of use rather than on long term use behavior studies.

Furthermore, demonstration of actual use is not needed: what is important is the relative degree to which users versus nonusers are likely to use the product. This relative estimate (or ratio) of likelihood of use can be derived, for both users and nonusers, from assessment of their willingness to try and to use the product following exposure to marketing and promotional materials.

While estimation of the likely adoption rate for nonusers of tobacco is sufficient to meet the statutory requirement to assess “the increased or decreased likelihood that those who do not use tobacco products will start using such products,” more information is needed to address the statutory requirement for current cigarette smokers. This is because the adoption rate for this group, measured through adults who smoke’ responses to marketing and promotion materials, yields the likelihood that this group will use the new ENDS product. It does not provide an estimation of the rate at which adults who smoke who use the product will fully switch from cigarette smoking (“stop using such products”) to exclusive use of the new ENDS product.

Fortunately, the likely switch rate can be estimated from smokers’ subjective responses to actual use of the product. Measures such as formally assessed Satisfaction (i.e., using validated measurements scales) have been shown to predict switching in the year after product adoption of JUUL products,^{47, 48} making them valuable surrogate outcomes for assessing switch potential efficiently.⁴⁹ These measures derive from tests that assess abuse liability – i.e., the likelihood of

⁴⁴ Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, § 905 i(1), 123 Stat. 1776 (2009). Available at, <https://www.govinfo.gov/content/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf>.

⁴⁵ Actual product use can only be assessed among tobacco product users as it is unethical to provide tobacco products to nonusers.

⁴⁶ Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, § 911 d(6), 123 Stat. 1776 (2009). Available at, <https://www.govinfo.gov/content/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf>.

⁴⁷ Goldenson, N. I., Shiffman, S., Sembower, M. A., Selya, A., Pype, S., & Black, R. A. (2025). Evaluating the effect of the JUUL2 system with 5 flavors on cigarette smoking and tobacco product use behaviors among adults who smoke cigarettes: 6-week actual use study. *Interactive Journal of Medical Research*, 14, Article e60620. <https://doi.org/10.2196/60620>

⁴⁸ Goldenson, N. I., Shiffman, S., Hatcher, C., Lamichhane, D., Gaggar, A., Le, G. M., Prakash, S., & Augustson, E. M. (2021). Switching away from cigarettes across 12 months among adult smokers purchasing the JUUL System. *American Journal of Health Behavior*, 45(3), 443–463. <https://doi.org/10.5993/AJHB.45.3.4>

⁴⁹ Mavreles Ogrodnick, M., Kute, N. G., Van Do, V., Wiley, P., Henderson, K., Spears, C. A., Pechacek, T. F. & Weaver, S. R. (2024). Examining longitudinal associations between initial perceptions and experiences with

potential dependence – which is a benefit to adults who smoke switching and potentially a risk to nonusers initiating. It is reasonable to assess likelihood of switching among adults who smoke through a study design in which this group actually uses the product, albeit briefly. Simply, this group might be motivated to try the product by marketing and promotion materials, but, having tried it, they may not find the product likeable or satisfying thus diminishing the potential public health benefit of the new ENDS product because they will not fully switch to exclusive use. An example of this is the early generation ENDS products, which were tried by a large number of adults who smoke but, because they were found to be unsatisfying, did not facilitate significant complete switching.

Overall, straightforward and short-term study designs exist through which manufacturers can provide FDA sufficient information to address statutory requirements regarding likely behaviors of users and nonusers of tobacco. This is particularly so as projections of likely behavior can be bridged to existing data from long-term use studies that have already been conducted, further bolstering confidence in behavioral projections from short term studies of behavioral intentions. Furthermore, these data provide FDA sufficient information to conduct an APPH analysis when coupled with estimation of the likely health risks of the new ENDS product.

6.4 Population Health Impact

The statute lays out a simple and clear standard by which FDA is to evaluate whether an applicant product qualifies for an authorization as being APPH using the following parameters, as discussed above:

- FDA must determine the likely health risks of a new ENDS product to quantify the ERR of a product.
- FDA must determine the likelihood of adoption of new ENDS products among nonusers of tobacco products.
- FDA can determine the likelihood of adoption and the switch rate among adopters for adult tobacco consumers.

These three parameters are sufficient for FDA to conduct a robust analysis of whether a new ENDS product is APPH. The dynamic relationship among these three parameters is enumerated in the statute and should be weighed to estimate the impact to population health. For a given ERR, relative magnitude of these harms to non-users and benefits to smokers determines APPH. For example, if the data demonstrate that a new ENDS product is likely to be adopted almost entirely by adult cigarette smokers, the population as a whole is likely to benefit provided the ERR and switch rates are within reasonable bounds. Finally, even if a new ENDS product is less effective at switching adults who smoke it may still benefit population health if, again, other parameters remain within reasonable bounds.

Population benefit under this rubric is defined as the likely impact of launching a new ENDS product on population mortality over time. Population mortality is the correct metric to measure the impact of a new product on the population as a whole. One of the purposes of the Act defined by Congress is “to reduce disease risk and the social costs associated with tobacco-related

electronic nicotine delivery system (ENDS) use and use patterns among adults who smoke and recently initiated ENDS. Tobacco Induced Diseases, 22(September), 164. <https://doi.org/10.18332/tid/193009>

diseases.”⁵⁰ Estimating overall population mortality captures and quantifies the extent to which a new ENDS product “reduce[s] disease risk.”

This analysis could incorporate key parameters such as US population demographics, tobacco use characteristics, ERR estimates for ENDS and cigarettes, and data-based initiation, adoption, and switching parameters. Many of these model parameters are the same as those used in population models generated by FDA in support of proposed regulatory activities.⁵¹ Just as FDA has relied upon the results of population modeling in the past to support proposed regulations, it should also leverage population modeling to simplify and streamline the premarket tobacco product application process.

7 The Role of Comprehensive Postmarket Surveillance

FDA’s premarket decisions, no matter how made, entail a degree of uncertainty. Postmarket surveillance provides the Agency with “an overall assessment of how the marketing of the tobacco products continues to be appropriate for the protection of public health.” Recognizing this, Congress granted FDA broad authority to withdraw marketing authorizations granted under § 910 of the Tobacco Control Act. Grounds for withdrawal include “that the continued marketing of such tobacco product no longer is appropriate for the protection of the public health” among several other reasons. FDA recognizes this authority as it states in its letters authorizing new tobacco products that “[T]he products subject to these marketing granted orders are subject to withdrawal or temporary suspension as described in section 910(d) of the FD&C Act.”

FDA can draw on myriad sources to determine if an authorized product remains APPH. FDA places a substantial postmarket reporting burden upon manufacturers with market authorization of a new product. For example, manufacturers must submit all labeling, advertising, and promotional materials to the FDA at least 30 days before they are released to the public. Manufacturers must also retain records of manufacturing deviations as well as serious and unexpected adverse experiences relating to product use. Serious and unexpected adverse events must be submitted within 15 calendar days of being received.

Effective postmarket surveillance also requires a coordinated, comprehensive population-based data-collection system to monitor all authorized (and non-authorized) products, so as to understand what is happening in the real world. CTP should implement effective monitoring tools to gather rigorous, timely data on the health and behavioral effects of the full range of ENDS and other alternative nicotine products. This would allow CTP to periodically re-evaluate products’ appropriateness for the protection of public health and would also provide a scientific foundation for other efforts CTP might undertake to benefit public health.

Such a monitoring system would need to be population-based and cover the full range of tobacco products. It should assess the following in U.S. adults and youth:

- Current tobacco product use, and product use history.

⁵⁰ Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, § 9, 123 Stat. 1776 (2009). Available at, <https://www.govinfo.gov/app/details/PLAW-111publ31>.

⁵¹ U.S. Food and Drug Administration. (2023). *Methodological approach to modeling the potential impact of a nicotine product standard on tobacco use, morbidity, and mortality in the U.S.* U.S. Department of Health and Human Services, Center for Tobacco Products. <https://www.fda.gov/media/185056/download>

- Tobacco product use patterns, including switching from more hazardous to less hazardous tobacco products (and vice versa), dual product use, and initiation of tobacco products among non-users.
- Behavioral intentions of both tobacco-users and non-users. Among current tobacco product users, assessments should include intentions to quit their current product, try and use alternative nicotine products, and intentions to dual use alternative products along with cigarette smoking.
- Health changes associated with changes in tobacco product use.
- Health risk perceptions pertaining to using particular alternative nicotine products (absolute and relative to cigarettes).

Separate from such population-based surveillance, collection of real-world data from health providers could support timely identification of trends in adverse health impacts, including potential serious and unexpected adverse experiences (SAEs and UAEs, respectively), attributable to the use of tobacco products, including alternative nicotine products. Companies that go through the PMTA process are already required to provide this information to FDA post-authorization.

Such a centralized and comprehensive effort would provide CTP with an accurate, timely, and holistic view of how tobacco use is evolving in the real-world market and would be superior to the fragmented view that is provided by multiple limited sources, including that from multiple companies, each monitoring their own products in isolation.

By better utilizing its postmarket surveillance authority, FDA can shift its focus away from a risk-averse posture. CTP can authorize more smokefree products that are highly likely to benefit the public health with assurance that the products' real-world effects will be assessed, and can be acted upon if necessary. If warranted, FDA's revocation of market orders would demonstrate it is responsive to a product's APPH status being dynamic and not static or permanent. Increasing postmarket surveillance tools gives the American public confidence that products that have been authorized as "appropriate for the protection of public health" continue to be so.

8 Opening More Pathways for ENDS That Have Been Deemed APPH

A critical need exists for more efficient regulatory pathways for manufacturers to bring modified versions of products that have already been determined to be APPH onto the market more quickly. ENDS products, unlike traditional tobacco products, are based on complex supply chains and innovative technology. Tobacco products with electronic components were virtually non-existent when the TCA was enacted. These products require maintenance and updates to delay becoming functionally obsolete.

While any modification must remain demonstrably APPH, the specific standard for making routine updates through the sPMTA pathway remains unclear. We believe the evidence necessary for such updates should be analogous to the comparative review used for SE reports, focusing on the health impact of the modification rather than requiring a de novo review of a small change to an already authorized product.

This offers the most common sense and efficient framework for the supplemental PMTA review — where the modification, when compared to the authorized product, does not raise different

questions of public health — which would serve as a crucial and efficient path to confirming the product, as modified, still meets the APPH standard.

To maximize the efficiency gained from this targeted review standard, we also encourage the Agency to establish predictable review timelines for sPMTAs, similar to the goals CTP sets for the SE pathway. If the scientific review is correctly scoped to the modification, a full statutory 180-day PMTA review period should be unnecessary. By establishing performance goals for review periods—such as a 90-day review cycle for an sPMTA—manufacturers would be better able to make additional investments in R&D, and both the agency and industry would benefit from a resource allocation planning perspective, bringing the process in line with other comparative review pathways.

JLI also believes that the EX pathway, currently only benefitting deadly combustible products and other non-innovative products, should be open to facilitating minor ingredient changes for ENDS and other novel smokefree products. While FDA has permitted over 1500 Exemption Requests for conventional tobacco products, it has not yet permitted e-cigarettes to utilize this pathway.

Use Statute-Granted Discretion to Advance Public Health

Congress trusted FDA with the discretion to decide if exemption requests are “otherwise appropriate,” and FDA should use this discretion to review ENDS. CTP can simply look to its 2018 action to remove 1500 products from SE review as guiding precedent:

With the years of experience conducting thousands of SE reviews, and with a greater understanding of tobacco products, FDA is announcing a change in its approach: The Agency will continue to review the approximately 1,000 pending provisional SE Reports that were determined to have the greatest potential to raise different questions of public health and will remove from review the approximately 1,500 provisional SE Reports that were determined less likely to do so.⁵²

Extending this logic to utilizing the Exemption Request pathway for minor modifications to the ingredients in ENDS could similarly reduce review burden for FDA while ensuring products are scientifically validated.

This clarity would also benefit both industry and the Agency by creating predictable expectations for review timelines and data requirements, allowing for faster product enhancements and reducing redundant testing and reviews for products already determined to be appropriate for the protection of public health.

9 Conclusion

The state of the U.S. ENDS market is unsustainable. Without a meaningful shift in how FDA considers PMTAs and other premarket pathways, the illicit market will subsume the licit market. To address this, FDA must reestablish the incentives for participating in the regulatory process. JLI staunchly believes the most effective deterrent to the illicit market is a functioning PMTA

⁵²See, FDA Update on Provisional Substantial Equivalence (SE) Review Process, April 8, 2018. Available at, <https://web.archive.org/web/20190207192205/https://www.fda.gov/TobaccoProducts/NewsEvents/ucm583226.htm>.

pathway with rigorous but efficient scientific standards that expands authorized flavored options for adults who smoke. JLI respectfully urges FDA to take decisive, near-term action to establish a regulated marketplace that advances the intent of the TCA and meets the needs of the 25 million American adults who continue to smoke.

Sincerely,

A handwritten signature in black ink, reading "Robert Gougelet". The signature is written in a cursive style with a large, prominent initial "R".