[PUBLISH]

In the United States Court of Appeals

For the Eleventh Circuit

No. 21-13340

BIDI VAPOR LLC,

Petitioner,

versus

U.S. FOOD AND DRUG ADMINISTRATION,
ACTING COMMISSIONER OF U.S. FOOD AND
DRUG ADMINISTRATION,
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,

Respondents.

Petitions for Review of a Decision of the
Food and Drug Administration
Agency No. PM0003460

No. 21-13387

DIAMOND VAPOR LLC,

Petitioner,

versus

U.S. FOOD AND DRUG ADMINISTRATION,

Respondent.

Petitions for Review of a Decision of the
Food and Drug Administration
Agency No. PM0003472

No. 21-13438

JOHNNY COPPER, L.L.C.,

Petitioner,

versus

U.S. FOOD AND DRUG ADMINISTRATION,

Respondent.

Petitions for Review of a Decision of the
Food and Drug Administration
Agency No. PM0003757

No. 21-13454

VAPOR UNLIMITED LLC,

Petitioner.

versus

U.S. FOOD AND DRUG ADMINISTRATION,

Respondent.

Petitions for Review of a Decision of the
Food and Drug Administration
Agency No. PM0003581

No. 21-13521

UNION STREET BRANDS L.L.C.,

Petitioner,

versus

U.S. FOOD AND DRUG ADMINISTRATION,

Respondent.

Petitions for Review of a Decision of the
Food and Drug Administration
Agency No. PM0003525

No. 21-13522

POP VAPOR CO. LLC,

Petitioner,

versus

U.S. FOOD AND DRUG ADMINISTRATION,

Respondent.

Petitions for Review of a Decision of the
Food and Drug Administration
Agency No. PM0002546

Before WILLIAM PRYOR, Chief Judge, ROSENBAUM, and BRASHER, Circuit Judges.

WILLIAM PRYOR, Chief Judge:

These petitions for review concern whether it was arbitrary and capricious for the Food and Drug Administration to issue marketing denial orders to six tobacco companies for their electronic nicotine-delivery systems without considering the companies' marketing and sales-access-restriction plans designed to minimize youth exposure and access. The Administration refused to consider the marketing and sales-access-restriction plans based on both its need for efficiency and its experience that marketing and sales-access restrictions do not sufficiently reduce youth use of electronic nicotine products. Because "agency action is lawful only if it rests 'on a consideration of the relevant factors,'" *Michigan v. Env't Prot. Agency*, 135. S. Ct. 2699, 2706 (2015) (quoting *Motor Vehicle Mfrs. Ass'n U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)), and the Administration failed to consider the relevant marketing and sales-access-restrictions plans, the marketing denial orders were arbitrary and capricious. So, we grant the petitions for review, set aside the marketing denial orders, and remand to the Administration.

I. BACKGROUND

The Tobacco Control Act of 2009 prohibits manufacturers from selling any "new tobacco product" without approval from the Food and Drug Administration. *See* 21 U.S.C. § 387j. Any tobacco

product that was not on the market as of February 15, 2007, is a "new tobacco product." *Id.* § 387j(a)(1). The Act instructs the Administration to deny applications for new tobacco products if, based on the information before it, the Administration finds "a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." *Id.* § 387j(c)(2), (2)(A). Whether a new product is "appropriate for the protection of the public health" is determined by evaluating "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." *Id.* § 387j(c)(4). To make this determination, the Administration must consider both the "likelihood that existing users of tobacco products will stop using such products" and the "likelihood that those who do not use tobacco products will start using such products." *Id.*

In 2016, the Administration deemed that electronic nicotine-delivery systems using nicotine derived from tobacco—including e-liquids and e-cigarettes—were "tobacco products" within the Administration's regulatory authority. Deeming Tobacco Products to Be Subject to the Federal Food, Drug, and Cosmetic Act, 81 Fed. Reg. 28,974, 29,028 (May 10, 2016) (hereinafter *Deeming Rule*). The Administration defines e-cigarettes as "electronic device[s] that deliver[] e-liquid in aerosol form into the mouth and lungs when inhaled." U.S. FOOD & DRUG ADMIN., PREMARKET TOBACCO PRODUCT APPLICATIONS FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS: GUIDANCE FOR INDUSTRY 6 (2019) (hereinafter *2019 Guidance*). E-liquids are defined to "include liquid nicotine, nicotine-

containing liquids," and other liquids "that are intended or reasonably expected to be used with or for the human consumption of a tobacco product." *Id.*

There are two categories of e-cigarettes: open and closed. Open e-cigarettes are typically larger and require the user to re-fill a tank with e-liquid. *Id.* Closed e-cigarettes tend to be smaller and are either entirely disposable or use disposable, pre-filled cartridges. *Id.*

Because many electronic nicotine-delivery systems were already on the market by 2016, the Administration decided to stagger its evaluation of the products and allow the products to stay on the market in the interim. *Deeming Rule*, 81 Fed. Reg. at 29,009–10. The Administration explained that as it gained more experience regulating electronic nicotine-delivery systems, it expected to provide more guidance to manufacturers as to what information would be required in the premarket authorization applications to show that a product was "appropriate for the protection of [the] public health." *See id.* at 28,997. The original application deadline for flavored electronic nicotine-delivery systems was September 2018, but "a series of schedule changes implemented by the [Administration] and federal courts" moved the final deadline to September 9, 2020. *Breeze Smoke, LLC v. U.S. Food & Drug Admin.*, 18 F.4th 499, 504 (6th Cir. 2021); *accord* Enforcement Priorities for Electronic Nicotine Delivery Systems and Other Deemed Products on the Market Without Premarket Authorization (Revised), 85 Fed. Reg. 23,973, 23,974 (Apr. 30, 2020).

Before the September 2020 application deadline, the Administration issued nonbinding guidance, hosted public meetings, and published a proposed rule to explain to manufacturers what evidence would be required in their applications. The Administration repeatedly represented to tobacco companies that marketing and sales-access-restriction plans were relevant to its determination of whether their products were "appropriate for the protection of the public health." *See* 21 U.S.C. § 387j(c)(4). For example, at a public meeting in 2018, an Administration representative stated that one of the considerations the Administration "ha[d] used in deciding whether a [tobacco] product [wa]s appropriate for the protection of the public health" was whether "the marketing of the new [product] [would] affect the likelihood of nonuser uptake, cessation rates[,] or other significant shifts in user demographics in a manner to decrease morbidity and mortality from tobacco product use." IILUN MURPHY, PREMARKET TOBACCO PRODUCT APPLICATION CONTENT OVERVIEW, U.S. FOOD & DRUG ADMIN. (Oct. 23, 2018), https://www.fda.gov/media/117507/download.

The Administration repeated this advice when it published final guidance on premarket authorization applications for electronic nicotine-delivery-system products in June 2019. *See 2019 Guidance*, *supra*. The Administration recommended companies include any applicable "restrictions on the sales and distribution" of their products in their applications "to help support a showing that the marketing of the product would be [appropriate for the protection of the public health]." *Id.* at 20–21; *accord id.* at 12.

The Administration communicated its expectation that companies submit marketing and sales-access-restriction plans in a proposed rule published in September 2019. The proposed rule included a requirement for applicants to submit marketing plans, including "[a]ny means by which youth-access or youth-exposure to the products' labeling, advertising, marketing, and promotion would be limited." Premarket Tobacco Product Applications and Recordkeeping Requirements, 84 Fed. Reg. 50,566, 50,643 (proposed Sept. 25, 2019) (to be codified at 21 C.F.R. pt. 1114). The proposed rule explained that the information in an applicant's marketing plan "is critical to [the Administration's] determination of the likelihood of changes in tobacco product use behavior." *Id.* at 50,581; *accord id.* (stating that the Administration "*will review* the marketing plan to evaluate potential youth access to, and youth exposure to the labeling, advertising, marketing, or promotion of, a new tobacco product" (emphasis added)). As an example, the proposed rule stated that "heavy use of online social media to promote a tobacco product without access restrictions, as opposed to actions such as paper mailings directed only to current smokers of legal age, indicates the potential for youth to be exposed to the promotion of the product." *Id.*

In April 2020, the Administration published a guidance document about its enforcement priorities and "current thinking" on electronic nicotine-delivery systems, which detailed the most-current data on youth electronic nicotine-delivery-systems use, the enforcement measures employed by the Administration in its attempt

to curb minor use, and the considerations of the Administration going forward. *See* U.S. FOOD & DRUG ADMIN., ENFORCEMENT PRIORITIES FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (ENDS) AND OTHER DEEMED PRODUCTS ON THE MARKET WITHOUT PREMARKET AUTHORIZATION (REVISED): GUIDANCE FOR INDUSTRY 2–3 (Apr. 2020) (hereinafter *2020 Guidance*). The 2020 Guidance stated that, since 2017, the Administration had seen "an alarming increase in the use of [electronic nicotine-delivery systems] by middle and high school students." *Id.* at 6. The 2020 Guidance explained that, in response, the Administration increased enforcement against and sent warning letters to manufacturers and retailers who marketed or sold products to youth. *Id.* at 6–7. Guidance also explained that certain kinds of marketing—such as making products "resemble kid-friendly foods and drinks" or "ordinary items that may not draw the attention of adults"—"can increase youth appeal." *Id.* at 25–26; *see also id.* at 25–27 (identifying cartoon figures and entertainment media popular with children as marketing tools that increase popularity with minors). And the Guidance stated that 71 percent of current youth users reported using the products "because they come in flavors [they] like." *Id.* at 14 (internal quotation marks omitted).

The 2020 Guidance also expressed the Administration's position that "age verification alone is not sufficient to address [the youth-use] issue" and that "many youth obtain their [products] from friends or sources in their social networks." *Id.* at 44–45. The Administration stated that the policy outlined in the 2020 Guidance

"[wa]s a more appropriate means to combat youth use of, and access to, these products." *Id.* at 44. And in response to these data, the Administration explained its rationale for treating flavored, cartridge-based electronic nicotine-delivery systems different from other electronic-nicotine-delivery systems.

With respect to flavored, cartridge-based systems, the Administration explained that "focusing on how the product was sold would not appropriately address youth use of the products that are most popular among youth." *Id.* at 21. The Administration reasoned that "[t]hese products are produced on a large scale, are easy to conceal, can be used discretely, and are not the products typically produced in vape shops that mix nicotine with e-liquid flavors." *Id.* And "[g]iven the urgent need to address the dramatic rise in youth use," the 2020 Guidance explained the Administration's decision to "prioritize[] enforcement with respect to any flavored, cartridge-based [electronic nicotine-delivery system] products . . . without regard to the location or method of sale." *Id.*

But with respect to other electronic nicotine-delivery systems, the Administration explained that it "intend[ed] to prioritize enforcement for lack of marketing authorization for any" electronic nicotine-delivery system products "when the manufacturer has not taken or is not taking adequate measures to prevent minors' access to these products." *Id.* To that end, the Guidance listed "factors the [Administration] intend[ed] to consider" when deciding if a manufacturer had taken adequate precautions to avoid youth use for these other products. *Id.* at 22. Those factors included

"[w]hether the manufacturer ha[d] implemented adequate programs to monitor retailer compliance with age-verification and sales restrictions" such as hotlines for reporting noncompliant sales and mystery shopper programs; "ha[d] established and enforce[d] penalties against retailers that fail to comply with age-verification and sales restrictions"; was "us[ing] adequate age-verification technology" for online sales, such as "an independent, third-party age- and identity-verification service that compares customer information against third-party data sources, such as public records"; and was "limit[ing] . . . the quantity of . . . products that a customer may purchase within a given period of time." *Id.*

On July 9, 2021, the Administration circulated an internal memorandum instructing staff on how to evaluate the remaining applications not yet in substantive scientific review. The memorandum explained that the "Office of Science ha[d] been tasked with developing a new plan to effectively manage the remaining non-tobacco flavored [product applications] not in . . . substantive scientific review . . . in order to take final action on as many applications as possible by September 10, 2021." The Administration's "objective [wa]s to address these applications by applying a standard for evidence necessary to demonstrate an incremental benefit to adult smokers of non-tobacco flavored [electronic nicotine-delivery systems] products." To do so, the Administration adopted a "fatal flaw" approach: "the evidence necessary for this evaluation would be provided by either a randomized controlled trial . . . or a longitudinal cohort study" and "[t]he absence of these types of

studies [wa]s considered a fatal flaw, meaning any application lacking this evidence w[ould] likely receive a marketing denial order."

On August 17, 2021, the Administration circulated another internal memorandum about the standard of review for non-tobacco-flavored products for "a streamlined scientific review." The memorandum reiterated that, "most likely," the evidence that would be necessary to meet the "high burden for applicants seeking to demonstrate a potential benefit to adult smokers that could justify th[e] risk" to youth would be a randomized controlled trial or a longitudinal cohort study. (Footnote omitted.) But the new memorandum also stated that the Administration "would also consider evidence from another study design, provided that it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco-flavored products." The memorandum detailed the risks to youth and potential benefits to adults justifying this standard of review.

The August 17 memorandum also addressed the marketing and sales-access-restriction plans contained within many of the applications. It acknowledged that "[l]imiting youth access and exposure to marketing is a critical aspect of product regulation." But it explained that, although "[i]t is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal such that the risk for youth initiation would be reduced," the Administration had not yet evaluated an application that had "proposed advertising and promotion restrictions that would

decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use." The Administration also stated that it was "not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use [electronic nicotine-delivery systems]," so "for the sake of efficiency, the evaluation of the marketing plans in applications w[ould] not occur at this stage of review." memorandum was rescinded one week later on August 25, 2021.

On August 26, 2021, the Administration announced that it had denied authorization for 55,000 flavored products from three manufacturers in its first adjudications for the applications that progressed to substantive scientific review. Press Release, U.S. Food & Drug Admin., FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health (Aug. 26, 2021), https://bit.ly/32ehP8C. The Administration explained that it denied the applications for "lack[] [of] sufficient evidence that they have a benefit to adult smokers sufficient to overcome the public health threat posed by the well-documented, alarming levels of youth use of such products." *Id.* It explained that the agency received applications for 6.5 million products from over 500 companies, with one company accounting for 4.5 million of the applications. *Id.* It reiterated the evidentiary standard from the rescinded August 17 memorandum: that "evidence of benefits to adult smokers for such products would likely be in the form of a randomized

controlled trial or longitudinal cohort study, although the [Administration] does not foreclose the possibility that other types of evidence could be adequate if sufficiently robust and reliable." *Id.* The Administration explained that it issued marketing denial orders "[b]ecause this evidence was absent in th[o]se applications." *Id.* And the Administration stated that it would "continue to review other premarket tobacco applications for non-tobacco flavored [products] to determine whether there is sufficient product-specific scientific evidence of a benefit to adult smokers to overcome the risk posed to youth" and that "in the absence of this evidence, the agency intend[ed] to issue a[marketing denial order]." *Id.*

Petitioners are tobacco companies that manufacture electronic nicotine-delivery system products and applied for premarket authorization before the September 2020 deadline. Bidi Vapor LLC applied for premarket authorization for eleven electronic nicotine-delivery systems called "BIDI Sticks." BIDI Sticks are disposable, closed electronic nicotine-delivery systems pre-filled with flavored e-liquid. BIDI Sticks come in eleven flavors: one tobacco and ten non-tobacco flavors. Bidi's application included product information, scientific safety testing, literature reviews, consumer insight surveys, and details about the company's youth-access-prevention measures, distribution channels, and adult-focused marketing practices. Regarding its marketing and sales-access restrictions, Bidi stated in its application that the company's "marketing strategies target only existing adult vapor product users, including current adult smokers." Toward that end, Bidi discontinued

direct sales through its website, declines to advertise anywhere other than its age-gated website and adult-only brick-and-mortar stores, and monitors its limited distribution channels for compliance with its adult-only marketing and sales policies. Bidi requires all "downstream business partners to establish and publicize a hotline for anonymous reporting of non-compliant sales and [to] implement a policy of notifying the [Administration] of retailer violations." "Bidi . . . uses a state-of-the-art authentication system to ensure supply chain security and prevent counterfeit . . . products from getting in the hands of consumers . . . [and] to safeguard against procurement by minors." And Bidi renamed the flavors of its products "to more neutral names" that would be less attractive to youth.

Diamond Vapor LLC, Johnny Copper, L.L.C., Vapor Unlimited LLC, and Union Street Brands L.L.C. applied for premarket authorization for numerous e-liquids meant for use in open-tank devices. These tobacco companies submitted survey information from their customers about smoking cessation, literature reviews, scientific studies about switching to e-cigarettes, smoking cessation, and the role of flavors, and details about its marketing and youth-access-prevention plans. For example, Diamond uses technology for its online sales that relies on public records to verify a purchaser's age. Johnny Copper implemented "Trace/Verify technology" on all of its bottles of e-liquids, which involved placing a unique QR code on each bottle connected to the driver's license of

the purchaser so that authorities can identify the purchaser if the product is later found in the possession of a minor.

Pop Vapor Co. LLC applied for premarket authorization for 132 e-liquids and 18 disposable devices. In its application, Pop submitted a literature review, a marketing plan, proposed reseller requirements, and post-market surveillance plans. Pop uses age-verification technology that uses public records for its online sales, limits its "sales channels to online retail sites with adequate online age verification software," and uses only black-and-white labeling to "minimize the visual appeal of [its] products."

Between September 1 and September 16, 2021, the Administration issued nearly identical marketing denial orders to each of the tobacco companies for their non-tobacco flavored products. The orders stated that the "key basis for [the Administration's] determination" was that "[a]ll of [the applications] lack[ed] sufficient evidence demonstrating that [the] flavored [products] will provide a benefit to adult users that would be adequate to outweigh the risks to youth." Because the Administration did not find such evidence in the tobacco companies' applications, it could not "find that permitting the marketing of [the] new tobacco products would be appropriate for the protection of the public health" and did not conduct scientific review of "other aspects of the applications."

Alongside the orders, the Administration provided Technical Project Lead Reviews for each of the applications. The Reviews explained the scope of review: an evaluation as to "whether the subject [applications] contain[ed] evidence from a randomized

controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new products on switching or cigarette reduction that could potentially demonstrate the added benefit to adult users of their flavored [products] over an appropriate comparator tobacco-flavored [product]." Because the applications did not include such evidence, the Administration issued marketing denial orders to each of the tobacco companies for all of their flavored products. The discussion sections of the Reviews were nearly identical to the rescinded August 17 memorandum. The Reviews also included the same footnote from the August 17 memorandum explaining that the Administration did not evaluate the marketing plans "for the sake of efficiency" because the Administration was "not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use [electronic nicotine-delivery systems]."

Finally, the record includes the forms that Administration staff used to evaluate the authorization applications. The forms had only three criteria: whether the application included a randomized controlled trial on new product use and smoking behavior, a longitudinal cohort study on the same, or other evidence related to the potential benefit to adults of flavored products compared to tobacco-flavored products. For each of the tobacco companies' applications, the checkboxes next to the randomized-controlled-trial and longitudinal-cohort-study criteria were marked "absent," and the "[o]ther evidence" criterion was marked "N/A."

After the tobacco companies had received marketing denial orders, the Administration published its Final Rule. Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. 55,300 (Oct. 5, 2021) (to be codified at 21 C.F.R. pt. 1100 *et seq.*). Section 1114.7(f)(2) of the Final Rule explicitly requires applications to contain a "Description of Marketing Plans," which must include a description of the companies' intended audience, its plan to target that audience in its labeling, advertising, and marketing, and a discussion of how access to the new products would be restricted with respect to youth. *See* 86 Fed. Reg. at 55,419–20 (to be codified at 21 C.F.R. § 1114.7(f)(2)). The explanation accompanying the Final Rule stated that information contained in marketing plans is "necessary for [the Administration] to properly evaluate the extent of youth exposure . . . and youth access to the product" and "is directly relevant to the . . . [Administration's] consideration of the likelihood that youth will use the tobacco product and its determination that permitting the product to be marketed would be [appropriate for the protection of the public health]." *Id.* at 55,324.

In response to the marketing denial orders, the tobacco companies each timely filed petitions for review. We stayed the marketing denial orders for Bidi Vapor, Diamond Vapor, Johnny Copper, and Vapor Unlimited. Some of the petitions were consolidated before oral argument, and we consolidate the remaining petitions for decision.

II. STANDARDS OF REVIEW

We "hold unlawful and set aside agency action[s]" that are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2), (2)(A); *VHV Jewelers, LLC v. Wolf*, 17 F.4th 109, 114 (11th Cir. 2021). We consider only "the basis articulated by the agency itself," not "appellate counsel's *post hoc* rationalizations." *State Farm*, 463 U.S. at 50; s*ee also Dep't Homeland Sec. v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020) ("An agency must defend its actions based on the reasons it gave when it acted.").

III. DISCUSSION

The "arbitrary-and-capricious standard requires that agency action be reasonable and reasonably explained." *Fed. Commc'ns Comm'n v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). "It follows that agency action is lawful only if it rests 'on a consideration of the relevant factors.'" *Michigan*, 135 S. Ct. at 2706 (quoting *State Farm*, 463 U.S. at 43). "Normally, an agency rule would be arbitrary and capricious if the agency . . . entirely failed to consider an important aspect of the problem . . . ." *State Farm*, 463 U.S. at 43. To determine if an agency considered all the "relevant factors" and "important aspect[s] of the problem," a court may look to the language of the relevant statutes, *see, e.g.*, *Michigan*, 135 S. Ct. at 2706–08 (determining whether cost was a relevant factor by interpreting the statutory phrase "appropriate and necessary") (internal quotation marks omitted), regulations, *see, e.g.*, *Ctr. for Biological Diversity v. U.S. Bureau of Land Mgmt.*, 698 F.3d 1101, 1122 (9th Cir. 2012) (determining whether "groundwater

withdrawals were a relevant factor" by looking to the Endangered Species Act regulations), the administrative record, *see, e.g.*, *id.* at 1123–24 (finding support in the record of "the possible impact of ground water withdrawal on surface water levels" and concluding that "therefore . . . the Biological Opinion should have addressed it") and even "beyond the administrative record," *id.* at 1123 n.14.

To decide if a new tobacco product is "appropriate for the protection of the public health," 21 U.S.C. § 387j(c)(2)(A), the Tobacco Control Act requires the Administration to consider "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product," and explicitly instructs the Administration to consider both the "likelihood that existing users of tobacco products will stop using such products" and the "likelihood that those who do not use tobacco products will start using such products," *id.* § 387j(c)(4). The Administration's 2019 Guidance recommended that companies include any applicable "restrictions on the sales and distribution" of their products in their applications "to help support a showing that the marketing of the product would be [appropriate for the protection of the public health], *2019 Guidance*, *supra*, at 20–21, and the Administration's 2020 Guidance included marketing and sales-access-restriction plans in the "factors the [Administration] intend[ed] to consider" when deciding if a manufacturer had taken adequate precautions to avoid youth use, *2020 Guidance*, *supra*, at 22. Although there was not a final, published regulation in effect at the time the marketing denial orders were issued in September 2021, both the proposed rule published

in 2019 and the final rule published in October 2021 identify marketing and sales-access-restriction plans as "critical," "necessary," and "directly relevant" to its determination. *See* 84 Fed. Reg. at 50,581 (proposed rule describing applicants' marketing and sales-access-restriction plans as "*critical* to [the Administration's] determination of the likelihood of changes in tobacco product use behavior" (emphasis added)); 86 Fed. Reg. at 55,324 (to be codified at 21 C.F.R. § 1114.7(f)(2)) (final rule describing the required marketing plans as including "information *necessary* for [the Administration] to properly evaluate the extent of youth exposure . . . and youth access to the product" and "*directly relevant* to the . . . [Administration's] consideration of the likelihood that youth will use the tobacco product and its determination that permitting the product to be marketed would be [appropriate for the protection of the public health]" (emphases added)). And the record includes the companies' proposed marketing and sales-access restrictions that go to the heart of the Act's requirements and the Administration's concerns about youth access to the companies' products.

The marketing and sales-access-restriction plans in the tobacco companies' applications were relevant factors to the Administration's determination as to whether marketing the companies' products would be "appropriate for the protection of the public health." *See* 21 U.S.C. § 387j(c)(2)(A). The marketing and sales-access-restriction plans bear on the statutory requirement to consider the "likelihood that those who do not use tobacco products will start using such products." *See id.* § 387j(c)(4). The many guidance

documents recommending that the companies include their marketing and sales-access-restriction plans establish that the Administration recognized the plans to be relevant to its analysis. *See 2019 Guidance*, *supra*, at 12, 20–21; *2020 Guidance*, *supra*, at 22; *Ctr. for Biological Diversity*, 698 F.3d at 1122–24. Both the proposed rule and the final rule explicitly require applicants to submit detailed marketing and sales-access-restriction plans, and the explanations accompanying the proposed and final rules identify this information as "critical," "necessary," and "directly relevant" to the Administration's analysis. *See* 84 Fed. Reg. at 50,581; 21 C.F.R. § 1114.7(f)(2); 86 Fed. Reg. at 55,324. Although neither the proposed rule nor the final rule governed this matter when the marketing denial orders issued, together they confirm that the Administration has consistently recognized that the marketing and sales-access-restriction plans are relevant factors to the determination. And the record includes marketing and sales-access-restriction plans submitted by the companies that directly address an "important aspect of the problem"—youth access to the companies' products. *See State Farm*, 463 U.S. at 43; *Ctr. for Biological Diversity*, 698 F.3d at 1123–24.

Because the marketing and sales-access-restriction plans were relevant factors and addressed "an important aspect of the problem," *State Farm*, 463 U.S. at 43, it was arbitrary and capricious for the Administration not to consider them. The Administration explicitly stated in marketing denial orders and Technical Project Lead Reviews that it did not consider the marketing or sales-access-

restriction plans in the tobacco companies' applications. It is also unclear from the record before this Court what marketing plans or sales-access restrictions the Administration considered before making the decision to ignore the plans proposed by these six tobacco companies. The footnote explaining that the Administration did not consider the marketing plans because of its experience apparently was included in every Technical Project Lead report, as it appears in every report given to the six tobacco companies here and appears in the sample report provided on the Administration's website. *See* U.S. FOOD & DRUG ADMIN., TECHNICAL PROJECT LEAD (TPL) REVIEW OF PMTAS (Sept. 17, 2021) , https://www.fda.gov/media/152482/download. So, it is unclear which applications the Administration evaluated before making the decision not to consider any marketing or sales-access-restriction plans or which marketing and sales-access proposals were included in the applications allegedly evaluated.

The Administration offers its experience as its primary excuse for its refusal to consider the marketing and sales-access-restriction plans. The Administration cites its "extensive experience with sales[-]access and marketing restrictions" and repeats its explanation from the marketing denial orders that it was "not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use [e-cigarettes]." (Internal quotation marks omitted.) It asserts that the tobacco companies "did not purport to propose novel measures outside of [the Administration's] experience" and points to statements made in its

2020 Guidance about how sales-access restrictions on their own had failed to reduce youth use. *See 2020 Guidance*, *supra*, at 44–45. And it argues that it "reasonably determined that consideration of [the companies'] proposed advertising and sales[-]access restrictions would not tip the balance between adult benefits and youth risks and therefore would not alter [its] conclusion."

Experience fails as a justification for ignoring the marketing and sales-access-restrictions plans. Although "[a]gencies, the [Food and Drug Administration] among them, have expertise and experience in administering their statutes that no court can properly ignore," *see Judulang v. Holder*, 565 U.S. 42, 53 (2011), reviewing courts must ensure that an agency "consider[ed] . . . the relevant factors" and made no "clear error of judgment," *id.* (quoting *State Farm*, 463 U.S. at 43). The Administration ignored the marketing and sales-access-restriction plans because the Administration had not yet evaluated an application that had "proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use" and was "not aware of access restrictions that, to date, ha[d] been successful in sufficiently decreasing the ability of youth to obtain and use [electronic nicotine-delivery systems]." But this excuse is akin to a federal district court judge refusing to hear a convicted criminal defendant at sentencing about his reformation plans or the impact on his family because, in the judge's experience, he found that those things do not matter. Like the

federal judge considering the convicted criminal's pleas at sentencing, the Administration is not required to find the marketing and sales-access-restriction plans convincing or decide that this evidence tilts the scales—but it is required to *consider* it because it is a "relevant factor[]" and "important aspect of the problem." *See State Farm*, 463 U.S. at 43 (internal quotation marks omitted).

The Administration offered an additional excuse in the Technical Project Lead Reviews for refusing to consider the marketing and sales-access-restriction plans: efficiency. The Administration seems to have abandoned that argument on appeal. But to the extent that the Administration maintains that efficiency is an adequate excuse, it is not. By definition, the requirement that federal agencies consider all "relevant factors," *see Michigan*, 135 S. Ct. at 2706 (internal quotation marks omitted), prohibits agency shortcuts. If an agency could excuse considering all the relevant factors by appealing to efficiency, the requirement would cease to have any effect.

Finally, ignoring the marketing and sales-access-restriction plans was not harmless error. The Administrative Procedure Act instructs courts to take "due account . . . of the rule of prejudicial error" when reviewing agency decisions. *See* 5 U.S.C. § 706. The Administration argues that because the tobacco companies do not purport to have proposed marketing and sales-access-restriction plans different from the measures that the Administration had previously determined were inadequate to "counter-balance" the problem of youth use, no harm flowed from the failure to consider

this evidence. But an agency decision is harmless only "when a mistake of the administrative body is one that clearly had no bearing on the procedure used or the substance of the decision reached." *United States v. Schwarzbaum*, 24 F.4th 1355, 1366 (11th Cir. 2022) (internal quotation marks omitted). It is difficult to imagine how failure to consider a relevant factor would "clearly ha[ve] no bearing on the *procedure* used or substance of the decision reached." *See id.* (emphasis added).

But even assuming that failure to consider a relevant factor could be harmless error, it was not here. The 2020 Guidance did not state that existing marketing and sales-access-restriction plans were categorically ineffective for electronic nicotine-delivery systems other than flavored, cartridge-based products. *See 2020 Guidance*, *supra*, at 21–22, 44–45. *Contra Wages & White Lion Invs., L.L.C. v. Food & Drug Admin.*, No. 21-60766, slip op. at 20–21 (5th Cir. July 18, 2022); *Prohibition Juice Co. v. U.S. Food & Drug Admin.*, No. 21-1201, slip op. at 31 (D.C. Cir. July 26, 2022). And the tobacco companies submitted marketing and sales-access-restriction plans that conformed with the recommendations for their kinds of products in the 2020 Guidance, directly addressed the concerns of youth access and popularity, and included measures not specifically mentioned in the 2020 Guidance, such as Johnny Copper's "Trace/Verify technology" and Bidi's authentication system designed to prevent counterfeit products from becoming accessible to youth. Because "the [Administration] *may* reach a different result when it" considers the marketing and sales-access-restriction

plans, "we cannot say that the [Administration's] error was harmless." *See Schwarzbaum*, 24 F.4th at 1366 (internal quotation marks omitted); *see also Shinseki v. Sanders*, 556 U.S. 396, 410 (2009) ("To say that the claimant has the 'burden' of showing that an error was harmful is not to impose a complex system of 'burden shifting' rules or a particularly onerous requirement. . . . Often the circumstances of the case will make clear to the appellate judge that the ruling, if erroneous, was harmful and nothing further need be said.").

Our conclusion that it was arbitrary and capricious for the Administration to ignore the relevant marketing and sales-access-restriction plans does not mandate a different result on remand. We acknowledge the evidence in the record catalogued by the dissent of the serious risk to youth, and it may be that the Administration will conclude on remand that the marketing and sales-access-restriction plans submitted in the tobacco companies' applications do not outweigh those risks. We do not make a moral judgment—only a procedural one. Our review of the administrative orders is limited, and we decide only that the Administration must at least consider the relevant evidence before it, which includes the companies' marketing and sales-access-restriction plans.

The crux of our disagreement with the dissent is whether it is the role of this Court or of the Administration to consider the novel marketing and sales-access-restriction plans submitted by the tobacco companies. The dissent admits that the Administration "said that" marketing and sales-access restrictions "would be

relevant," *see* Dissenting Op. at 1, and that at least some of the tobacco companies submitted novel marketing and sales-access restrictions, *see id.* at 20. But the dissent concludes that "these plans . . . do nothing to change the attractiveness to kids of using flavored vaping products," as the Administration "has found that kids generally get their vaping products from friends and their social networks, not directly from retailers." *See id.* at 18–19. But this determination is not ours to make.

"[F]ederal appellate courts . . . are not factfinders," *Holsey v. Warden, Ga. Diagnostic Prison*, 694 F.3d 1230, 1259 (11th Cir. 2012), and "a remand is the proper course unless the record permits only one resolution of the factual issue," *Pullman-Standard v. Swint*, 456 U.S. 273, 292 (1982). Because it is outside of our competency to determine what interventions make flavored vapes more or less accessible to minors, remand to the Administration is the proper remedy. *See Schwarzbaum*, 24 F.4th at 1365 ("Remand is the appropriate remedy when an administrative agency makes an error of law, for it affords the agency an opportunity to receive and examine the evidence in light of the correct legal principle." (internal quotation marks omitted)); *Pres. Endangered Areas of Cobb's Hist., Inc. v. U.S. Army Corps of Eng'rs*, 87 F.3d 1242, 1246 (11th Cir. 1996) ("[I]f the agency has not considered all relevant factors . . . the proper course, except in rare circumstances, is to remand to the agency for additional investigation or explanation." (internal quotation marks omitted); *cf. United States v. Phifer*, 909 F.3d 372, 386 (11th Cir. 2018) (remanding to the district court to conduct an

evidentiary hearing to determine which definitions of a scientific term in a regulation "are generally accepted within the scientific community.").

We also disagree with our sister circuits' contrary decisions in *Wages & White Lion*, slip op. at 19–24, and *Prohibition Juice*, slip op. at 29–32. For starters, we are not persuaded by our sister circuits' readings of the 2020 Guidance. Both of our sister circuits read the 2020 Guidance to make categorical statements about the efficacy and relevance of marketing and sales-access restrictions with respect to flavored electronic nicotine-delivery systems. *See Wages & White Lion*, slip op. at 20 ("[The tobacco companies] should have known that marketing plans on their own are not particularly useful. [The Administration] explained as much in its 2020 Guidance, in which it noted that youth usage continued to rise *despite* [the Administration's] 2018 efforts to curb predatory marketing . . . ."); *Prohibition Juice*, slip op. at 31 ("Yet [the tobacco companies'] plans—to require customers' self-verification of age at the point of sale and to use what they characterize as less vibrant marketing unappealing to youth—track measures the [Administration] in its 2020 [G]uidance deemed inadequate to prevent or otherwise materially limit youth access to favored [products]."). To be sure, the 2020 Guidance states that "youth usage continued to rise *despite* [the Administration's] 2018 efforts to curb predatory marketing," *Wages & White Lion*, slip op. at 20 (citing *2020 Guidance*, *supra*, at 6–9), and that "age verification alone is not sufficient to address this issue," *2020 Guidance*, *supra*, at 44. But those

observations were not the end of the Administration's analysis; they were only the beginning.

As explained above, the Administration responded to these data by setting forth two frameworks. With respect to flavored, cartridge-based systems, the Administration determined that "focusing on how the product was sold would not appropriately address youth use of the products that are most popular among youth," as "[t]hese products are produced on a large scale, are easy to conceal, can be used discreetly, and are not the products typically produced in vape shops that mix nicotine with e-liquid flavors." *2020 Guidance*, *supra*, at 21. And "[g]iven the urgent need to address the dramatic rise in youth use," the 2020 Guidance "prioritize[d] enforcement with respect to any flavored, cartridge-based [electronic nicotine-delivery system] products . . . without regard to the location or method of sale." *Id.*

But with respect to other electronic nicotine-delivery systems, the Administration explained that it "intend[ed] to prioritize enforcement for lack of marketing authorization for any" electronic nicotine-delivery system products "*when the manufacturer has not taken or is not taking adequate measures to prevent minors' access to these products*." *Id.* (emphasis added). And "[i]n assessing whether a manufacturer is taking (or has taken) adequate measures to prevent minors' access," the Administration "intend[ed] to consider" "factors . . . includ[ing] . . . [w]hether the manufacturer ha[d] implemented adequate programs to monitor retailer compliance with age-verification and sales restrictions"

such as hotlines for reporting noncompliant sales and mystery shopper programs; "ha[d] established and enforce[d] penalties against retailers that fail to comply with age-verification and sales restrictions"; was "us[ing] adequate age-verification technology" for online sales, such as "an independent, third-party age- and identity-verification service that compares customer information against third-party data sources, such as public records"; and was "limit[ing] . . . the quantity of . . . products that a customer may purchase within a given period of time." *Id.* at 22.

So, the 2020 Guidance did not express a determination by the Administration that marketing and sales-access-restriction plans for flavored electronic nicotine-delivery systems are categorically ineffective. The 2020 Guidance provided that those measures were insufficient to curb youth use of flavored, cartridge-based products based on their nature and popularity. But with respect to other kinds of electronic nicotine-delivery systems, including the flavored but not cartridge-based products submitted by the tobacco companies here, the 2020 Guidance stated that the Administration intended to consider the companies' marketing and sales-access-restriction plans. And the Administration's responses to submitted comments about the failure of marketing and sales-access restrictions to prevent youth use, are, when read in context, about flavored, cartridge-based products, not all flavored electronic nicotine-delivery systems. *Compare id.* at 42 ("[The Administration] determined that focusing on how the product was sold would not be sufficient to address youth use of these products."), *with id.* at 21

("[The Administration] determined that focusing on how the product was sold would not appropriately address youth use of the products that are the most popular among youth—*i.e.*, flavored, cartridge-based products."), *and id.* ("[The Administration] intends to prioritize enforcement for lack of a marketing authorization for any other [electronic nicotine-delivery system] products (*i.e.*, any tobacco-, menthol-, or non-flavored [electronic nicotine-delivery system] products and any non-cartridge-based, flavored [electronic nicotine-delivery system] products) when the manufacturer has not taken or is not taking adequate measures to prevent minors' access to these products . . . ."). The 2020 Guidance did not absolve the Administration of the requirement to consider the tobacco companies' youth-prevention plans.

This appeal is also different from those before our sister circuits in several ways. First, our harmless-error standard is different from the standard imposed by the Fifth Circuit. *Compare Schwarzbaum*, 24 F.4th at 1366 ("An agency decision is harmless when a mistake of the administrative body is one that clearly had no bearing on the procedure used or the substance of decision reached." (internal quotation marks omitted)), *with Wages & White Lion*, slip op. at 23 ("The burden falls on [the tobacco companies] to show that they would have received authorization had [the Administration] considered these plans."). Second, the statements made before the Fifth Circuit at oral argument by the Administration that it "review[ed] . . . a summary of the marketing plans," *Wages & White Lion*, slip op. at 22, were not made before this Court. And

third, the concessions of harmless error made before the D.C. Circuit at oral argument by the tobacco companies, *see Prohibition Juice*, slip op. at 31, were not made here. *See id.* at 35–36 (Katsas, J., concurring) ("As [the majority opinion] persuasively demonstrates, the petitioners here made no serious argument that the [Administration's] failure to consider their marketing plans was prejudicial, as required for them to obtain relief under the [Administrative Procedure Act]. . . . In joining the Court's opinion, I do not understand it to foreclose the possibility of our finding prejudicial error in other cases where manufacturers press the prejudice point more forcefully.").

IV. CONCLUSION

The petitions for review are **GRANTED,** the orders of the Administration are **SET ASIDE**, and the matters are **REMANDED** to the Administration.

ROSENBAUM, Circuit Judge, Dissenting:

SPOILER ALERT: THIS OPINION CONTAINS SPOILERS ON HOW THE U.S. FOOD AND DRUG ADMINISTRATION ("FDA") WILL RESOLVE PETITIONER VAPING-PRODUCT[1] COMPANIES' PREMARKET TOBACCO PRODUCT APPLICATIONS ON REMAND FROM THIS APPEAL.

Then again, never mind. There's nothing to spoil here. Anyone who knows all the relevant facts necessarily already knows how this one ends. On remand, the FDA will deny Petitioner Companies' applications to sell their fruit-, mint-, and candy-flavored ("flavored") vaping products.[2] The record makes that clear. I would not waste everyone's time and money with a remand. The Majority faults the FDA for not considering the Companies' proposed restrictions on kids' use. And to be sure, the FDA said that factor would be relevant. But even assuming that the FDA erred when it didn't consider the Companies' proposed marketing and

---

[1] The industry and the FDA refer to vaping products as electronic-nicotine-delivery-system ("ENDS") products. Because ENDS products are commonly known as "vaping products," that is the term I use in this dissent.

[2] To be clear, I use the term "flavored" to refer to vaping products with flavors like fruit, mint, and candy—in other words, nontraditional tobacco-product flavors. Vaping-product companies also make tobacco-flavored products. I do not include tobacco-flavored products in my defined term "flavored" vaping products. Rather, I refer to them distinctly as "tobacco-flavored."

access-restriction plans, the FDA's framework for evaluating premarket tobacco product applications leaves no room for doubt that the FDA will deny—in fact, under the Family Smoking Prevention and Tobacco Control Act, must deny—the applications on remand. To paraphrase the Borg,[3] then, remand is futile.

Here's how we know: The FDA has established that the sale of flavored (as opposed to tobacco-flavored) vaping products amplifies the risk that kids will start vaping and—because vaping has been shown to be a gateway to smoking combustible cigarettes—smoking. Yet at the same time, there's no reliable evidence that flavored vaping products offer any real advantage over tobacco-flavored vaping products in helping existing smokers quit or reduce their habits. Nor, despite years of trying (and consideration of various creative programs), has the FDA been able to identify any marketing or access restrictions that work in a meaningful way to prevent kids from obtaining flavored vaping products in the first place. In fact, the FDA has concluded that access restrictions at points of sale do not work because most kids get their vaping products through friends or their social networks.

So the FDA has stated that applications that don't reliably establish that flavored vaping products impart an advantage over tobacco-flavored vaping products in decreasing smoking among

---

[3] *See* https://nerdist.com/article/star-trek-history-of-the-borg/ (last visited Aug. 10, 2022).

existing smokers, or that don't include marketing plans and access restrictions for kids that significantly cut off all avenues for kids to obtain these products will be denied because they are not appropriate for the protection of the public health. And the Tobacco Control Act requires the FDA to deny any application that is not appropriate for the protection of the public health.

Here, none of the Companies' applications include reliable evidence that flavored vaping products offer an advantage over tobacco-flavored vaping products in decreasing smoking among existing smokers. And while some applications suggest some new ways to reduce kids' access to flavored products, none contain marketing and access plans that provide new methods (that the FDA has not already considered and found wanting) that significantly decrease kids' access to their flavored products through all avenues kids use to obtain the products. But the FDA's evidence shows that when companies apply pressure to one aspect of the current access system, youth simply flock to other avenues to obtain flavored vaping products. So the FDA has made it clear that applications like the ones here—which fail to offer new plans that significantly curtail youth access across all avenues of obtaining flavored products—cannot be appropriate for the protection of the public health and must be denied.

When, as here, the outcome on agency remand is "not seriously contestable," remanding "would be an idle and useless formality." *NLRB v. Wyman-Gordon Co.*, 394 U.S. 759, 766 n.6

(1969) (plurality opinion). The Administrative Procedure Act authorizes the denial of a petition for review under these circumstances because any error the agency may have committed is then, by definition, harmless. And as the Supreme Court has expressly explained—and contrary to the Majority Opinion's contention—"the ruling in [*SEC v. Chenery Corp.*, 318 U.S. 80 (1943),] [does] not require[] [us] to remand in futility." *Thornburgh v. Am. Coll. of Obstetricians & Gynecologists*, 476 U.S. 747, 756 n.7 (1986), *overruled on other grounds by Planned Parenthood of Se. Penn. v. Casey,* 505 U.S. 833 (1992).

I see no point in sending these petitions back for the FDA to do what everyone paying attention here knows that, under the framework the FDA has established for evaluating whether a new flavored vaping product is appropriate for the protection of the public health, the FDA will and must do: deny the applications. Engaging in this futile activity only delays the inevitable—and in the process imposes unnecessary time, effort, and financial costs on all involved. I therefore respectfully dissent.

I divide my discussion into two parts. In Section I, I set forth the facts in the administrative record that show that the FDA will deny these applications on remand. In Section II, I explain why, assuming without deciding that the FDA erred in denying the applications without reviewing the marketing and access plans, remand is not appropriate.

I.

A. The Regulatory Framework

Congress enacted the Family Smoking Prevention and Tobacco Control Act ("Act") in 2009. In so doing, Congress wanted to be sure its intent in passing the law was clear. So as part of the legislation and so no confusion could exist, Congress made legislative findings of fact. Foremost among those factual findings, Congress determined that "[t]he use of tobacco products by the Nation's children is a pediatric disease of considerable proportions . . . ." 21 U.S.C. § 387 Findings at ¶ (1). It followed up, noting that "[v]irtually all new users of tobacco products are under the minimum legal age to purchase such products." *Id.* ¶ (4); *see also id.* ¶ (31) ("An overwhelming majority of Americans who use tobacco products begin using such products while they are minors and become addicted to the nicotine in those products before reaching the age of 18.").[4]

Besides these findings, Congress attributed the problem of underage use of tobacco products largely to the tobacco industry's marketing practices. Recounting that, in 2005, manufacturers "spent more than $13 [billion]" on advertising, marketing, and

---

[4] Among other evidence, the FDA conducted a study in 1996 and found that, at that time, 82% of all adults who had ever smoked had their first cigarette before they turned 18. *Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 272 (D.C. Cir. 2019) (citing Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents, 61 Fed. Reg. 44,396, 44,398 (Aug. 28, 1996)).

promotion of their products, Congress found that these efforts were "especially directed to attract young persons to use tobacco products, and these efforts have resulted in increased use of such products by youth." *Id.* ¶¶ (16), (15); *see also id.* ¶ (31) ("Tobacco advertising and promotion play a crucial role in the decision of these minors to begin using tobacco products."). For these reasons, Congress concluded that "[i]t [was] in the public interest for Congress to adopt legislation to address the public health crisis created by actions of the tobacco industry." *Id.* ¶ (29).

Because the window for starting to use tobacco products is open widest for younger users, Congress reasoned, if that window were closed, many would-be younger users would never begin using tobacco products. Indeed, Congress theorized that even if better control of access to tobacco products for youth reduced the products' use by minors by only 50%, that would "sav[e] over [3 million] of them from premature death due to tobacco-induced disease." *Id.* ¶ (14). And at least as of the time Congress enacted the Act, it figured that cutting minors' use of tobacco products in half "would also result in approximately [$75 billion] in savings attributable to reduced health care costs." *Id.* No doubt that figure is considerably higher now.

Congress also expressly identified the problem that "products that purport to reduce the risks to the public of tobacco use" but actually do not, present to creating new tobacco-product users. *Id.* ¶ (37).

To address these problems, through the Act, Congress required manufacturers to submit all new tobacco products for FDA review and approval before they could be marketed in interstate commerce. *See* 21 U.S.C. § 387j. The Act imposes strict limitations on new tobacco products the FDA can approve for marketing. More specifically, the Act prohibits the FDA from approving any such application when "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." *Id.* § 387j(c)(2). And it defines this standard as requiring a showing "with respect to the risks and benefits to the population as a whole, including users and nonusers" of the new product. *Id.* § 387j(c)(4). That showing must account for both "the increased or decreased likelihood that existing users of tobacco products will stop using such products; and the increased or decreased likelihood that those who do not use tobacco products will start using such products." *Id.*

Put simply, for a new product to be appropriate for the protection of the public health (and therefore even be eligible to obtain FDA approval), the Act requires the applicant to show that, on balance, the new product will result in more existing product users (like smokers) stopping or meaningfully drawing back their usage than existing nonusers becoming users. On its face, this equation prioritizes Congress's concern to shut down tobacco-product usage as a "pediatric disease of considerable proportions."

Enter vaping products. Believe it or not, Joseph Robinson filed a patent for the first e-cigarette design nearly a century ago—in 1927.[5] But it wasn't until the 2000s that vaping products began to be sold in the United States and hit the bigtime here.[6]

Under the authority the Act gave it, the FDA issued a final rule, effective August 2016, in which it deemed vaping products to be "tobacco products." *See* Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, 81 Fed. Reg. 28,973 (May 10, 2016) (codified at C.F.R. pts. 1100, 1140, 1143) ("Deeming Rule").[7] As a result, products that were not on the market as of February 15, 2007, became subject to the Act. *See id.* at 28,978. But in exercising its discretion, the FDA announced that it wouldn't enforce the Act against those vaping products for certain

---

[5] Hilary Brueck, Insider, *The Wild History of Vaping, From a 1927 'Electric Vaporizer' to Today's Mysterious Lung Injury Crisis* (Nov. 12, 2019), *available at* https://www.insider.com/history-of-vaping-who-invented-e-cigs-2019-10#in-1927-joseph-robinson-dreamed-up-what-might-be-the-very-first-electric-vaporizer-a-device-he-said-was-for-medicinal-compounds-2 (last visited Aug. 16, 2022).

[6] *See id.*

[7] That final rule is not at issue, and our sister circuits that have considered the issue have upheld the rule. *See*, *e.g.*, *Nicopure Labs*, 944 F.3d at 293 (upholding final rule against challenges under the Administrative Procedure Act and the First Amendment); *Big Time Vapes, Inc. v. FDA*, 963 F.3d 436 (5th Cir. 2020) (upholding final rule against nondelegation-doctrine challenge).

delineated periods to allow for the development of more information about the products. *See id.*

Ultimately, companies wound up having until September 9, 2020, to submit their applications for premarket review of their vaping products and establish that the marketing of those products was "appropriate for the protection of the public health." *Breeze Smoke, LLC v. U.S. Food & Drug Admin.*, 18 F.4th 499, 504 (6th Cir. 2021); *accord* Enforcement Priorities for Electronic Nicotine Delivery Systems and Other Deemed Products on the Market Without Premarket Authorization (Revised), 85 Fed. Reg. 23,973, 23,974 (Apr. 30, 2020) ("2020 Guidance").

B. The Underage Vaping Problem

In the meantime, though, the FDA learned a lot more about vaping. It turns out that vaping dishes out a double-whammy of detrimental health effects on kids who engage in it: (1) vaping itself has been associated with direct and profound health consequences, including, among others, "the development of acute or chronic lung injuries" and even death (not to mention battery explosions from vaping products),[8] and (2) those who vape are substantially

[8] And nicotine in vaping products can permanently harm developing adolescent brains and can "induce short and long-term deficits in attention, learning, and memory." Bidi Vapor Technical Project Lead Rev. ("Bidi TPL"), at 8; Diamond Vapor Technical Project Lead Rev. ("Diamond TPL"), at 8; Johnny Copper Technical Project Lead Rev. ("Johnny Copper TPL"), at 8; Vapor Unlimited Technical Project Lead Rev. ("Unlimited TPL"), at 8; Union Street

more likely to become smokers of combustible cigarettes, which in turn inflict significant adverse health consequences of their own. 2020 Guidance at 9, 13, 29; *see also* Bidi TPL[9] at 8 ("A 2017 systematic review and meta-analysis that summarized nine prospective cohort studies found significantly higher odds of smoking initiation . . . among youth who had used [vaping products] a[s] compared to youth who had not . . . . The 2018 NASEM report concluded that there is substantial evidence that [vaping-product] use increases risk of ever using combusted tobacco cigarettes among youth and young adults."); 9 ("Two studies found associations between [vaping] and self-reported history of asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease . . . ."); *see also* Diamond TPL at 8–9; Johnny Copper TPL at 8–9; Unlimited TPL at 8–9; Union TPL at 8–9; Pop TPL at 8–9.

Flavored vaping products in particular play an outsized role in the problem of kids' vaping. In fact, among kids between the ages of 12 and 17 who have reported vaping, nearly all—93.2%—have said that they had their first vaping experience with a flavored product. 2020 Guidance at 14. Perhaps that's no surprise, given that many companies (including some Petitioners here) name their flavors things like Rainbow Nerds, Captain Loopy, Berry Gogurt,

---

Technical Project Lead Rev. ("Union TPL"), at 8; Pop Vapor Technical Project Lead Rev. ("Pop TPL"), at 8.

[9] "TPL" is short for "technical project lead review," which is what the FDA calls its evaluation of a premarket tobacco application.

Nanner Puddin, Scrumdiddlyumptious, Teacher's Pet, Cap'n Crunk, and Blue Razz Cotton Candy[10]—which seem designed to appeal to kids. Not only do most kids have their first vaping experience with flavored products, but flavored vaping products remain "extraordinar[ily] popular[]" with kids even after that first introduction. 2020 Guidance at 13–14. Indeed, kids "overwhelmingly" use flavored vaping products, *id.* at 24, and are "more likely to use flavored [vaping products] than adult [vapers are]," Bidi TPL at 12; Diamond TPL at 12; Johnny Copper TPL at 12; Unlimited TPL at 12; Union TPL at 12; Pop TPL at 9.

As the problem with youth vaping began to come into focus in 2018, the FDA tried to solve it with a two-pronged approach: (1) regulatory actions against manufacturers and retailers who marketed and sold to kids and (2) direct enlistment of vaping-product manufacturers to reduce youth interest and access. 2020 Guidance at 6–7. To accomplish the second part of this approach, the FDA asked manufacturers to submit plans to "address minors' access to and use of [their] products." *Id.* at 7.

As directed, manufacturers responded by introducing various programs intended to safeguard against underage use of their products. *See id.* As a sampling, they tried things like mystery shopper programs that monitored retailer compliance with age-

---

[10] Readers may notice that some of these names seem to allude to—or outright invoke—breakfast cereals, snacks, and candies marketed to kids.

verification and sales restrictions, contractual penalties for retailers who sold vaping products to kids, age-verification and identity-verification services for sales over websites, and limiting single-purchase quantities. *Id.*

Nothing worked. And here's why, in large part: as the FDA explained in its 2020 Guidance, "many [kids] obtain their [vaping products] from friends or sources in their social networks." *Id.* at 44–45. So "age verification," "focusing on how the product [is] sold, . . . legal prohibitions, and . . . voluntary actions by some manufacturers" are "not sufficient to address youth use of these products, given the many sources of products available for youth access." *Id.* That's an important point: the FDA announced in its 2020 Guidance that it had concluded, after studying the problem for years, that sales-access restrictions and marketing plans just aren't enough to protect against youth use.[11]

---

[11] The FDA reiterated this point at oral argument: its 2020 Guidance concludes that sales-access restrictions and marketing plans aren't sufficient to protect youth. Oral Argument, Case No. 21-13522, at 22:49–23:12. As the FDA emphasized, "The problem here is that when you limit who you can sell e-cigarettes to—for instance, only sell them to adults with very good ID—the problem is that kids often get e-cigarettes from friends or family, and so limiting just who you sell an e-cigarette to is not going to be enough to mitigate that substantial risk to kids from flavored e-cigarettes." *Id.* at 22:08–22:28. The FDA then confirmed, "FDA's saying that sales-access restrictions and advertising restrictions, although they certainly can be helpful, they themselves are not sufficient to mitigate the substantial risk to kids when you have this scientific consensus on a substantial risk to kids, and you have a lack of a showing

Indeed, despite companies' marketing and access-restriction efforts in response to the FDA's attempts to stem the underage-vaping problem, underage vaping instead accelerated. *See id.* at 8. By 2019, youth vaping had hit the highest levels recorded until then. *Id.* Between 2017 and 2019, vaping more than doubled among middle-school and high-school students, reaching levels of 10.5% of middle-school students and 27.5%—more than a quarter—of all high-school students. *Id.* at 12. In absolute numbers, that's more than 5 million kids. *Id.*

To state the obvious, youth vaping had reached crisis proportions. And the FDA came to the well-supported conclusion that marketing plans and access restrictions alone were not solving the problem.

But it wasn't all bad news. It turns out that vaping products may help existing smokers to quit or switch to vaping, which is less detrimental than smoking. *See* Bidi TPL at 10; Diamond TPL at 10; Johnny Copper TPL at 10; Unlimited TPL at 10; Union TPL at 10; Pop TPL at 10; *see also* FDA Technical Project Lead Rev. for Apps. Submitted by R.J. Reynolds Vapor Co. (Oct. 12, 2021) ("R.J. Reynolds TPL"), at 4. And in the existing-smoker population, "the most preferred flavor . . . [is] the tobacco . . . flavor compared to

---

of a benefit, marketing plans, including sales-access restrictions and advertising restrictions, they can't close the gap." *Id.* at 22:49–23:12.

non-tobacco flavors (e.g., mint, nectar, and tropical)." R.J. Reynolds TPL at 4.

It's just that studies don't reveal significant added benefits that flavored products offer over tobacco-flavored products in this regard. *See* 2020 Guidance at 38; *see also* Bidi TPL at 11 ("[T]he evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive.[] In fact, the findings are quite mixed and as a result the literature does not establish that flavors differentially promote switching amongst [vaping product] users in general."); Diamond TPL at 11; Johnny Copper TPL at 11; Unlimited TPL at 11; Union TPL at 11; Pop TPL at 11–12; *see also* R.J. Reynolds TPL at 20 ("[F]indings from the applicant's likelihood-of-use study suggest that current established cigarette smokers are more likely to prefer original (tobacco) flavor relative to other flavors . . . ."). In other words, the FDA was aware of no reliable evidence showing that existing smokers who used vaping products to quit or reduce their smoking would decide not to use vaping products in that way if manufacturers sold only tobacco-flavored vaping products.

Yet while the evidence did not show that the flavored vaping products made any significant difference to whether existing smokers would quit, those products played the starring role in introducing a whole new generation to the dangers of vaping and smoking. *See* 2020 Guidance at 14; *see also* R.J. Reynolds TPL at 4 ("Existing evidence consistently indicates that use of tobacco-flavored [vaping

products] is less common compared to . . . flavored [vaping products] among youth."), 17 (noting that research showed that "the prevalence of tobacco flavor was 2.9% among 10th and 12th graders"[12]). And on top of that—and despite the manufacturers' repeated and concentrated efforts—no manufacturer to that point had devised a marketing or sales-access plan that slashed youth vaping.

C. The FDA's Denial of the Petitioners' Applications

To sum up, the FDA tried to address the underage vaping problem by cutting it off at what it originally believed to be the source: manufacturers and retailers of vaping products. But the FDA discovered that access restrictions do not work because kids often get their vaping products from friends and through their social networks—not directly from manufacturers or retailers.

For this reason, the FDA recognized that the very existence of flavored vaping products themselves is the problem when it comes to kids' use: as long as the products exist, kids will get their hands on them. So without an effective means of making the products significantly less attractive to kids, no sales-access restrictions or marketing plans matter. Indeed, the FDA's efforts to solve the problem of kids' use by securing the cooperation of the

---

[12] Ninth- and eleventh-graders were not included in the survey. *See* https://nida.nih.gov/research-topics/related-topics/trends-statistics/infographics/monitoring-future-2020-survey-results (last visited Aug. 10, 2022).

manufacturing companies failed. But in the meantime, the FDA learned that flavored vaping products in particular are what kids find attractive about vaping and that no reliable evidence to date shows that those products offer any significant advantage over tobacco-flavored vaping products when it comes to cessation or meaningful reduction of existing smokers' smoking.

So after a few years of learning these things the hard way, by the time the September 2020 deadline for filing applications for premarket approval for the marketing of vaping products came around, the FDA found itself left with a no-brainer under the Act's appropriate-for-the-protection-of-the-public-health standard. On one side of the equation, flavored vaping products overwhelmingly inspired a new generation to take up vaping and (and then smoking). And on the other side, the companies that sought approval of those flavored products could not establish any significant benefit over tobacco-flavored vaping products in helping existing smokers quit or meaningfully reduce their smoking. Given that situation, the plain text of the Act required the FDA to conclude that—barring some new evidence that meaningfully altered either (or both) of these circumstances—flavored vaping products were not appropriate for the protection of the public health. After all, they did not come close to having a net positive effect on the public health. Just the opposite.

That brings us to the Companies' applications for premarketing approval. Only those aspects of these applications that

concern flavored vaping products are at issue. The Companies' applications included marketing and sales-access restriction plans. Those plans identified some strategies aimed at reducing youth use, such as eliminating kid-friendly advertising and labeling, using age-gated websites to sell the Companies' vaping products, and limiting the quantity of vaping products that one person could purchase at a time. Bidi Vapor's marketing plan also showed it had ceased selling its vaping products directly to consumers online through its website. And Johnny Copper's showed it planned to implement a program called "Trace/Verify" to identify the adult purchaser of its vaping product if that product ended up in the hands of a kid. In other words, all the Companies' applications included only marketing and sales-access restrictions plans—the same types of plans that the FDA had already announced in its 2020 Guidance were not enough to mitigate the dangers that flavored vaping products present to kids.

So not surprisingly, the FDA denied the Companies' applications, despite their inclusion of these marketing and access-restriction strategies. When it denied the applications, the FDA noted in the TPLs for each Company that "[l]imiting youth access and exposure to marketing is a critical aspect of product regulation." Bidi TPL at 11 n.xix; Diamond TPL at 11 n.xix; Johnny TPL at 11 n.xix; Unlimited TPL at 11 n.xix; Union TPL at 11 n.xix; Pop TPL at 9 n.xxii.

Yet, the FDA observed, in its extensive experience reviewing marketing plans and access restrictions, it had yet to see anything that worked to decrease the allure of vaping to kids and kids' access to vaping products "such that the risk for youth initiation would be reduced." *Id.* And given "the substantial concerns, and supporting evidence" about kids' pervasive use of flavored vaping products, the FDA reasoned that, without any reliable evidence "to address and counter-balance" that problem (meaning kids would not use the flavored vaping products under review or the products would provide a meaningful enough (or even any) proven advantage over tobacco-flavored vaping products in helping existing smokers quit so as to "counter-balance" kids' use), the Companies' marketing and sales-access-restriction plans, in the real world, could never be enough. *Id.* [13] So, the FDA opined, there was no point in reviewing them.

---

[13] The complete text of the footnote that the FDA included in each TPL providing this information stated,

> Limiting youth access and exposure to marketing is a critical aspect of product regulation. It is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal such that the risk for youth initiation would be reduced. However, to date, none of the ENDS PMTAs that FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use. Similarly, we are not aware of

Assuming without deciding that the FDA erred in not evaluating the Companies' marketing and sales-access-restriction plans, then, the question we must consider is whether the FDA's review of these things in the Companies' applications could possibly matter to the FDA's new decision if we remand.

We know the answer to that: It couldn't. The record unmistakably shows the futility in remanding.

We know this because, as the FDA recounted in its 2020 Guidance, the FDA's experience already shows that nearly all the marketing plans and access restrictions the Companies submitted have a proven track record of failing to make any significant headway in the reduction of kids' use of flavored vaping products. For example, FDA's 2020 Guidance explained that it had already issued warning letters to retailers using kid-friendly advertising—but stopping that advertising wasn't enough to eliminate kids' interest in vaping. The Guidance also specifically referenced age-gating websites and limiting the quantity of vaping products sold to a single customer as "potential safeguards" that FDA thought, in 2018, could help. But by 2020, the data revealed that these types of fixes

---

> access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use ENDS. Accordingly, for the sake of efficiency, the evaluation of the marketing plans in applications will not occur at this stage of review, and we have not evaluated any marketing plans submitted with these applications.

were not effective in preventing the real-world problem of keeping kids from obtaining vaping products.

As for any novel access-restriction plans the Companies submitted, there were only two among all the Companies' plans: Bidi proposed not to sell its products online at all, and Johnny Copper proposed its "Trace/Verify" strategy. But these plans—admirable as they may be—do nothing to change the attractiveness to kids of using flavored vaping products. And as the FDA has established its framework for evaluation of the premarket applications, that's where the heart of the problem lies, since the FDA has found that kids generally get their vaping products from friends and their social networks, not directly from retailers. It is that finding that, in the absence of evidence showing that flavored vaping products significantly contribute to smoking cessation among existing smokers—drives the conclusion that the marketing of flavored vaping products is necessarily not appropriate for the protection of the public health. So there can be no question that, on remand, the FDA will again deny the Companies' applications. Indeed, the TCA requires it to do so.

II.

Given that we know the FDA will again deny these applications on remand, we must consider whether we must remand them to the FDA, anyway. We need not. And on this record, we should not. Remanding here ensures wasted time, energy, and money.

The Administrative Procedure Act requires courts to "du[ly] account" for "the rule of prejudicial error" when considering whether to remand matters to the deciding agency. 5 U.S.C. § 706. In other words, if it's clear from the record that correcting the FDA's error would not change the outcome of the Companies' applications, the error did not result in "prejudicial error," and remand is not warranted.

As I've explained, that's precisely the case here. Remand is futile.

The Majority Opinion relies on *United States v. Schwarzbaum*, 24 F.4th 1355, 1367 (11th Cir. 2022), to reach the opposite conclusion. But *Schwarzbaum* itself acknowledged that the remand rule from *Chenery*, 318 U.S. 80, "does not require courts to remand in futility." 24 F.4th at 1367 (quoting *Ridgewood Health Care Ctr., Inc. v. NLRB*, 8 F.4th 1263, 1276 (11th Cir. 2021)). Judge Posner, relying on the words of Judge Friendly, has explained why: "*Chenery* was intended only to establish the important point that a reviewing court could not affirm an agency on a principle the agency might not embrace." *Illinois v. ICC*, 722 F.2d 1341, 1349 (7th Cir. 1983) (internal quotation marks omitted). As Judge Posner and Judge Friendly have further noted, *Chenery* was "not [intended] to require the tedious process of administrative adjudication and judicial review to be needlessly dragged out while court and agency engage in a nigh endless game of battledore and shuttlecock with respect to subsidiary findings." *Id.*

The Majority Opinion disagrees. *See* Maj. Op. at 27–28. It asserts that this dissent makes "fact[ual] find[ings]" and suggests I engage in a "moral judgment." *Id.* at 30, 29.

But as the administrative record reflects, that's just not accurate. Rather, as I've shown above, the administrative record itself unambiguously reveals that, as of the time the FDA denied the Companies' petitions, it had concluded that (1) eliminating advertising and labeling overtly to attract kids didn't stop kids' demand for and access to vaping products; (2) strategies like age-gating websites and monitoring retailers' sales also didn't cease the youth-vaping problem because kids get their vaping products from older friends and through their social networks (not through buying them online or at a store), anyway; and (3) it was primarily the flavoring itself in the vaping products that attracted kids. In the FDA's own words from its 2020 Guidance "age verification," "focusing on how the product [is] sold, . . . legal prohibitions, and . . . voluntary actions by some manufacturers" are just "***not sufficient*** to address youth use of these products, given the many sources of products available for youth access." 2020 Guidance at 44–45 (emphasis added). It's hard to imagine the FDA could have been any clearer.

All these things will still be true on remand. And as I've discussed, nothing in the Companies' petitions neutralizes or meaningfully otherwise addresses these problems. So the FDA's conclusions about the source of the youth vaping problem and the inefficacy of marketing and sales-access-restriction plans in resolving this

problem *necessarily require* the FDA to deny the Companies' marketing applications, as currently composed, on remand. When, as here, "only one conclusion [by the agency] would be supportable," we have recognized that remand is futile. *Schwarzbaum*, 24 F.4th at 1367. And when the FDA does what we know it will—indeed, must—do, the Companies will be back here again on appeal, and we will have no choice but to deny their petitions then.

Put simply, the FDA's analysis of the problem up through its denial of the Companies' applications—an analysis that is entirely unaffected by anything in the Companies' marketing and access-restriction plans[14]—leaves no doubt that remand is an exercise in futility. And it's not because the FDA has supposedly changed its analysis or because I have allegedly made factual findings. Rather, remand is futile *because of* the FDA's analysis of the problem of kids' use of flavored vaping products and *because of* the FDA's

---

[14] To illustrate just how little effect the marketing plans will have on FDA's analysis on remand, I've attached as an appendix two of the "plans" that FDA will now have to review. One is Union Street's "Youth Prevention Policy," a five-page document that suggests youth-prevention strategies such as "check[ing] for proof of age for any customer who is attempting to purchase vapor products." The other is Pop Vapor's "Marketing Plan," which, in all of four pages, states its position that its "products should only be sold to, and used by, adults age 21 and older." It's not that these statements take a position contrary to the FDA's view that vaping products are dangerous for kids. But these "marketing plans" aren't exactly groundbreaking. And on this record, it's clear that they aren't capable of changing FDA's mind about the dangers of youth use of and access to vaping products.

findings of fact about the inefficacy of marketing plans and sales-access restrictions, and its related findings of fact about where kids get their products from.

So it's wrong to describe my analysis as "fact[-]find[ing]" or some type of "moral judgment." Maj. Op. at 30, 29. Rather, my analysis is a straight-forward application of the administrative record here. And that administrative record belies all the mischaracterizations of this dissent that the Majority Opinion engages in.

I am also not the first to conclude that remand of applications for flavored vaping products is futile. Both the Fifth and the District of Columbia Circuits have likewise held that remand to the FDA under circumstances like these is not appropriate under the Administrative Procedure Act's harmless-error provision. *See Wages & White Lion Invs., L.L.C. v. FDA*, ___ F.4th ___, No. 21-60766, 2022 WL 2799797, *11 (5th Cir. July 18, 2022); *Prohibition Juice Co. v. FDA*, ___ F.4th ___, No. 21-1201, 2022 WL 2920823, *12-14 (D.C. Cir. July 26, 2022); *see also id.* at 15 (Katsas, J., concurring). For good reason.

We should not engage in what we all know will be an exercise in futility. On this record, the Majority Opinion's decision to remand when it's clear that the FDA's decisional framework requires denial of the Companies' applications unnecessarily clogs the administrative process and increases the costs to all concerned. I respectfully dissent.

APPENDIX

Youth Prevention Policy for Union Street Brands LLC

Union Street is committed to doing our part in preventing underage use of ENDS products in our local and worldwide communities. As this Youth Prevention Policy will demonstrate, we have implemented thorough methods of preventing youth access to Union Street's e-liquid products.

I. Vapor Sales Policy and Procedure

Union Street has spent a significant amount of time and resources to ensure that the company is doing everything it can to prevent youth access to our products. Union Street prohibits entry of minors into our locations. We require ID verification for all purchases. All employees undergo thorough training on our age verification procedures.

Each employee has a moral, ethical and legal responsibility to refuse to sell vapor products to anyone under the age of 21. Vapor products must not be sold to anyone under the age of 21. We require all employees to check for proof of age for any customer who is attempting to purchase vapor products.

a. Verify the customer's age before selling vapor products.

The customer must have an acceptable and valid Driver's License, Non Driver ID, or Commercial Driver's License to purchase tobacco products. All wholesale customers must provide valid identification including but not limited to photo identification and tax identification documentation.

b. Other points

It is illegal for a minor to purchase vapor products for anyone for any reason. A minor may not purchase these products for a parent. It is illegal for an adult to purchase these products for a minor. Never sell vapor products to anyone if you have reason to believe they are going to give them to someone under the age of 21. Remember, no one under 21 may possess vapor products of any kind.

c. Training

Upon beginning employment, all employees will receive training to ensure that they understand all state laws and company policies regarding the prohibition against selling tobacco products to minors.

A7474

Union Street Brands
Youth Prevention Policy
Page 2 of 5

II. Online E-Commerce Age-Restrictions

Online sales are restricted to adults following age verification through independent, third-party agencies using public records databases. Union Street e-commerce platform (www.mamaseliquid.com) utilizes third-party age verification technology through AgeChecker.net.

a. Age Restriction. Company product sales must comply with all county, city, and state age restriction laws for e-vapor product purchase.

b. Age Verification. Online company product sales are restricted to adults age verified by independent third-party companies using public records databases.

c. Attempt to match the name, address and date of birth provided by the customer to information contained in records in a database of individuals whose age has been verified to be 21 years or older by reference to an appropriate database of government records kept by the distributor, a direct marketing firm, or any other entity.

d. Verify that the billing address on the check or credit card offered for payment by the purchaser matches the address listed in the database.

e. If unable to verify that the purchaser is 21 years of age through the above, require the customer or recipient to submit an age-verification kit consisting of an attestation signed by the customer that he or she is 21 years of age or older and a copy of a valid form of government identification.

f. Verify that the billing address on the check or credit card provided by the consumer matches the address listed in the form of government identification.

g. Deliver only to the purchaser or recipient's verified billing address on the check or credit card used for payment. Delivery to a post office box address is prohibited.

A7475

Union Street Brands
Youth Prevention Policy
Page 3 of 5

III. Child Resistant Packaging

Union Street's open-system e-liquid products will use child resistant packaging in compliance with the Child Nicotine Poisoning Prevention Act of 2015. Union Street Utilizes the following Child Resistant Packaging:

Package Types:

30ml - Glass Dropper Bottle with child resistant 20/400 cap-closure and tamper evident seal. *The 30ml Bottle 20/400 Closure fulfills the requirements for a Poison Prevention Package as per the current Code of Federal Regulations (C.F.R.) Title 16, Part 1700.20.*

60ml - Chubby Gorilla CGUB1-60MLV3 PET plastic bottles with Child Resistant Cap (CRC) child resistant cap and tamper evident seal/bands. Include flow restriction tips. *CGUB1-60MLV3 models were tested using the PPPA standards and they meet effectiveness specifications (16 CFR 1700.15(b)) when tested by 16 CFR1700.20 methods. These models were also tested using the Child Nicotine Poisoning Prevention Act (CNPPA) protocols set forth by CPSC and all meet the requirements for nicotine flow restriction.*

IV. Appropriate Marketing and Packaging

1. As a member of the Vapor Technology Association (VTA), Smoke Free Alternatives Trade Association (SFATA), and Florida Smoke Free Association (FSFA), we adhere to their strict marketing guidelines. VTA Marketing Standards for Membership are based on the following core principles:

   a. VTA is committed to educating and informing its members on the best ways to comply with applicable laws and regulations governing electronic cigarettes, vaporizers and related electronic nicotine delivery systems ("Vapor Products"), which laws include, but are not limited to, the Federal Food Drug & Cosmetic Act (21 USC Ch. 9 et seq.) as modified by the Family Smoking Prevention and Tobacco Control Act and 21 CFR Parts 1100, 1140 and 1143 (Deeming Tobacco Products To Be Subject to the Federal Food, Drug and Cosmetic Act, May 10, 2016) (the "Tobacco Control Act")and the Child Nicotine Poisoning Prevention Act of 2015, 15 U.S.C. §§ 1471, et seq.

   b. Vapor Products are for adults only and should not be intentionally marketed to, sold to or used by those who have not attained the age of 21 years (or the appropriate age restriction within the subject territory) ("Minors").

A7476

Union Street Brands
Youth Prevention Policy
Page 4 of 5

   c. VTA Members' marketing activities must refrain from knowingly marketing Vapor Products to Minors, which is strictly prohibited.

2. Our social media accounts are age restricted to 21+, meaning that no one under the age of 21 can view them.

3. Our website utilizes an age gate which requires users to confirm they are of legal vaping age (21+) before viewing the site.

4. Our packaging is never labeled in a way that is misleading or resembles copyright protected or kid-friendly food products.

5. Our vapor products do not include content which is directed towards Minors.

6. Our marketing of vapor products is not directed at Minors and no channel of marketing is employed if more than 15% of its audience is Minors. This restriction includes, but is not necessarily limited to, TV, print and radio advertising, as well as event marketing or sponsorships. Our advertising is limited to radio stations whose target market is age 25 and up. *(Note: Union Street does not utilize TV, print, or radio advertising.)*

7. Our vapor products do not use in commerce names, imagery or designs that intentionally mimic, play upon, invoke or otherwise infringe upon existing trademarks, trade names or trade dress, particularly if they are associated with products that are or were primarily marketed to Minors.

8. Our vapor products are not portrayed as any sort of smoking cessation device or as a product which may be used to help quit smoking.

9. Our vapor products are not marketed as providing a therapeutic value, as being safe or healthy for consumers, or as products which do not produce secondhand health effects.

10. Our vapor products are not marketed or sold using modified risk descriptors or claims (e.g., "light," "low," and/or "mild"). Our vapor products are not marketed as (a) having no ash or smoke, (b) having no tar, (c) being less harmful, (d) posing a lower risk of disease or (e) as containing reduced or zero levels of harmful ingredients.

11. We accurately represent the ingredients contained in our Vapor Products and, in particular, the ingredients contained in any e-liquid. We do not deceive the consumer regarding the contents of our vapor products.

A7477

Union Street Brands
Youth Prevention Policy
Page 5 of 5

12. We ensure that all product sampling is restricted to adults and follow all applicable laws.

13. We do not use health professionals to market or otherwise endorse our vapor products, directly or indirectly.

14. Our marketing is directed towards those who are current users of tobacco products and are never designed to encourage non-tobacco users to start using Vapor Products.

V. Conclusion

Union Street's goal in its efforts is to provide adult consumers who would otherwise be smoking combustible cigarettes with an alternative source of nicotine, while preventing minors from accessing vapor products. To that end, Union Street has implemented robust youth prevention methods for its operations including preventing entry of minors into its manufacturing location, and third party age-verification technology.

Union Street's consumer survey data demonstrates that the company's safeguards and stringent age-verification protocols have made the company successful in its mission of providing quality products to an older adult consumer base of former combustible tobacco smokers. Furthermore, Union Street's consumer demographic and age data shows that this Youth Prevention Policy is successful in its effort to prevent underage use of Union Street's products.

[Pop Vapor Marketing Plan]

Marketing Plan

Our company is committed to responsible labeling, advertising, marketing, promotion and honest consumer-directed activities. The goal of our marketing initiative includes alignment of our product with federal, state, and local standards. Our strategic plan encompasses the following core values and principles:

1) Our company only markets and sells our products to legal adult tobacco product users.
2) Our company is honest about our products, including providing information on potential health risks.
3) Our company respects the law and views compliance with the law as a minimum standard that we must constantly meet and exceed.
4) Our company follows a strict standardized ethical code, with some local adaptation

Market Program

After receiving premarket submission clearance from the FDA, our company proposes to implement a strategic approach to our marketing plan. The purpose for advertising and promoting our product is to (a) provide information to tobacco consumers regarding product choice, (b) capture brand share from competitors, and (c) promote brand awareness.

Target Market

Our intended target audience for our marketing is adult smokers over the age of 21. Specific demographic characteristics for focus include individuals aged 25-44 years old, and current smokers who are interested in smoking cessation.

Advertising and Media Outreach

Planned Media and PR Distribution Channels

- Our marketing tactics include the use of US-based social media channels (Instagram, Facebook), magazine advertisements, and radio announcements. All media channels will include statements that our products are intended for ADULT USE only.
- We do not use knowingly use earned media to promote our products.
- We grow our brand organically with quality products and superior customer service.

Partnerships and Sponsors

- We do engage with partners and influencer marketing to advertise and promote our products. Our influencers regularly reinforce the use of our products as an ADULT USE, 21+ product.

JA308

Global Media Channels/Affiliates

- We maintain relationships we have with our wholesalers, distributors, and industry affiliates.

Marketing Budget

- We have not dedicated a budget for media buys, marketing, and promotional activities.

Marketing Timeline

- We do not have a specific marketing timeline for our marketing activities
- Our marketing timeline consists of consistent consumer engagement via social media posts

Consumer Engagements/Sampling

- We do not have plans to participate in consumer engagements, including events at specific direct-to-consumer tradeshows only

Product Samples

- Our company is not engaging in end user promotion with sampling.
- Our company only provides product sampling, in limited quantities, to verified businesses who responsibly sell tobacco products through adult only sales channels.

Company Marketing Standards

Our company recognizes our responsibility to provide conscientious communication to consumers and the public. As part of a sound ongoing marketing campaign, we have implemented specific rules and principles to guide our PR, advertising and promotional efforts.

Quality Content Standard

- Our company will employ carefully curated processes to provide relevant, credible, and diligent content.
- Our company prohibits the use of imagery or design that might perceived as violation or infringement of trademark and/or trade dress.

Accurate and Non-Misleading standard

- Our marketing campaign will ensure that our brand and specific content conveys an accurate and non-misleading impression of the promoted product.
- All statements and content will comply with applicable laws.

JA309

- Our marketing campaign will include clear messaging detailing, including the risks associated with our product
- Our company will refrain from misleading and/or unauthorized claims about our products. All claims including customer reviews, social media posts, testimonials, and marketing made on any forum will always be substantiated, credible, authentic, and backed by reputable sources.
- Our company does not make any disease, health, safety, or modified risk claims about our products.
- Our company does not make smoking cessation claims about our products.

Labeling and Product Warnings Standard

- Our company is dedicated to diligent labeling that is not false or misleading.
- Our product will bear its established name prominently, adequate directions for use, and adequate warnings that are necessary for the protection of users

Our product warnings include:

- FDA Nicotine Warning Statement: "**WARNING: This product contains nicotine. Nicotine is an addictive chemical.**"
- California Proposition 65: [redacted] WARNING: This product can expose you to chemicals including formaldehyde, which is known to the State of California to cause cancer, and nicotine, which is known to the State of California to cause birth defects or other reproductive harm. For more information, go to www.P65Warnings.ca.gov.
- "WARNING: Contains nicotine, which can be poisonous. Avoid contact with skin and eyes. Do not drink. Keep out of reach of children and pets. In case of accidental contact, seek medical help. For use only in e-cigarettes or vaporizers by persons of legal age (at least 18). THIS IS NOT A FOOD."
- NOT FOR SALE TO PERSONS UNDER LEGAL SMOKING AGE.
- KEEP AWAY FROM CHILDREN AND PETS.

Preventing Youth Access and Appeal Standard

- Our products should only be sold to, and used by, adults age 21 and older.
- To prevent the sale and distribution of our products to young people and ensure appropriate marketing for the protection of the public health, we have adopted the following policies and practices:
  - Our company complies with the local, state, and federal age restrictions
  - Our company's online sales are restricted to adults only following age verification through independent, third-party agencies using public records databases.
  - Our company educates and supports our distributors, wholesalers, and retailers to ensure that they have appropriate systems in place for age verification for in-person and online sales.

JA310

  - Our company PR and marketing campaign will comply with all applicable promotion and advertising restrictions, with an emphasis on reducing exposure of our promotional content to children and adolescents.

- Our company PR and marketing campaign will comply with all applicable promotion and advertising restrictions, with an emphasis on reducing exposure of our promotional content to children and adolescents.
  - To further these efforts to limit access and reduce youth interest in our product, we have taken the additional following steps:
    - Converted to using only a plain black and white label and external packaging to minimize the visual appeal of our products
    - Prohibited the use of youth appealing content for product naming and labeling. Our company will not use images or names such as candy, candy flavors or other child/teen content and imagery.
    - Emphasized the barring of underage sales in our marketing and promotion strategy
    - Restricted social media marketing and ensure all content intended for the US market is age-restricted
      - Limiting social media marketing to only utilizing age-appropriate influencers to promote our brand
      - Excluded the use of images/pictures appealing to youth
    - Limited our sales channels to online retail sites with adequate online age verification software

Overall, our company is committed to responsible marketing and industry-leading consumer engagement. We will continue to comply and collaborate with federal and state agencies in order to ensure the communication of our products is appropriate for the protection of public health.

JA311

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

ELBERT PARR TUTTLE COURT OF APPEALS BUILDING
56 Forsyth Street, N.W.
Atlanta, Georgia 30303

David J. Smith
Clerk of Court

For rules and forms visit
www.ca11.uscourts.gov

August 23, 2022

MEMORANDUM TO COUNSEL OR PARTIES

Appeal Number: 21-13340-DD ; 21-13387 -JJ ; 21-13438 -JJ ; 21-13454 -JJ ; 21-13521 -JJ ; 21-13522 -BB
Case Style: Bidi Vapor LLC v. U.S. Food and Drug Administration, et al
Agency Docket Number: PM0003460

Electronic Filing
All counsel must file documents electronically using the Electronic Case Files ("ECF") system, unless exempted for good cause. Although not required, non-incarcerated pro se parties are permitted to use the ECF system by registering for an account at www.pacer.gov. Information and training materials related to electronic filing are available on the Court's website. Enclosed is a copy of the court's decision filed today in this appeal. Judgment has this day been entered pursuant to FRAP 36. The court's mandate will issue at a later date in accordance with FRAP 41(b).

The time for filing a petition for rehearing is governed by 11th Cir. R. 40-3, and the time for filing a petition for rehearing en banc is governed by 11th Cir. R. 35-2. Except as otherwise provided by FRAP 25(a) for inmate filings, a petition for rehearing or for rehearing en banc is timely only if received in the clerk's office within the time specified in the rules. Costs are governed by FRAP 39 and 11th Cir.R. 39-1. The timing, format, and content of a motion for attorney's fees and an objection thereto is governed by 11th Cir. R. 39-2 and 39-3.

Please note that a petition for rehearing en banc must include in the Certificate of Interested Persons a complete list of all persons and entities listed on all certificates previously filed by any party in the appeal. See 11th Cir. R. 26.1-1. In addition, a copy of the opinion sought to be reheard must be included in any petition for rehearing or petition for rehearing en banc. See 11th Cir. R. 35-5(k) and 40-1 .

Counsel appointed under the Criminal Justice Act (CJA) must submit a voucher claiming compensation for time spent on the appeal no later than 60 days after either issuance of mandate or filing with the U.S. Supreme Court of a petition for writ of certiorari (whichever is later) via the eVoucher system. Please contact the CJA Team at (404) 335-6167 or cja_evoucher@ca11.uscourts.gov for questions regarding CJA vouchers or the eVoucher system.

Pursuant to Fed.R.App.P. 39, costs taxed against respondents.

Please use the most recent version of the Bill of Costs form available on the court's website at www.ca11.uscourts.gov.

For questions concerning the issuance of the decision of this court, please call the number referenced in the signature block below. For all other questions, please call Bradly Wallace Holland, DD at 404-335-6181.

Sincerely,

DAVID J. SMITH, Clerk of Court

Reply to: Djuanna H. Clark
Phone #: 404-335-6151

OPIN-1A Issuance of Opinion With Costs

FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking number (STNs)	(b) (4) See Appendix A
Common Attributes	
Submission date	September 7, 2020
Receipt date	September 7, 2020
Applicant	(b) (4)
Product manufacturer	(b) (4)
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submission	
All new products	None
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):

Digitally signed by David B. Portnoy -S
Date: 2021.09.17 10:42:36 -04'00'

David B. Portnoy, Ph.D., M.P.H.
Branch Chief, Social Science Branch 2
Division of Population Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2021.09.17 10:59:24 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

[i] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application. Scientific references (if any) are listed at the end of this document and referred to with Arabic numerals; general footnotes are referred to with Roman numerals.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 3

2. BACKGROUND 4

2.1. NEW PRODUCTS 4

2.2. REGULATORY ACTIVITY 4

2.3. BASIS FOR REQUIRING RELIABLE, ROBUST EVIDENCE TO DEMONSTRATE BENEFIT 4

2.3.1. The Risk to Youth of Flavored ENDS Products 5

2.3.2. Balancing Known Risks to Youth with a Potential Benefit to Adults 9

2.4. SCOPE OF REVIEW 13

3. SCIENTIFIC REVIEW 14

4. ENVIRONMENTAL DECISION 14

5. CONCLUSION AND RECOMMENDATION 14

6. APPENDIX 16

7. REFERENCES 17

1. EXECUTIVE SUMMARY

These applications for flavored ENDS[ii] products lack evidence to demonstrate that permitting the marketing of these products would be appropriate for the protection of the public health (APPH). Given the known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use, applicants would need reliable and robust evidence of a potential benefit to adult smokers[iii] that could justify that risk. Accordingly, in order to show that a flavored ENDS is APPH, the applicant must show that the benefit to adults switching from or reducing cigarettes outweighs the risk to youth.

Based on existing scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined for these applications that, to effectively demonstrate this benefit in terms of product use behavior, only the strongest types of evidence will be sufficiently reliable and robust —most likely product specific evidence from a randomized controlled trial (RCT)[iv] or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis.[v,vi] Moreover, tobacco-flavored ENDS may offer the same type of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Therefore, to demonstrate the potential benefit to current users, FDA has reviewed these applications for any acceptably strong evidence that the flavored products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking.

We have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate APPH. Our review determined that the applications do <u>not</u> contain evidence from a randomized controlled trial or longitudinal cohort study regarding the impact of the ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over tobacco-flavored ENDS. The PMTAs do contain other evidence regarding the potential benefit to adult users; however, for the reasons explained below, this other evidence is not adequate.

[ii] The term *flavored ENDS* in this review refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS. Tobacco-flavored ENDS are discussed below. Applications for menthol-flavored ENDS will be addressed separately. When it comes to evaluating the risks and benefits of a marketing authorization, the assessment for menthol ENDS, as compared to other non-tobacco-flavored ENDS, raises unique considerations. The term *flavored ENDS* also includes unflavored "base" e-liquids that are designed to have flavors added to them. This includes e-liquids made for use with open systems as well as closed system ENDS (e.g., cartridges or disposable ENDS) containing e-liquids.

[iii] The standard described in Section 910 requires an accounting of the risks and benefits to the population as a whole, balancing the potential impacts to both current tobacco users and non-users. This review is focused on the risk to youth nonusers as well as the potential benefit to adult smokers as current users, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth.

[iv] A randomized controlled trial is a clinical investigation or a clinical study in which human subject(s) are prospectively, and randomly assigned to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on behavioral, biomedical, or health-related outcomes. *Control or controlled* means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (*e.g.,* historical controls, including a human subject's own baseline data), as reflected in the pre-specified primary or secondary outcome measures.

[v] A longitudinal cohort study is an observational study in which human subjects from a defined population are examined prospectively over a period of time to assess an outcome or set of outcomes among study groups defined by a common characteristic (e.g., smoking cessation among users of flavored ENDS compared with users of tobacco-flavored ENDS).

[vi] For example, we would consider evidence from another study design if it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco-flavored products. In our review of PMTAs for flavored ENDS so far, we have learned that, in the absence of strong evidence generated by directly observing the behavioral impacts of using a flavored product vs. a tobacco-flavored product over time, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth.

As a result, the applicant has failed to provide evidence to overcome the risk to youth and show a net population health benefit necessary to determine that permitting the marketing of the new tobacco product is APPH.

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the new products listed on the cover page and in Appendix A.

2.2. REGULATORY ACTIVITY

FDA issued an Acceptance letter to the applicant on October 8, 2020. FDA issued a Filing letter to the applicant on November 9, 2020.

2.3. BASIS FOR REQUIRING RELIABLE, ROBUST EVIDENCE TO DEMONSTRATE BENEFIT

The rationale for FDA's decision for these flavored ENDS applications is consistent with previous decisions for other flavored ENDS and is set forth below.

The Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) requires that "new tobacco products" receive marketing authorization from FDA under one of the pathways specified by the Act in order to be legally marketed in the United States. Under one pathway, the applicant submits a PMTA to FDA. Section 910 of the FD&C Act requires that, for a product to receive PMTA marketing authorization, FDA must conclude, among other things, that the marketing of the product is APPH. The statute specifies that, in assessing APPH, FDA consider the risks and benefits to the population as a whole including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products.[vii]

It is well recognized that ENDS, and particularly flavored ENDS, pose a significant risk to nonusers, especially youth.[1,2] After observing a dramatic increase in the prevalence of ENDS use among U.S. youth in 2018, FDA's Commissioner characterized the problem as a youth vaping epidemic. FDA has initiated a series of actions to address the risk and reduce youth use. Since August 2016, FDA has issued more than 10,000 warning letters and more than 1,400 civil money penalty complaints to retailers for the sale of ENDS products to minors. FDA has also issued a guidance that described a policy of prioritizing enforcement of non-tobacco/non-menthol flavored ENDS, "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market without Premarket Authorization" (2020 Enforcement Priorities Guidance). In this guidance, FDA described evidence that shows flavors (other than tobacco and menthol) were a key driver of

[vii] This review focuses on risk to youth nonusers and the potential benefit to adult smokers as current tobacco product users, given that these are the subpopulations that raise the most significant public health concerns and therefore are the most relevant in evaluating the impact on the population as a whole. FDA has also considered the APPH standard with respect to the likelihood that an authorization will increase or decrease the number of tobacco users in the overall population. The availability of such products has generally led to greater tobacco use among youth overall, notwithstanding the decrease in cigarette smoking for youth, which reinforces the focus in this review on having sufficiently reliable and robust evidence to justify authorization of these PMTAs. Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students – United States, 2011-2018," Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018.

the surge in ENDS use among youth and thus prioritized enforcement against certain flavored ENDS products, with the goal of protecting youth from these products.[viii]

After FDA implemented this enforcement policy prioritizing enforcement against a subset of ENDS products known to appeal to youth, there was a meaningful reduction in youth use prevalence. Youth ENDS use peaked in 2019 when these products were widely available. Although several other policy changes and interventions were occurring during this same time period,[ix] it is reasonable to infer that prioritizing enforcement against many flavored products resulting in their removal from the market contributed to the decline in use in 2020. Despite this decline, ENDS remained the most widely used tobacco product among youth, with youth use at levels comparable to what originally led FDA to declare a youth vaping epidemic. Moreover, despite the overall reduction in ENDS youth use observed in 2020, there was simultaneously a substantial rise in youth use of disposable ENDS, products that were largely excluded from the enforcement policy described in the 2020 Enforcement Priorities Guidance because, at that time that policy was developed, those products were the least commonly used device type among high school ENDS users and therefore remained on the market as a flavored option.[3,4]

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be [APPH]." Through the PMTA review process, FDA conducts a science-based evaluation to determine whether marketing of a new tobacco product is APPH. Section 910(c)(4) requires FDA, in making the APPH determination, to consider the risks and benefits to the population as a whole, including users and nonusers of tobacco, and take into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to considering only information in a PMTA, but also extends to any other information before the Agency, including the relevant existing scientific literature (See Section 910(c)(2)). As described in greater detail below, in reviewing PMTAs for flavored ENDS, FDA evaluates, among other things, the potential benefit to adult smokers who may transition away from combustible cigarettes to the ENDS product, weighed against the known risks of flavored ENDS to youth.

2.3.1. The Risk to Youth of Flavored ENDS Products

As noted, the APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood[5] and thus youth are at particular risk of tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Indeed, almost 90 percent of adult daily smokers started smoking by the age of 18.[6] Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood.[7] On the other hand, youth and young adults who

[viii] Due to the overwhelming amount of evidence showing a substantial increase in youth use of flavored ENDS products, as well as their demonstrated popularity among youth, in January 2020, FDA finalized a guidance prioritizing enforcement against flavored (other than tobacco or menthol) prefilled pod or cartridge-based e-cigarettes, as well as other categories of unauthorized products.

[ix] The change in ENDS product availability coincided with other events such as the enactment of legislation raising the federal minimum age for sale of tobacco products from 18 to 21 years (Tobacco 21), the outbreak of e-cigarette, or vaping, product-use associated lung injury (EVALI), and public education campaigns which also may have contributed to the decline in ENDS use.

reach the age of 26 without ever starting to use cigarettes will most likely never become a daily smoker.[6] Because of the lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

2.3.1.1. Youth use of flavored ENDS

ENDS are now the most commonly used type of tobacco product among youth. In 2020, approximately 19.6% of U.S. high school students and 4.7% of middle school students were current users of ENDS, corresponding to 3.6 million youth and making ENDS the most widely used tobacco product among youth by far.[8] As noted above, this was a decline from 2019, when 27.5% of high school and 10.5% of middle school students reported ENDS use,[9] which necessitated the FDA enforcement policy described above.

The evidence shows that the availability of a broad range of flavors is one of the primary reasons for the popularity of ENDS among youth. The majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time. In the 2014 National Youth Tobacco Survey (NYTS), 65.1% of high school and 55.1% of middle school e-cigarette[x] users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xi] increased to 84.7% of high school users and 73.9% of middle school users.[3] Among high school e-cigarette users, the most common flavors used in 2020 were fruit (73.1%); mint (55.8%); menthol (37.0%); and candy, dessert, or other sweets (36.4%).[3] Among middle school e-cigarette users, the most common flavors used in 2020 were fruit (75.6%); candy, desserts, or other sweets (47.2%); mint (46.5%); and menthol (23.5%).[3]

Youth ENDS users are also more likely to use flavored ENDS compared to adult ENDS users. In PATH Wave 5.5 from 2020, 66.8% of youth ENDS users aged 13 to 17 reported using fruit, followed by 53.8% for mint/menthol[xii], 23.5% for candy/dessert/other sweets, and 13.3% for tobacco flavor (internal analysis). In the 2020 PATH Adult Telephone Survey, 51.5% of adult ENDS users 25 and older used fruit, 30.4% used mint/menthol, 23.8% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal analysis). Youth current ENDS users were also more likely than adult current ENDS users to use more than one flavor and to use combinations that did not include tobacco flavors.[11]

Studies show that flavors influence youth initiation of ENDS use. In particular, data show that flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a flavored product. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first e-cigarette that they used was flavored.[12] In another PATH study, more youth, young adults and adults who initiated e-cigarette use between Wave 1 and Wave 2 reported use of a flavored product than a non-flavored product.[13] Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older.[14]

In addition, nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason.[15,16] In fact, among Wave 4 youth current ENDS users, 71% reported using ENDS "because they come in flavors I like."[14]

---

[x] We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.
[xi] Flavored product use in these studies means use of flavors other than tobacco.
[xii] The PATH Study Questionnaire from Wave 5.5 did not assess mint and menthol separately. However, subsequent data collections (ATS and Wave 6) have separated the two flavors.

One explanation for this high prevalence and increase in frequency of use is that flavors can influence the rewarding and reinforcing effects of e-liquids, thereby facilitating ENDS use and increasing abuse liability. Research shows that flavored ENDS are rated as more satisfying than non-flavored ENDS, and participants will work harder for and take more puffs of flavored ENDS compared to non-flavored ENDS.[17] Research also shows that flavors can increase nicotine exposure by potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use.[18] Together, this evidence suggests flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth, particularly due to the vulnerability of the developing adolescent brain, which is discussed further below.

Finally, existing literature on flavored tobacco product use suggests that flavors not only facilitate initiation, but also promote established regular ENDS use. In particular, the flavoring in tobacco products (including ENDS) make them more palatable for novice youth and young adults, which can lead to initiation, more frequent and repeated use, and eventually established regular use. For example, regional studies have found that the use of flavored e-cigarettes was associated with a greater frequency of e-cigarettes used per day among a sample of adolescents in Connecticut in 2014[19] and continuation of e-cigarette use in a sample of adolescents in California from 2014-2017.[20] Use of non-traditional flavors (vs. tobacco, mint/menthol, flavorless) was associated with increased likelihood of continued use and taking more puffs per episode.[20] Data from a regional survey in Philadelphia, PA found initial use of a flavored (vs. unflavored or tobacco-flavored) ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months.[21] Finally, similar effects have been found in the nationally representative PATH study among young adults (18-24 years), where "ever use" of flavored e-cigarettes at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2.[22] In sum, flavored ENDS facilitate both experimentation and progression to regular use, which could lead to a lifetime of nicotine dependence.

2.3.1.2. The appeal of flavors across ENDS devices

The role of flavors in increasing the appeal of tobacco products to youth — across tobacco product categories — is well-established in the literature.[23-26] The published literature is sufficient to demonstrate the substantial appeal to youth of flavored ENDS, because it is robust and consistent. As described above, the preference for use of flavored ENDS among youth is consistently demonstrated across large, national surveys and longitudinal cohort studies.

National surveillance data suggest that, within the ENDS category, there is variability in the popularity of device types among youth, suggesting there may be differential appeal of certain product styles. Still, across these different device types, the role of flavor is consistent. As described above, the majority of youth ENDS use involves flavored products: in 2020, the majority of high school and middle school current e-cigarette users reported use of non-tobacco-flavored products (82.9%)[3] and flavored use was favored among both users of closed (87%) and open (76%) ENDS (internal analysis). In particular, across device types, including prefilled pods/cartridges, disposables, tanks, and mod systems, fruit was the most commonly used flavor type among youth, with 66.0% for prefilled pods/cartridges, 82.7% for disposables, 81.7% for tanks, and 78.9% for mod systems among youth reporting using a fruit flavor.[3]

It is also worth noting that the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace, that is, the options, especially flavors, that are available for consumers to choose from. Some evidence for this was observed in the trends both leading up to, and coinciding with, the shifting marketplace following the 2020 Enforcement Priorities Guidance. In particular, the enormous rise in youth ENDS use from 2017-2019 coincided with the ascendance

of JUUL (and copy-cat devices) in the marketplace, suggesting a relationship between the availability of JUUL as an option, and the sudden popularity of pod-based devices.[xiii] Then, as noted earlier, when FDA changed its enforcement policy to prioritize pod-based flavored ENDS, which were most appealing to youth at the time, we subsequently observed a substantial rise in use of disposable flavored ENDS[xiv]--a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users.[4] This trend illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired flavor options, underscoring the fundamental role of flavor in driving appeal.

2.3.1.3. The harms of youth ENDS use: The adolescent brain and risk for addiction

In addition to the high prevalence of youth ENDS use, the data also suggest this use is leading to increases in nicotine dependence.[10] Indeed, responding to concerns related to youth ENDS dependence, at the end of 2018, FDA held a public hearing to discuss the potential role of drug therapies to support e-cigarette cessation.[xv]

In 2019, an estimated 30.4% of middle and high school student ENDS users reported frequent use (i.e., use on ≥20 of the past 30 days).[9] By school type, 34.2% (95% CI, 31.2%-37.3%) of high school student ENDS users and 18.0% (95% CI, 15.2%-21.2%) of middle school student ENDS users reported frequent use.[27] Among current ENDS users, 21.4% of high school users and 8.8% of middle school users reported daily ENDS use.[27] Additionally, in a study that examined changes in ENDS use in youth ages 13-18 over a 12-month period, nicotine dependence (measured using the Penn State Electronic Cigarette Dependence Index (PS-ECDI)[28,29] and salivary cotinine concentrations increased, indicating continued ENDS use and greater nicotine exposure over time.[30]

Youth and young adult brains are more vulnerable to nicotine's effects than the adult brain due to ongoing neural development.[31,32] Adolescence is a developmental period consisting of major neurobiological and psychosocial changes and is characterized by increased reward-seeking and risk-taking behaviors (e.g., experimentation with drugs), coupled with heightened sensitivity to both natural and drug rewards and an immature self-regulatory system that is less able to modulate reward-seeking impulses (e.g., diminished harm avoidance, cognitive control, self-regulation).[33-37] Furthermore, evidence from animal studies suggests that nicotine exposure during adolescence enhances the rewarding and reinforcing effects of nicotine in adulthood [38-41]; and can induce short and long-term deficits in attention, learning, and memory.[42-45]

2.3.1.4. Risk of progression from ENDS to other tobacco products of different health risk

Among youth who use ENDS, there is a risk of progression to other tobacco products of generally greater health risk. A 2017 systematic review and meta-analysis that summarized nine prospective cohort studies found significantly higher odds of smoking initiation (OR = 3.50, 95% CI: 2.38, 5.16) and past 30-day combusted cigarette use (OR = 4.28, 95% CI: 2.52, 7.27) among youth who had used ENDS at compared to youth who had not used ENDS.[46] Similar associations have been observed in longitudinal studies that have been published since the Soneji et al. review.[42,47-56] The 2018 NASEM report concluded that there is substantial evidence that ENDS use increases risk of ever using combusted tobacco cigarettes among youth and young adults.[57] The transition from non-cigarette

[xiii] This is borne out by the data from 2019 NYTS, in which 59.1% of high school ENDS users reported use of this one brand. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. Jama. 2019;322(21):2095-2103.

[xiv] In July 2020, FDA issued Warning letters to three companies for illegally marketing disposable e-cigarettes and for marketing unauthorized modified risk tobacco products.

[xv] On December 5, 2018, FDA hosted a public hearing on "Eliminating Youth Electronic Cigarette and Other Product Use: The Role of Drug Therapies."

product use to combusted cigarette use has been observed for other non-cigarette products, such as cigars, as well.[58] Although it is challenging to empirically separate causality from shared risk factors among youth combusted cigarette and ENDS users, some studies have found an association between ENDS and subsequent combusted cigarette use while controlling for similar risk profiles.[54]

The precise relationship between youth ENDS use and youth smoking remains undetermined. On the one hand, the prevalence of combusted cigarette smoking in youth has continued to decline,[9,59,60] suggesting that youth use of ENDS has not significantly slowed or impeded that positive public health trajectory. On the other hand, there is a growing body of evidence showing a link between ENDS use and subsequent smoking among youth that raises significant concerns. This evidence also increases concern that over time—and particularly if youth ENDS use were to return to the rates seen in 2019 or worsen--the trend of declining cigarette smoking could slow or even reverse.

2.3.1.5. Other health risks associated with ENDS use

In addition to the risk of tobacco initiation and progression among youth, there is epidemiologic evidence from the cross-sectional[xvi] Behavioral Risk Factor Survey system (BRFSS) suggesting positive associations between ENDS use among those who never smoked and some health outcomes. Two studies found associations between ENDS use and self-reported history of asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease with increased ENDS use (i.e., daily use) relating to increased odds of disease.[61,62] Another found an association between ENDS use and respiratory symptoms in younger adults (ages 18-34) but not in older adults.[63] ENDS use has also resulted in acute harm to individuals through battery explosion-related burns and e-liquid nicotine poisoning.[64-66] Ultimately, as this is still a relatively novel product category, much remains unknown about other potential long-term health risks.

2.3.1.6. Conclusion

The exponential growth in youth ENDS use observed from 2017 to 2019, and the enduring prevalence of youth ENDS use in the U.S. is alarming. Despite a reduction in youth use of ENDS from 2019 to 2020, there were still 3.6 million youth ENDS users in 2020 and the majority used a flavored ENDS product. Youth users are more likely to use flavored ENDS than adult ENDS users. Flavors are associated with ENDS initiation and progression among youth. The full extent of the harms of ENDS use are not yet known, but evidence to date suggests they include permanent effects of nicotine on the developing adolescent brain and the risk of nicotine addiction. Studies indicate an additive effect of e-liquid flavorings on the rewarding and reinforcing effects of nicotine containing e-liquids. Studies also demonstrate that e-liquid flavors affect nicotine exposure. Among youth who use ENDS, there is a risk of progression to other tobacco products with greater health risks including combustible cigarettes. Finally, though long-term health risks are not fully understood, studies suggest an association between never-smoking ENDS users and respiratory and cardiovascular health effects. This evidence demonstrates that flavored ENDS pose a significant risk to youth.

2.3.2. Balancing Known Risks to Youth with a Potential Benefit to Adults

Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be overcome by a sufficient benefit to adult users, and as the

[xvi] Cross-sectional surveys examine these relationships at a single point in time, and as a result, do not establish causality.

known risks increase, so too does the burden of demonstrating a substantial enough benefit. In the case of a new flavored ENDS product, the risk of youth initiation and use is substantial, given the clearly documented evidence described above. In order for marketing of a new flavored ENDS product to be found APPH, an applicant would have to show that the significant risk to youth could be overcome by likely benefits substantial enough such that the net impact to public health would be positive, taking into account all relevant evidence and circumstances, including whether there are effective limitations on youth access.

2.3.2.1. Potential benefit of new flavored ENDS

Current scientific literature demonstrates that ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than combustible cigarettes, and biomarker studies demonstrate significantly lower exposure to HPHCs among current exclusive ENDS users than current smokers.[57] However, whether this is true for any particular new ENDS product, and the implications for health risks from a particular product, are considered on a case-by-case basis during the course of FDA's scientific review of a PMTA.

FDA also considers the potential that current cigarette smokers may experience a reduction in health risks if they switch completely to an ENDS, or if they use both products but substantially reduce their cigarette smoking. For a flavored ENDS product, assuming that the evaluation of the product shows the likelihood for lower HPHC exposure, then to demonstrate the likely individual and population benefit, applicants must demonstrate that current smokers are likely to start using the new ENDS product exclusively or predominantly (e.g., dual use with a significant smoking reduction).[64]

2.3.2.2. Behavioral evidence appropriate to demonstrate the potential benefit to smokers

FDA's PMTA review includes an evaluation of any potential benefits of the product for the likely users, such as a possible reduction in health risks. In general, as FDA stated in its guidance for PMTAs for ENDS,[xvii] an assessment of how a new product may be used by current smokers can be derived from a variety of sources. FDA may consider direct behavioral evidence on the specific products under review or indirect evidence derived from studies of behavioral intentions; pharmacological studies of nicotine delivery, abuse liability, and/or use topography; and bridging from studies based on comparable products. Further, in the case of a flavored ENDS product, to demonstrate that the marketing of the new product is APPH, the magnitude of the likely benefit would have to be substantial enough to overcome the significant risk of youth uptake and use posed by the flavored ENDS product.

Section 910(c)(5) of the FD&C Act provides that determining whether marketing of a new tobacco product is APPH shall, when appropriate, be based on "well-controlled investigations, which may include one or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product." FDA believes well-controlled investigations are "appropriate" for demonstrating that permitting the marketing of specific flavored ENDS would be APPH given the significant risks to youth of flavored ENDS. One type of well-controlled investigation that could effectively demonstrate a potential benefit of a flavored ENDS product would be an RCT. In addition, as CTP has previously described,[xviii] another well-controlled investigation that could serve as an alternative to conducting an RCT to demonstrate adequate benefit is a longitudinal cohort study.

[xvii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2019 Public Meeting on Deemed Tobacco Product Applications

[xviii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2019 Public Meeting on Deemed Tobacco Product Applications

For flavored ENDS, the known and substantial risk to youth in particular is high. Therefore, to show a net population health benefit, FDA has determined that these applications must demonstrate potential benefits to smokers from marketing such products with robust and reliable evidence – including both robust study design and methods and the strength of the study results. In other words, because the potential benefit to adults is gained through its impact on smoking behavior, FDA is reviewing these applications to determine whether they demonstrate that a benefit of a new product is significant enough to overcome the risk to youth. In particular, FDA's review of these applications has considered the degree of benefit to a flavored ENDS product over a tobacco-flavored variety in facilitating smokers completely switching or significantly reducing their smoking, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. Note that applications with this type of information may still not be APPH: applications containing this evidence would still be evaluated to determine that the totality of the evidence supports a marketing authorization. As it relates to the risk to youth, for example, this assessment includes evaluating the appropriateness of the proposed marketing plan.[xix]

We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS products. Our substantive review of PMTAs for ENDS and our completion of numerous scientific reviews over the last 10 months have deepened our understanding of the APPH evaluation with respect to behavior. In these reviews, the expectations for scientific evidence related to potential adult benefit can vary based on demonstrated risk to youth. Although indirect evidence or bridged data from the literature may still be appropriate for many new products, including tobacco-flavored ENDS, robust and direct evidence demonstrating potential benefit has been needed when the known risks are high as with all flavored ENDS products. At the same time, we have learned from experience that, in the absence of strong direct evidence, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth. For instance, applicants who do not conduct their own behavioral studies must rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. To date, that approach has not been sufficient in our evaluation of flavored ENDS PMTAs because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions--the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive.[xx] In fact, the findings are quite mixed and as a result the literature does not establish that flavors differentially promote switching amongst ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due, at least in part, to differences in the products studied. Therefore, given the state of the science on flavored ENDS, and the known risks to youth, FDA has reviewed these applications for any acceptably strong product-specific evidence.

[xix] Limiting youth access and exposure to marketing is a critical aspect of product regulation. It is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal such that the risk for youth initiation would be reduced. However, to date, none of the ENDS PMTAs that FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use. Similarly, we are not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use ENDS. Accordingly, for the sake of efficiency, the evaluation of the marketing plans in applications will not occur at this stage of review, and we have not evaluated any marketing plans submitted with these applications.

[xx] This discrepancy between the literature for youth initiation and adult switching also likely reflects fundamental differences in the two outcomes being assessed—youth initiation and switching among adult smokers—and their determinants. For switching among adult smokers, the behavior change is occurring in the context of nicotine dependence. Thus, the specific product's ability to provide adequate reinforcement and continue to satisfy a smoker's cravings over time, which is a function of the design of the specific product itself, are critical factors in determining likelihood of continued use and the product's ability to promote switching. Whereas for youth initiation, experimentation among naïve or novice users is not driven by these factors.

More specifically, in order to adequately assess whether such an added benefit has been demonstrated, FDA has reviewed these applications for product-specific[xxi] evidence that would enable a comparison between the applications' new flavored products and an appropriate comparator tobacco-flavored product (both ENDS) in terms of their impact on tobacco use behavior among adult smokers. Consistent with section 910(c)(5), evidence generated using either an RCT design or longitudinal cohort study design is mostly likely to demonstrate such a benefit, although other types of evidence could be adequate if sufficiently reliable and robust, and will be evaluated on a case-by-case basis. [xxii]

CTP will consider other types of evidence if it is sufficiently robust and direct to demonstrate the impact of the new ENDS on adult switching or cigarette reduction. Uptake and transition to ENDS use is a behavioral pattern that requires assessment at more than one time point. In addition, the transition from smoking to exclusive ENDS use typically involves a period of dual use. Therefore, evaluating the behavioral outcomes needed to show any benefit of the product requires observing the actual behavior of users over time. With both RCT and cohort study designs, enrolled participants are followed over a period of time, with periodic and repeated measurement of relevant outcomes.

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to recall their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Consumer perception studies (surveys or experiments) typically assess outcomes believed to be precursors to behavior, such as preferences or intentions related to the new products, but are not designed to directly assess actual product use behavior. Moreover, the general scientific literature, though informative for evaluation of some types of products, is not adequate to address this assessment because it does not provide product-specific information. This is because the effectiveness of a product in promoting switching among smokers arises from a combination of its product features—including labeled characteristics like flavor and nicotine concentration—as well as the sensory and subjective experience of use (taste, throat hit, nicotine delivery), and can also be influenced by how the device itself looks and feels to the use.

While RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity; cohort studies enable stronger generalizability because

[xxi] By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

[xxii] Conversely, such longitudinal or product-specific data are not necessarily required to assess experimentation and appeal among youth. The available literature on youth initiation contains valid scientific evidence sufficient to evaluate the risk to youth of ENDS. The literature includes longitudinal cohort studies, such as the PATH study, which have been used to assess uptake of tobacco products, including flavored ENDS, among youth and young adults. These studies have evaluated the impact of flavors on the promotion of established regular use. Additionally, the literature includes large, nationally representative cross-sectional surveys, which are among the best available evidence to understand patterns of youth ENDS use and the key characteristics associated with such use These studies enable observation of youth behavior as it naturally occurs in representative samples of the U.S. population. These data available in the literature provide clear and overwhelming evidence that ENDS are the most widely used products by youth, the majority of youth users use a flavored ENDS, and that youth users are more likely to use flavored ENDS than adult ENDS users. We note that, in assessing the risks to youth from flavored ENDS, RCTs are not possible because it would be unethical to randomize youth never or naive users to try a particular ENDS to examine what impact it would have on initiation, experimentation, or progression to regular use.

conditions are closer to real-world. We are aware of these as trade-offs and generally do not favor one type over the other for addressing this question.

To be informative, a study using one of these two designs would measure the impact of use of the new or appropriate comparator product tobacco-flavored ENDS and flavored products on adult smokers' tobacco use behavior over time[xxiii]; include outcomes related to ENDS use and smoking behavior to assess switching and/or cigarette reduction; and enable comparisons of these outcomes based on flavor type. In some cases, evidence on each individual flavor option may not be feasible; bridging data from one of the applicant's flavors to other flavors of the applicant's in the same flavor category (e.g., "fruit") may be appropriate. Furthermore, consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging.[xxiv] Likewise, if a flavor is tested with one nicotine concentration, it may be feasible for the applicant to bridge the study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging.

Data from one of these studies could support a benefit to adult users if the findings showed that, compared to the new tobacco-flavored product, use of (each) new flavored product is associated with greater likelihood of either of these behavioral outcomes for adult smokers: (1) complete switching from cigarettes to exclusive new product use or (2) significant reduction in cigarettes per day (CPD).

2.3.2.3. Conclusion

Given the known and substantial risk to youth posed by flavored ENDS, FDA has reviewed these applications for the presence of particularly reliable product-specific[xxv] evidence to demonstrate a potential for benefit to adult smokers that could justify that risk. Based on our current understanding, a demonstration with sufficiently reliable and robust evidence that the flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS.

2.4. SCOPE OF REVIEW

The reviews evaluated whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new products on switching or cigarette reduction that could potentially demonstrate the added benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. These reviews included a search of the PMTAs to determine whether the evidence is found anywhere within the PMTAs, and if present, if certain conditions were met (e.g., was the randomized controlled trial conducted using the new products that are the subject of the PMTA). Our review also included a

[xxiii] This could include studies that are long-term (i.e., six months or longer). In FDA's (2019) Guidance to Industry, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems", FDA has previously stated that it did not expect that applicants would need to conduct long-term studies to support an application for ENDS. Because the behavior change of interest (switching or cigarette reduction) occurs over a period of time, it is possible that to observe these outcomes, investigators designing these studies may decide to follow participants over a period of six months or longer. However, it is also possible that studies with a shorter duration would be adequately reliable.

[xxiv] Bridging is discussed in FDA's 2019 Guidance to Industry cited above (fn xxiii).

[xxv] By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

search for other studies that provided product-specific evidence related to the potential benefit to adult users.

3. SCIENTIFIC REVIEW

Reviews were completed by Allison Hoffman and Willa Dong on September 17, 2021.

The reviews determined that, although the PMTAs includes a RCT and longitudinal cohort study, the studies did not include the actual use of the new products or compare tobacco-flavored products to other flavored products. In particular, the data from the RCT did not sufficiently demonstrate the relative effect of the flavored products as compared to a tobacco-flavored product or include outcomes assessing switching or cigarette reduction and the data from the cohort study not sufficiently demonstrate the relative effect of the flavored products as compared to a tobacco-flavored product. Therefore, these are insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

The PMTAs referenced studies including those that that assessed exposure biomarkers and physiological response following (b)(4) use, the effects of (b)(4) on health outcomes such as lung function, and surveys on consumer perceptions and intentions to use (b)(4), but this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it was not clear that the referenced studies included the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time; or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors. Accordingly, this evidence is not adequate and therefore, we did not assess other aspects of the application as part of this scientific review.

4. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order under section 910(c) of the Federal Food, Drug, and Cosmetic Act that a new product may not be introduced or delivered for introduction into interstate commerce (i.e., a marketing denial order) falls within a class of actions that are ordinarily categorically excluded from the preparation of an environmental assessment (EA) or environmental impact statement (EIS). To the best of our knowledge, no extraordinary circumstances exist that would preclude application of this categorical exclusion. FDA concludes that categorical exclusion is warranted and no EA or EIS is required.

5. CONCLUSION AND RECOMMENDATION

FDA has reviewed these applications for evidence demonstrating that the new flavored products will provide an added benefit to adult smokers relative to tobacco-flavored products. Based on our review, we determined that the PMTAs for the applicant's new products, as described in the applications and specified in Appendix A, lack sufficient evidence to demonstrate that permitting the marketing of the new products would be APPH. Thus, a Denial letter should be issued to the applicant. The applicant cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

The following deficiency should be conveyed to the applicant as the key basis for our determination that marketing of the new products is not APPH:

1. All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth. In

light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial (RCT) and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS. Although your PMTA includes a RCT and cohort study, it is unclear if they included the actual use of the new products. Additionally, the RCT and cohort studies did not compare tobacco-flavored products to other flavored products or include outcomes assessing switching or cigarette reduction. In particular, the data from your RCT did not sufficiently demonstrate the relative effect of your flavored products as compared to a tobacco-flavored product or the effects on switching or cigarette reduction and the cohort study did not sufficiently demonstrate the relative effect of your flavored products as compared to a tobacco-flavored product. Therefore, these are insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs referenced studies including those that that assessed exposure biomarkers and physiological response following (b)(4) use, the effects of (b)(4) on health outcomes such as lung function, and surveys on consumer perceptions and intentions to use (b)(4), this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it was not clear that the referenced studies included the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time; or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors. Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

6. APPENDIX

Appendix A. New Products

Common Attributes	
Submission date	September 7, 2020
Receipt date	September 7, 2020
Applicant	(b) (4)
Product manufacturer	(b) (4)
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

7. REFERENCES

1. U.S. Department of Health and Human Services. *E-cigarette Use Among Youth and Young Adults. A Report of the Surgeon General.* Atlanta, GA: U.S. Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2016.
2. U.S. Food and Drug Administration. *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised). Guidance for Industry.* Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products;April 2020.
3. Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. E-cigarette Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(37):1310-1312.
4. Wang TW, Gentzke AS, Neff LJ, et al. Disposable E-Cigarette Use among U.S. Youth — An Emerging Public Health Challenge. *New England Journal of Medicine.* 2021;384(16):1573-1576.
5. U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General.* Atlanta, GA: U.S. Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2012.
6. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2014.
7. Apelberg BJ, Corey CG, Hoffman AC, et al. Symptoms of tobacco dependence among middle and high school tobacco users: results from the 2012 National Youth Tobacco Survey. *Am J Prev Med.* 2014;47(2 Suppl 1):S4-14.
8. Gentzke AS, Wang TW, Jamal A, et al. Tobacco Product Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(50):1881-1888.
9. Wang TW, Gentzke AS, Creamer MR, et al. Tobacco Product Use and Associated Factors Among Middle and High School Students - United States, 2019. *MMWR Surveill Summ.* 2019;68(12):1-22.
10. Cullen KA, Liu ST, Bernat JK, et al. Flavored Tobacco Product Use Among Middle and High School Students - United States, 2014-2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(39):839-844.
11. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'Connor RJ. Use of Flavored E-Cigarettes and the Type of E-Cigarette Devices Used among Adults and Youth in the US-Results from Wave 3 of the Population Assessment of Tobacco and Health Study (2015-2016). *Int J Environ Res Public Health.* 2019;16(16).
12. Villanti AC, Johnson AL, Glasser AM, et al. Association of Flavored Tobacco Use With Tobacco Initiation and Subsequent Use Among US Youth and Adults, 2013-2015. *JAMA Netw Open.* 2019;2(10):e1913804.
13. Rose SW, Johnson AL, Glasser AM, et al. Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2014-2015. *Tob Control.* 2020;29(4):432-446.
14. Rostron BL, Cheng YC, Gardner LD, Ambrose BK. Prevalence and Reasons for Use of Flavored Cigars and ENDS among US Youth and Adults: Estimates from Wave 4 of the PATH Study, 2016-2017. *Am J Health Behav.* 2020;44(1):76-81.
15. Ambrose BK, Day HR, Rostron B, et al. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. *JAMA.* 2015;314(17):1871-1873.

16. Tsai J, Walton K, Coleman BN, et al. Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2018;67(6):196-200.
17. Audrain-McGovern J, Strasser AA, Wileyto EP. The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug Alcohol Depend.* 2016;166:263-267.
18. St Helen G, Dempsey DA, Havel CM, Jacob P, 3rd, Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug Alcohol Depend.* 2017;178:391-398.
19. Morean ME, Butler ER, Bold KW, et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PLoS One.* 2018;13(1):e0189015.
20. Leventhal AM, Goldenson NI, Cho J, Kirkpatrick MG, McConnell RS, Stone MD, Pang RD, Audrain-McGovern J, Barrington-Trimis JL. Flavored E-cigarette Use and Progression of Vaping in Adolescents. *Pediatrics.* 2019 Nov;144(5):e20190789.
21. Audrain-McGovern J, Rodriguez D, Pianin S, Alexander E. Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents. *Drug Alcohol Depend.* 2019;202:149-155.
22. Villanti AC, Johnson AL, Halenar M, et al. Menthol and mint cigarettes and cigars: Initiation and progression in youth, young adults and adults in Waves 1 - 4 of the PATH Study, 2013 - 2017. *Nicotine Tob Res.* 2020.
23. Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: tobacco marketing strategies. *Health Aff (Millwood).* 2005;24(6):1601-1610.
24. Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tobacco Control.* 2016;25(Suppl 2):ii62.
25. Camenga DR, Morean M, Kong G, Krishnan-Sarin S, Simon P, Bold K. Appeal and Use of Customizable E-cigarette Product Features in Adolescents. *Tob Regul Sci.* 2018;4(2):51-60.
26. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Prev Med Rep.* 2017;5:33-40.
27. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. *Jama.* 2019;322(21):2095-2103.
28. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine Tob Res.* 2015;17(2):186-192.
29. Yingst J, Foulds J, Veldheer S, et al. Measurement of Electronic Cigarette Frequency of Use Among Smokers Participating in a Randomized Controlled Trial. *Nicotine Tob Res.* 2020;22(5):699-704.
30. Vogel EA, Prochaska JJ, Ramo DE, Andres J, Rubinstein ML. Adolescents' E-Cigarette Use: Increases in Frequency, Dependence, and Nicotine Exposure Over 12 Months. *J Adolesc Health.* 2019;64(6):770-775.
31. Slotkin TA. Nicotine and the adolescent brain: insights from an animal model. *Neurotoxicol Teratol.* 2002;24(3):369-384.
32. Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *J Physiol.* 2015;593(16):3397-3412.
33. Bava S, Tapert SF. Adolescent brain development and the risk for alcohol and other drug problems. *Neuropsychol Rev.* 2010;20(4):398-413.
34. Bernheim A, Halfon O, Boutrel B. Controversies about the enhanced vulnerability of the adolescent brain to develop addiction. *Front Pharmacol.* 2013;4:118.
35. Casey BJ, Jones RM. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. *J Am Acad Child Adolesc Psychiatry.* 2010;49(12):1189-1201; quiz 1285.
36. Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain Cogn.* 2010;72(1):114-123.

37. Shulman EP, Smith AR, Silva K, et al. The dual systems model: Review, reappraisal, and reaffirmation. *Dev Cogn Neurosci.* 2016;17:103-117.
38. Kota D, Sanjakdar S, Marks MJ, Khabour O, Alzoubi K, Damaj MI. Exploring behavioral and molecular mechanisms of nicotine reward in adolescent mice. *Biochem Pharmacol.* 2011;82(8):1008-1014.
39. Shram MJ, Lê AD. Adolescent male Wistar rats are more responsive than adult rats to the conditioned rewarding effects of intravenously administered nicotine in the place conditioning procedure. *Behav Brain Res.* 2010;206(2):240-244.
40. Natividad LA, Torres OV, Friedman TC, O'Dell LE. Adolescence is a period of development characterized by short- and long-term vulnerability to the rewarding effects of nicotine and reduced sensitivity to the anorectic effects of this drug. *Behav Brain Res.* 2013;257:275-285.
41. de la Peña JB, Ahsan HM, Tampus R, et al. Cigarette smoke exposure during adolescence enhances sensitivity to the rewarding effects of nicotine in adulthood, even after a long period of abstinence. *Neuropharmacology.* 2015;99:9-14.
42. Conner M, Grogan S, Simms-Ellis R, et al. Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study. *Tob Control.* 2017;27(4):365-372.
43. Holliday ED, Gould TJ. Chronic Nicotine Treatment During Adolescence Attenuates the Effects of Acute Nicotine in Adult Contextual Fear Learning. *Nicotine Tob Res.* 2017;19(1):87-93.
44. Counotte DS, Spijker S, Van de Burgwal LH, et al. Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. *Neuropsychopharmacology.* 2009;34(2):299-306.
45. Fountain SB, Rowan JD, Kelley BM, Willey AR, Nolley EP. Adolescent exposure to nicotine impairs adult serial pattern learning in rats. *Exp Brain Res.* 2008;187(4):651-656.
46. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr.* 2017;171(8):788-797.
47. Aleyan S, Cole A, Qian W, Leatherdale ST. Risky business: a longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users in Canada. *BMJ Open.* 2018;8(5):e021080.
48. Berry KM, Fetterman JL, Benjamin EJ, et al. Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths. *JAMA Netw Open.* 2019;2(2):e187794.
49. Hammond D, Reid JL, Cole AG, Leatherdale ST. Electronic cigarette use and smoking initiation among youth: a longitudinal cohort study. *Cmaj.* 2017;189(43):E1328-e1336.
50. Loukas A, Marti CN, Cooper M, Pasch KE, Perry CL. Exclusive e-cigarette use predicts cigarette initiation among college students. *Addict Behav.* 2018;76:343-347.
51. Treur JL, Rozema AD, Mathijssen JJP, van Oers H, Vink JM. E-cigarette and waterpipe use in two adolescent cohorts: cross-sectional and longitudinal associations with conventional cigarette smoking. *Eur J Epidemiol.* 2018;33(3):323-334.
52. Kintz N, Liu M, Chou CP, et al. Risk factors associated with subsequent initiation of cigarettes and e-cigarettes in adolescence: A structural equation modeling approach. *Drug Alcohol Depend.* 2020;207:107676.
53. Lozano P, Barrientos-Gutierrez I, Arillo-Santillan E, et al. A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents. *Drug Alcohol Depend.* 2017;180:427-430.
54. Stanton CA, Bansal-Travers M, Johnson AL, et al. Longitudinal e-Cigarette and Cigarette Use Among US Youth in the PATH Study (2013-2015). *J Natl Cancer Inst.* 2019;111(10):1088-1096.
55. Best C, Haseen F, Currie D, et al. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tob Control.* 2017;27(4):373-378.
56. Bold KW, Kong G, Camenga DR, et al. Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics.* 2018;141(1).

57. National Academies of Sciences Engineering Medicine. Public Health Consequences of E-Cigarettes. In. Washington, DC: National Academies Press; 2018.
58. Edwards KC, Sharma E, Halenar MJ, et al. Longitudinal pathways of exclusive and polytobacco cigar use among youth, young adults and adults in the USA: findings from the PATH Study Waves 1-3 (2013-2016). *Tob Control.* 2020;29(Suppl 3):s163-s169.
59. Gentzke AS, Creamer M, Cullen KA, et al. Vital Signs: Tobacco Product Use Among Middle and High School Students - United States, 2011-2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(6):157-164.
60. Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. Tobacco Product Use Among Middle and High School Students - United States, 2011-2017. *MMWR Morb Mortal Wkly Rep.* 2018;67(22):629-633.
61. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association Between E-Cigarette Use and Chronic Obstructive Pulmonary Disease by Smoking Status: Behavioral Risk Factor Surveillance System 2016 and 2017. *Am J Prev Med.* 2020;58(3):336-342.
62. Osei AD, Mirbolouk M, Orimoloye OA, et al. The association between e-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS) 2016 & 2017. *BMC Pulm Med.* 2019;19(1):180.
63. Giovanni SP, Keller TL, Bryant AD, Weiss NS, Littman AJ. Electronic Cigarette Use and Chronic Respiratory Symptoms among U.S. Adults. *Am J Respir Crit Care Med.* 2020;201(9):1157-1160.
64. Chang JT, Anic GM, Rostron BL, Tanwar M, Chang CM. Cigarette Smoking Reduction and Health Risks: A Systematic Review and Meta-analysis. *Nicotine Tob Res.* 2021;23(4):635-642.
65. Vyncke T, De Wolf E, Hoeksema H, et al. Injuries associated with electronic nicotine delivery systems: A systematic review. *J Trauma Acute Care Surg.* 2020;89(4):783-791.
66. Rossheim ME, Livingston MD, Soule EK, Zeraye HA, Thombs DL. Electronic cigarette explosion and burn injuries, US Emergency Departments 2015–2017. *Tobacco Control.* 2019;28(4):472.

FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking number (STNs)	(b) (4) See Appendix A
Common Attributes	
Submission date	September 7, 2020
Receipt date	September 7, 2020
Applicant	(b) (4)
Product manufacturer	(b) (4)
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submission	
All new products	None
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):

Digitally signed by David B. Portnoy -S
Date: 2021.09.17 10:42:36 -04'00'

David B. Portnoy, Ph.D., M.P.H.
Branch Chief, Social Science Branch 2
Division of Population Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2021.09.17 10:59:24 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

[i] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application. Scientific references (if any) are listed at the end of this document and referred to with Arabic numerals; general footnotes are referred to with Roman numerals.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 3

2. BACKGROUND 4

2.1. NEW PRODUCTS 4

2.2. REGULATORY ACTIVITY 4

2.3. BASIS FOR REQUIRING RELIABLE, ROBUST EVIDENCE TO DEMONSTRATE BENEFIT 4

2.3.1. The Risk to Youth of Flavored ENDS Products 5

2.3.2. Balancing Known Risks to Youth with a Potential Benefit to Adults 9

2.4. SCOPE OF REVIEW 13

3. SCIENTIFIC REVIEW 14

4. ENVIRONMENTAL DECISION 14

5. CONCLUSION AND RECOMMENDATION 14

6. APPENDIX 16

7. REFERENCES 17

1. EXECUTIVE SUMMARY

These applications for flavored ENDS[ii] products lack evidence to demonstrate that permitting the marketing of these products would be appropriate for the protection of the public health (APPH). Given the known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use, applicants would need reliable and robust evidence of a potential benefit to adult smokers[iii] that could justify that risk. Accordingly, in order to show that a flavored ENDS is APPH, the applicant must show that the benefit to adults switching from or reducing cigarettes outweighs the risk to youth.

Based on existing scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined for these applications that, to effectively demonstrate this benefit in terms of product use behavior, only the strongest types of evidence will be sufficiently reliable and robust —most likely product specific evidence from a randomized controlled trial (RCT)[iv] or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis.[v,vi] Moreover, tobacco-flavored ENDS may offer the same type of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Therefore, to demonstrate the potential benefit to current users, FDA has reviewed these applications for any acceptably strong evidence that the flavored products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking.

We have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate APPH. Our review determined that the applications do <u>not</u> contain evidence from a randomized controlled trial or longitudinal cohort study regarding the impact of the ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over tobacco-flavored ENDS. The PMTAs do contain other evidence regarding the potential benefit to adult users; however, for the reasons explained below, this other evidence is not adequate.

[ii] The term *flavored ENDS* in this review refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS. Tobacco-flavored ENDS are discussed below. Applications for menthol-flavored ENDS will be addressed separately. When it comes to evaluating the risks and benefits of a marketing authorization, the assessment for menthol ENDS, as compared to other non-tobacco-flavored ENDS, raises unique considerations. The term *flavored ENDS* also includes unflavored "base" e-liquids that are designed to have flavors added to them. This includes e-liquids made for use with open systems as well as closed system ENDS (e.g., cartridges or disposable ENDS) containing e-liquids.

[iii] The standard described in Section 910 requires an accounting of the risks and benefits to the population as a whole, balancing the potential impacts to both current tobacco users and non-users. This review is focused on the risk to youth nonusers as well as the potential benefit to adult smokers as current users, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth.

[iv] A randomized controlled trial is a clinical investigation or a clinical study in which human subject(s) are prospectively, and randomly assigned to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on behavioral, biomedical, or health-related outcomes. *Control or controlled* means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (*e.g.,* historical controls, including a human subject's own baseline data), as reflected in the pre-specified primary or secondary outcome measures.

[v] A longitudinal cohort study is an observational study in which human subjects from a defined population are examined prospectively over a period of time to assess an outcome or set of outcomes among study groups defined by a common characteristic (e.g., smoking cessation among users of flavored ENDS compared with users of tobacco-flavored ENDS).

[vi] For example, we would consider evidence from another study design if it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco-flavored products. In our review of PMTAs for flavored ENDS so far, we have learned that, in the absence of strong evidence generated by directly observing the behavioral impacts of using a flavored product vs. a tobacco-flavored product over time, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth.

As a result, the applicant has failed to provide evidence to overcome the risk to youth and show a net population health benefit necessary to determine that permitting the marketing of the new tobacco product is APPH.

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the new products listed on the cover page and in Appendix A.

2.2. REGULATORY ACTIVITY

FDA issued an Acceptance letter to the applicant on October 8, 2020. FDA issued a Filing letter to the applicant on November 9, 2020.

2.3. BASIS FOR REQUIRING RELIABLE, ROBUST EVIDENCE TO DEMONSTRATE BENEFIT

The rationale for FDA's decision for these flavored ENDS applications is consistent with previous decisions for other flavored ENDS and is set forth below.

The Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) requires that "new tobacco products" receive marketing authorization from FDA under one of the pathways specified by the Act in order to be legally marketed in the United States. Under one pathway, the applicant submits a PMTA to FDA. Section 910 of the FD&C Act requires that, for a product to receive PMTA marketing authorization, FDA must conclude, among other things, that the marketing of the product is APPH. The statute specifies that, in assessing APPH, FDA consider the risks and benefits to the population as a whole including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products.[vii]

It is well recognized that ENDS, and particularly flavored ENDS, pose a significant risk to nonusers, especially youth.[1,2] After observing a dramatic increase in the prevalence of ENDS use among U.S. youth in 2018, FDA's Commissioner characterized the problem as a youth vaping epidemic. FDA has initiated a series of actions to address the risk and reduce youth use. Since August 2016, FDA has issued more than 10,000 warning letters and more than 1,400 civil money penalty complaints to retailers for the sale of ENDS products to minors. FDA has also issued a guidance that described a policy of prioritizing enforcement of non-tobacco/non-menthol flavored ENDS, "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market without Premarket Authorization" (2020 Enforcement Priorities Guidance). In this guidance, FDA described evidence that shows flavors (other than tobacco and menthol) were a key driver of

[vii] This review focuses on risk to youth nonusers and the potential benefit to adult smokers as current tobacco product users, given that these are the subpopulations that raise the most significant public health concerns and therefore are the most relevant in evaluating the impact on the population as a whole. FDA has also considered the APPH standard with respect to the likelihood that an authorization will increase or decrease the number of tobacco users in the overall population. The availability of such products has generally led to greater tobacco use among youth overall, notwithstanding the decrease in cigarette smoking for youth, which reinforces the focus in this review on having sufficiently reliable and robust evidence to justify authorization of these PMTAs. Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students – United States, 2011-2018," Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018.

the surge in ENDS use among youth and thus prioritized enforcement against certain flavored ENDS products, with the goal of protecting youth from these products.[viii]

After FDA implemented this enforcement policy prioritizing enforcement against a subset of ENDS products known to appeal to youth, there was a meaningful reduction in youth use prevalence. Youth ENDS use peaked in 2019 when these products were widely available. Although several other policy changes and interventions were occurring during this same time period,[ix] it is reasonable to infer that prioritizing enforcement against many flavored products resulting in their removal from the market contributed to the decline in use in 2020. Despite this decline, ENDS remained the most widely used tobacco product among youth, with youth use at levels comparable to what originally led FDA to declare a youth vaping epidemic. Moreover, despite the overall reduction in ENDS youth use observed in 2020, there was simultaneously a substantial rise in youth use of disposable ENDS, products that were largely excluded from the enforcement policy described in the 2020 Enforcement Priorities Guidance because, at that time that policy was developed, those products were the least commonly used device type among high school ENDS users and therefore remained on the market as a flavored option.[3,4]

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be [APPH]." Through the PMTA review process, FDA conducts a science-based evaluation to determine whether marketing of a new tobacco product is APPH. Section 910(c)(4) requires FDA, in making the APPH determination, to consider the risks and benefits to the population as a whole, including users and nonusers of tobacco, and take into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to considering only information in a PMTA, but also extends to any other information before the Agency, including the relevant existing scientific literature (See Section 910(c)(2)). As described in greater detail below, in reviewing PMTAs for flavored ENDS, FDA evaluates, among other things, the potential benefit to adult smokers who may transition away from combustible cigarettes to the ENDS product, weighed against the known risks of flavored ENDS to youth.

2.3.1. The Risk to Youth of Flavored ENDS Products

As noted, the APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood[5] and thus youth are at particular risk of tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Indeed, almost 90 percent of adult daily smokers started smoking by the age of 18.[6] Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood.[7] On the other hand, youth and young adults who

[viii] Due to the overwhelming amount of evidence showing a substantial increase in youth use of flavored ENDS products, as well as their demonstrated popularity among youth, in January 2020, FDA finalized a guidance prioritizing enforcement against flavored (other than tobacco or menthol) prefilled pod or cartridge-based e-cigarettes, as well as other categories of unauthorized products.

[ix] The change in ENDS product availability coincided with other events such as the enactment of legislation raising the federal minimum age for sale of tobacco products from 18 to 21 years (Tobacco 21), the outbreak of e-cigarette, or vaping, product-use associated lung injury (EVALI), and public education campaigns which also may have contributed to the decline in ENDS use.

reach the age of 26 without ever starting to use cigarettes will most likely never become a daily smoker.[6] Because of the lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

2.3.1.1. Youth use of flavored ENDS

ENDS are now the most commonly used type of tobacco product among youth. In 2020, approximately 19.6% of U.S. high school students and 4.7% of middle school students were current users of ENDS, corresponding to 3.6 million youth and making ENDS the most widely used tobacco product among youth by far.[8] As noted above, this was a decline from 2019, when 27.5% of high school and 10.5% of middle school students reported ENDS use,[9] which necessitated the FDA enforcement policy described above.

The evidence shows that the availability of a broad range of flavors is one of the primary reasons for the popularity of ENDS among youth. The majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time. In the 2014 National Youth Tobacco Survey (NYTS), 65.1% of high school and 55.1% of middle school e-cigarette[x] users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xi] increased to 84.7% of high school users and 73.9% of middle school users.[3] Among high school e-cigarette users, the most common flavors used in 2020 were fruit (73.1%); mint (55.8%); menthol (37.0%); and candy, dessert, or other sweets (36.4%).[3] Among middle school e-cigarette users, the most common flavors used in 2020 were fruit (75.6%); candy, desserts, or other sweets (47.2%); mint (46.5%); and menthol (23.5%).[3]

Youth ENDS users are also more likely to use flavored ENDS compared to adult ENDS users. In PATH Wave 5.5 from 2020, 66.8% of youth ENDS users aged 13 to 17 reported using fruit, followed by 53.8% for mint/menthol[xii], 23.5% for candy/dessert/other sweets, and 13.3% for tobacco flavor (internal analysis). In the 2020 PATH Adult Telephone Survey, 51.5% of adult ENDS users 25 and older used fruit, 30.4% used mint/menthol, 23.8% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal analysis). Youth current ENDS users were also more likely than adult current ENDS users to use more than one flavor and to use combinations that did not include tobacco flavors.[11]

Studies show that flavors influence youth initiation of ENDS use. In particular, data show that flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a flavored product. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first e-cigarette that they used was flavored.[12] In another PATH study, more youth, young adults and adults who initiated e-cigarette use between Wave 1 and Wave 2 reported use of a flavored product than a non-flavored product.[13] Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older.[14]

In addition, nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason.[15,16] In fact, among Wave 4 youth current ENDS users, 71% reported using ENDS "because they come in flavors I like."[14]

---

[x] We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.
[xi] Flavored product use in these studies means use of flavors other than tobacco.
[xii] The PATH Study Questionnaire from Wave 5.5 did not assess mint and menthol separately. However, subsequent data collections (ATS and Wave 6) have separated the two flavors.

One explanation for this high prevalence and increase in frequency of use is that flavors can influence the rewarding and reinforcing effects of e-liquids, thereby facilitating ENDS use and increasing abuse liability. Research shows that flavored ENDS are rated as more satisfying than non-flavored ENDS, and participants will work harder for and take more puffs of flavored ENDS compared to non-flavored ENDS.[17] Research also shows that flavors can increase nicotine exposure by potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use.[18] Together, this evidence suggests flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth, particularly due to the vulnerability of the developing adolescent brain, which is discussed further below.

Finally, existing literature on flavored tobacco product use suggests that flavors not only facilitate initiation, but also promote established regular ENDS use. In particular, the flavoring in tobacco products (including ENDS) make them more palatable for novice youth and young adults, which can lead to initiation, more frequent and repeated use, and eventually established regular use. For example, regional studies have found that the use of flavored e-cigarettes was associated with a greater frequency of e-cigarettes used per day among a sample of adolescents in Connecticut in 2014[19] and continuation of e-cigarette use in a sample of adolescents in California from 2014-2017.[20] Use of non-traditional flavors (vs. tobacco, mint/menthol, flavorless) was associated with increased likelihood of continued use and taking more puffs per episode.[20] Data from a regional survey in Philadelphia, PA found initial use of a flavored (vs. unflavored or tobacco-flavored) ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months.[21] Finally, similar effects have been found in the nationally representative PATH study among young adults (18-24 years), where "ever use" of flavored e-cigarettes at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2.[22] In sum, flavored ENDS facilitate both experimentation and progression to regular use, which could lead to a lifetime of nicotine dependence.

2.3.1.2. The appeal of flavors across ENDS devices

The role of flavors in increasing the appeal of tobacco products to youth — across tobacco product categories — is well-established in the literature.[23-26] The published literature is sufficient to demonstrate the substantial appeal to youth of flavored ENDS, because it is robust and consistent. As described above, the preference for use of flavored ENDS among youth is consistently demonstrated across large, national surveys and longitudinal cohort studies.

National surveillance data suggest that, within the ENDS category, there is variability in the popularity of device types among youth, suggesting there may be differential appeal of certain product styles. Still, across these different device types, the role of flavor is consistent. As described above, the majority of youth ENDS use involves flavored products: in 2020, the majority of high school and middle school current e-cigarette users reported use of non-tobacco-flavored products (82.9%)[3] and flavored use was favored among both users of closed (87%) and open (76%) ENDS (internal analysis). In particular, across device types, including prefilled pods/cartridges, disposables, tanks, and mod systems, fruit was the most commonly used flavor type among youth, with 66.0% for prefilled pods/cartridges, 82.7% for disposables, 81.7% for tanks, and 78.9% for mod systems among youth reporting using a fruit flavor.[3]

It is also worth noting that the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace, that is, the options, especially flavors, that are available for consumers to choose from. Some evidence for this was observed in the trends both leading up to, and coinciding with, the shifting marketplace following the 2020 Enforcement Priorities Guidance. In particular, the enormous rise in youth ENDS use from 2017-2019 coincided with the ascendance

of JUUL (and copy-cat devices) in the marketplace, suggesting a relationship between the availability of JUUL as an option, and the sudden popularity of pod-based devices.[xiii] Then, as noted earlier, when FDA changed its enforcement policy to prioritize pod-based flavored ENDS, which were most appealing to youth at the time, we subsequently observed a substantial rise in use of disposable flavored ENDS[xiv]--a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users.[4] This trend illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired flavor options, underscoring the fundamental role of flavor in driving appeal.

2.3.1.3. The harms of youth ENDS use: The adolescent brain and risk for addiction

In addition to the high prevalence of youth ENDS use, the data also suggest this use is leading to increases in nicotine dependence.[10] Indeed, responding to concerns related to youth ENDS dependence, at the end of 2018, FDA held a public hearing to discuss the potential role of drug therapies to support e-cigarette cessation.[xv]

In 2019, an estimated 30.4% of middle and high school student ENDS users reported frequent use (i.e., use on ≥20 of the past 30 days).[9] By school type, 34.2% (95% CI, 31.2%-37.3%) of high school student ENDS users and 18.0% (95% CI, 15.2%-21.2%) of middle school student ENDS users reported frequent use.[27] Among current ENDS users, 21.4% of high school users and 8.8% of middle school users reported daily ENDS use.[27] Additionally, in a study that examined changes in ENDS use in youth ages 13-18 over a 12-month period, nicotine dependence (measured using the Penn State Electronic Cigarette Dependence Index (PS-ECDI)[28,29] and salivary cotinine concentrations increased, indicating continued ENDS use and greater nicotine exposure over time.[30]

Youth and young adult brains are more vulnerable to nicotine's effects than the adult brain due to ongoing neural development.[31,32] Adolescence is a developmental period consisting of major neurobiological and psychosocial changes and is characterized by increased reward-seeking and risk-taking behaviors (e.g., experimentation with drugs), coupled with heightened sensitivity to both natural and drug rewards and an immature self-regulatory system that is less able to modulate reward-seeking impulses (e.g., diminished harm avoidance, cognitive control, self-regulation).[33-37] Furthermore, evidence from animal studies suggests that nicotine exposure during adolescence enhances the rewarding and reinforcing effects of nicotine in adulthood [38-41]; and can induce short and long-term deficits in attention, learning, and memory.[42-45]

2.3.1.4. Risk of progression from ENDS to other tobacco products of different health risk

Among youth who use ENDS, there is a risk of progression to other tobacco products of generally greater health risk. A 2017 systematic review and meta-analysis that summarized nine prospective cohort studies found significantly higher odds of smoking initiation (OR = 3.50, 95% CI: 2.38, 5.16) and past 30-day combusted cigarette use (OR = 4.28, 95% CI: 2.52, 7.27) among youth who had used ENDS at compared to youth who had not used ENDS.[46] Similar associations have been observed in longitudinal studies that have been published since the Soneji et al. review.[42,47-56] The 2018 NASEM report concluded that there is substantial evidence that ENDS use increases risk of ever using combusted tobacco cigarettes among youth and young adults.[57] The transition from non-cigarette

[xiii] This is borne out by the data from 2019 NYTS, in which 59.1% of high school ENDS users reported use of this one brand. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. Jama. 2019;322(21):2095-2103.

[xiv] In July 2020, FDA issued Warning letters to three companies for illegally marketing disposable e-cigarettes and for marketing unauthorized modified risk tobacco products.

[xv] On December 5, 2018, FDA hosted a public hearing on "Eliminating Youth Electronic Cigarette and Other Product Use: The Role of Drug Therapies."

product use to combusted cigarette use has been observed for other non-cigarette products, such as cigars, as well.[58] Although it is challenging to empirically separate causality from shared risk factors among youth combusted cigarette and ENDS users, some studies have found an association between ENDS and subsequent combusted cigarette use while controlling for similar risk profiles.[54]

The precise relationship between youth ENDS use and youth smoking remains undetermined. On the one hand, the prevalence of combusted cigarette smoking in youth has continued to decline,[9,59,60] suggesting that youth use of ENDS has not significantly slowed or impeded that positive public health trajectory. On the other hand, there is a growing body of evidence showing a link between ENDS use and subsequent smoking among youth that raises significant concerns. This evidence also increases concern that over time—and particularly if youth ENDS use were to return to the rates seen in 2019 or worsen--the trend of declining cigarette smoking could slow or even reverse.

2.3.1.5. Other health risks associated with ENDS use

In addition to the risk of tobacco initiation and progression among youth, there is epidemiologic evidence from the cross-sectional[xvi] Behavioral Risk Factor Survey system (BRFSS) suggesting positive associations between ENDS use among those who never smoked and some health outcomes. Two studies found associations between ENDS use and self-reported history of asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease with increased ENDS use (i.e., daily use) relating to increased odds of disease.[61,62] Another found an association between ENDS use and respiratory symptoms in younger adults (ages 18-34) but not in older adults.[63] ENDS use has also resulted in acute harm to individuals through battery explosion-related burns and e-liquid nicotine poisoning.[64-66] Ultimately, as this is still a relatively novel product category, much remains unknown about other potential long-term health risks.

2.3.1.6. Conclusion

The exponential growth in youth ENDS use observed from 2017 to 2019, and the enduring prevalence of youth ENDS use in the U.S. is alarming. Despite a reduction in youth use of ENDS from 2019 to 2020, there were still 3.6 million youth ENDS users in 2020 and the majority used a flavored ENDS product. Youth users are more likely to use flavored ENDS than adult ENDS users. Flavors are associated with ENDS initiation and progression among youth. The full extent of the harms of ENDS use are not yet known, but evidence to date suggests they include permanent effects of nicotine on the developing adolescent brain and the risk of nicotine addiction. Studies indicate an additive effect of e-liquid flavorings on the rewarding and reinforcing effects of nicotine containing e-liquids. Studies also demonstrate that e-liquid flavors affect nicotine exposure. Among youth who use ENDS, there is a risk of progression to other tobacco products with greater health risks including combustible cigarettes. Finally, though long-term health risks are not fully understood, studies suggest an association between never-smoking ENDS users and respiratory and cardiovascular health effects. This evidence demonstrates that flavored ENDS pose a significant risk to youth.

2.3.2. Balancing Known Risks to Youth with a Potential Benefit to Adults

Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be overcome by a sufficient benefit to adult users, and as the

[xvi] Cross-sectional surveys examine these relationships at a single point in time, and as a result, do not establish causality.

known risks increase, so too does the burden of demonstrating a substantial enough benefit. In the case of a new flavored ENDS product, the risk of youth initiation and use is substantial, given the clearly documented evidence described above. In order for marketing of a new flavored ENDS product to be found APPH, an applicant would have to show that the significant risk to youth could be overcome by likely benefits substantial enough such that the net impact to public health would be positive, taking into account all relevant evidence and circumstances, including whether there are effective limitations on youth access.

2.3.2.1. Potential benefit of new flavored ENDS

Current scientific literature demonstrates that ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than combustible cigarettes, and biomarker studies demonstrate significantly lower exposure to HPHCs among current exclusive ENDS users than current smokers.[57] However, whether this is true for any particular new ENDS product, and the implications for health risks from a particular product, are considered on a case-by-case basis during the course of FDA's scientific review of a PMTA.

FDA also considers the potential that current cigarette smokers may experience a reduction in health risks if they switch completely to an ENDS, or if they use both products but substantially reduce their cigarette smoking. For a flavored ENDS product, assuming that the evaluation of the product shows the likelihood for lower HPHC exposure, then to demonstrate the likely individual and population benefit, applicants must demonstrate that current smokers are likely to start using the new ENDS product exclusively or predominantly (e.g., dual use with a significant smoking reduction).[64]

2.3.2.2. Behavioral evidence appropriate to demonstrate the potential benefit to smokers

FDA's PMTA review includes an evaluation of any potential benefits of the product for the likely users, such as a possible reduction in health risks. In general, as FDA stated in its guidance for PMTAs for ENDS,[xvii] an assessment of how a new product may be used by current smokers can be derived from a variety of sources. FDA may consider direct behavioral evidence on the specific products under review or indirect evidence derived from studies of behavioral intentions; pharmacological studies of nicotine delivery, abuse liability, and/or use topography; and bridging from studies based on comparable products. Further, in the case of a flavored ENDS product, to demonstrate that the marketing of the new product is APPH, the magnitude of the likely benefit would have to be substantial enough to overcome the significant risk of youth uptake and use posed by the flavored ENDS product.

Section 910(c)(5) of the FD&C Act provides that determining whether marketing of a new tobacco product is APPH shall, when appropriate, be based on "well-controlled investigations, which may include one or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product." FDA believes well-controlled investigations are "appropriate" for demonstrating that permitting the marketing of specific flavored ENDS would be APPH given the significant risks to youth of flavored ENDS. One type of well-controlled investigation that could effectively demonstrate a potential benefit of a flavored ENDS product would be an RCT. In addition, as CTP has previously described,[xviii] another well-controlled investigation that could serve as an alternative to conducting an RCT to demonstrate adequate benefit is a longitudinal cohort study.

[xvii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2019 Public Meeting on Deemed Tobacco Product Applications

[xviii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2019 Public Meeting on Deemed Tobacco Product Applications

For flavored ENDS, the known and substantial risk to youth in particular is high. Therefore, to show a net population health benefit, FDA has determined that these applications must demonstrate potential benefits to smokers from marketing such products with robust and reliable evidence – including both robust study design and methods and the strength of the study results. In other words, because the potential benefit to adults is gained through its impact on smoking behavior, FDA is reviewing these applications to determine whether they demonstrate that a benefit of a new product is significant enough to overcome the risk to youth. In particular, FDA's review of these applications has considered the degree of benefit to a flavored ENDS product over a tobacco-flavored variety in facilitating smokers completely switching or significantly reducing their smoking, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. Note that applications with this type of information may still not be APPH: applications containing this evidence would still be evaluated to determine that the totality of the evidence supports a marketing authorization. As it relates to the risk to youth, for example, this assessment includes evaluating the appropriateness of the proposed marketing plan.[xix]

We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS products. Our substantive review of PMTAs for ENDS and our completion of numerous scientific reviews over the last 10 months have deepened our understanding of the APPH evaluation with respect to behavior. In these reviews, the expectations for scientific evidence related to potential adult benefit can vary based on demonstrated risk to youth. Although indirect evidence or bridged data from the literature may still be appropriate for many new products, including tobacco-flavored ENDS, robust and direct evidence demonstrating potential benefit has been needed when the known risks are high as with all flavored ENDS products. At the same time, we have learned from experience that, in the absence of strong direct evidence, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth. For instance, applicants who do not conduct their own behavioral studies must rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. To date, that approach has not been sufficient in our evaluation of flavored ENDS PMTAs because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions--the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive.[xx] In fact, the findings are quite mixed and as a result the literature does not establish that flavors differentially promote switching amongst ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due, at least in part, to differences in the products studied. Therefore, given the state of the science on flavored ENDS, and the known risks to youth, FDA has reviewed these applications for any acceptably strong product-specific evidence.

[xix] Limiting youth access and exposure to marketing is a critical aspect of product regulation. It is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal such that the risk for youth initiation would be reduced. However, to date, none of the ENDS PMTAs that FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use. Similarly, we are not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use ENDS. Accordingly, for the sake of efficiency, the evaluation of the marketing plans in applications will not occur at this stage of review, and we have not evaluated any marketing plans submitted with these applications.

[xx] This discrepancy between the literature for youth initiation and adult switching also likely reflects fundamental differences in the two outcomes being assessed—youth initiation and switching among adult smokers—and their determinants. For switching among adult smokers, the behavior change is occurring in the context of nicotine dependence. Thus, the specific product's ability to provide adequate reinforcement and continue to satisfy a smoker's cravings over time, which is a function of the design of the specific product itself, are critical factors in determining likelihood of continued use and the product's ability to promote switching. Whereas for youth initiation, experimentation among naïve or novice users is not driven by these factors.

More specifically, in order to adequately assess whether such an added benefit has been demonstrated, FDA has reviewed these applications for product-specific[xxi] evidence that would enable a comparison between the applications' new flavored products and an appropriate comparator tobacco-flavored product (both ENDS) in terms of their impact on tobacco use behavior among adult smokers. Consistent with section 910(c)(5), evidence generated using either an RCT design or longitudinal cohort study design is mostly likely to demonstrate such a benefit, although other types of evidence could be adequate if sufficiently reliable and robust, and will be evaluated on a case-by-case basis. [xxii]

CTP will consider other types of evidence if it is sufficiently robust and direct to demonstrate the impact of the new ENDS on adult switching or cigarette reduction. Uptake and transition to ENDS use is a behavioral pattern that requires assessment at more than one time point. In addition, the transition from smoking to exclusive ENDS use typically involves a period of dual use. Therefore, evaluating the behavioral outcomes needed to show any benefit of the product requires observing the actual behavior of users over time. With both RCT and cohort study designs, enrolled participants are followed over a period of time, with periodic and repeated measurement of relevant outcomes.

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to recall their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Consumer perception studies (surveys or experiments) typically assess outcomes believed to be precursors to behavior, such as preferences or intentions related to the new products, but are not designed to directly assess actual product use behavior. Moreover, the general scientific literature, though informative for evaluation of some types of products, is not adequate to address this assessment because it does not provide product-specific information. This is because the effectiveness of a product in promoting switching among smokers arises from a combination of its product features—including labeled characteristics like flavor and nicotine concentration—as well as the sensory and subjective experience of use (taste, throat hit, nicotine delivery), and can also be influenced by how the device itself looks and feels to the use.

While RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity; cohort studies enable stronger generalizability because

[xxi] By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

[xxii] Conversely, such longitudinal or product-specific data are not necessarily required to assess experimentation and appeal among youth. The available literature on youth initiation contains valid scientific evidence sufficient to evaluate the risk to youth of ENDS. The literature includes longitudinal cohort studies, such as the PATH study, which have been used to assess uptake of tobacco products, including flavored ENDS, among youth and young adults. These studies have evaluated the impact of flavors on the promotion of established regular use. Additionally, the literature includes large, nationally representative cross-sectional surveys, which are among the best available evidence to understand patterns of youth ENDS use and the key characteristics associated with such use These studies enable observation of youth behavior as it naturally occurs in representative samples of the U.S. population. These data available in the literature provide clear and overwhelming evidence that ENDS are the most widely used products by youth, the majority of youth users use a flavored ENDS, and that youth users are more likely to use flavored ENDS than adult ENDS users. We note that, in assessing the risks to youth from flavored ENDS, RCTs are not possible because it would be unethical to randomize youth never or naive users to try a particular ENDS to examine what impact it would have on initiation, experimentation, or progression to regular use.

conditions are closer to real-world. We are aware of these as trade-offs and generally do not favor one type over the other for addressing this question.

To be informative, a study using one of these two designs would measure the impact of use of the new or appropriate comparator product tobacco-flavored ENDS and flavored products on adult smokers' tobacco use behavior over time[xxiii]; include outcomes related to ENDS use and smoking behavior to assess switching and/or cigarette reduction; and enable comparisons of these outcomes based on flavor type. In some cases, evidence on each individual flavor option may not be feasible; bridging data from one of the applicant's flavors to other flavors of the applicant's in the same flavor category (e.g., "fruit") may be appropriate. Furthermore, consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging.[xxiv] Likewise, if a flavor is tested with one nicotine concentration, it may be feasible for the applicant to bridge the study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging.

Data from one of these studies could support a benefit to adult users if the findings showed that, compared to the new tobacco-flavored product, use of (each) new flavored product is associated with greater likelihood of either of these behavioral outcomes for adult smokers: (1) complete switching from cigarettes to exclusive new product use or (2) significant reduction in cigarettes per day (CPD).

2.3.2.3. Conclusion

Given the known and substantial risk to youth posed by flavored ENDS, FDA has reviewed these applications for the presence of particularly reliable product-specific[xxv] evidence to demonstrate a potential for benefit to adult smokers that could justify that risk. Based on our current understanding, a demonstration with sufficiently reliable and robust evidence that the flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS.

2.4. SCOPE OF REVIEW

The reviews evaluated whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new products on switching or cigarette reduction that could potentially demonstrate the added benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. These reviews included a search of the PMTAs to determine whether the evidence is found anywhere within the PMTAs, and if present, if certain conditions were met (e.g., was the randomized controlled trial conducted using the new products that are the subject of the PMTA). Our review also included a

[xxiii] This could include studies that are long-term (i.e., six months or longer). In FDA's (2019) Guidance to Industry, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems", FDA has previously stated that it did not expect that applicants would need to conduct long-term studies to support an application for ENDS. Because the behavior change of interest (switching or cigarette reduction) occurs over a period of time, it is possible that to observe these outcomes, investigators designing these studies may decide to follow participants over a period of six months or longer. However, it is also possible that studies with a shorter duration would be adequately reliable.

[xxiv] Bridging is discussed in FDA's 2019 Guidance to Industry cited above (fn xxiii).

[xxv] By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

search for other studies that provided product-specific evidence related to the potential benefit to adult users.

3. SCIENTIFIC REVIEW

Reviews were completed by Allison Hoffman and Willa Dong on September 17, 2021.

The reviews determined that, although the PMTAs includes a RCT and longitudinal cohort study, the studies did not include the actual use of the new products or compare tobacco-flavored products to other flavored products. In particular, the data from the RCT did not sufficiently demonstrate the relative effect of the flavored products as compared to a tobacco-flavored product or include outcomes assessing switching or cigarette reduction and the data from the cohort study not sufficiently demonstrate the relative effect of the flavored products as compared to a tobacco-flavored product. Therefore, these are insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

The PMTAs referenced studies including those that that assessed exposure biomarkers and physiological response following (b)(4) use, the effects of (b)(4) on health outcomes such as lung function, and surveys on consumer perceptions and intentions to use (b)(4), but this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it was not clear that the referenced studies included the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time; or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors. Accordingly, this evidence is not adequate and therefore, we did not assess other aspects of the application as part of this scientific review.

4. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order under section 910(c) of the Federal Food, Drug, and Cosmetic Act that a new product may not be introduced or delivered for introduction into interstate commerce (i.e., a marketing denial order) falls within a class of actions that are ordinarily categorically excluded from the preparation of an environmental assessment (EA) or environmental impact statement (EIS). To the best of our knowledge, no extraordinary circumstances exist that would preclude application of this categorical exclusion. FDA concludes that categorical exclusion is warranted and no EA or EIS is required.

5. CONCLUSION AND RECOMMENDATION

FDA has reviewed these applications for evidence demonstrating that the new flavored products will provide an added benefit to adult smokers relative to tobacco-flavored products. Based on our review, we determined that the PMTAs for the applicant's new products, as described in the applications and specified in Appendix A, lack sufficient evidence to demonstrate that permitting the marketing of the new products would be APPH. Thus, a Denial letter should be issued to the applicant. The applicant cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

The following deficiency should be conveyed to the applicant as the key basis for our determination that marketing of the new products is not APPH:

1. All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth. In

light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial (RCT) and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS. Although your PMTA includes a RCT and cohort study, it is unclear if they included the actual use of the new products. Additionally, the RCT and cohort studies did not compare tobacco-flavored products to other flavored products or include outcomes assessing switching or cigarette reduction. In particular, the data from your RCT did not sufficiently demonstrate the relative effect of your flavored products as compared to a tobacco-flavored product or the effects on switching or cigarette reduction and the cohort study did not sufficiently demonstrate the relative effect of your flavored products as compared to a tobacco-flavored product. Therefore, these are insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs referenced studies including those that that assessed exposure biomarkers and physiological response following (b)(4) use, the effects of (b)(4) on health outcomes such as lung function, and surveys on consumer perceptions and intentions to use (b)(4), this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it was not clear that the referenced studies included the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time; or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors. Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

6. APPENDIX

Appendix A. New Products

Common Attributes	
Submission date	September 7, 2020
Receipt date	September 7, 2020
Applicant	(b) (4)
Product manufacturer	(b) (4)
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

7. REFERENCES

1. U.S. Department of Health and Human Services. *E-cigarette Use Among Youth and Young Adults. A Report of the Surgeon General.* Atlanta, GA: U.S. Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2016.
2. U.S. Food and Drug Administration. *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised). Guidance for Industry.* Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products;April 2020.
3. Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. E-cigarette Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(37):1310-1312.
4. Wang TW, Gentzke AS, Neff LJ, et al. Disposable E-Cigarette Use among U.S. Youth — An Emerging Public Health Challenge. *New England Journal of Medicine.* 2021;384(16):1573-1576.
5. U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General.* Atlanta, GA: U.S. Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2012.
6. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2014.
7. Apelberg BJ, Corey CG, Hoffman AC, et al. Symptoms of tobacco dependence among middle and high school tobacco users: results from the 2012 National Youth Tobacco Survey. *Am J Prev Med.* 2014;47(2 Suppl 1):S4-14.
8. Gentzke AS, Wang TW, Jamal A, et al. Tobacco Product Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(50):1881-1888.
9. Wang TW, Gentzke AS, Creamer MR, et al. Tobacco Product Use and Associated Factors Among Middle and High School Students - United States, 2019. *MMWR Surveill Summ.* 2019;68(12):1-22.
10. Cullen KA, Liu ST, Bernat JK, et al. Flavored Tobacco Product Use Among Middle and High School Students - United States, 2014-2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(39):839-844.
11. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'Connor RJ. Use of Flavored E-Cigarettes and the Type of E-Cigarette Devices Used among Adults and Youth in the US-Results from Wave 3 of the Population Assessment of Tobacco and Health Study (2015-2016). *Int J Environ Res Public Health.* 2019;16(16).
12. Villanti AC, Johnson AL, Glasser AM, et al. Association of Flavored Tobacco Use With Tobacco Initiation and Subsequent Use Among US Youth and Adults, 2013-2015. *JAMA Netw Open.* 2019;2(10):e1913804.
13. Rose SW, Johnson AL, Glasser AM, et al. Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2014-2015. *Tob Control.* 2020;29(4):432-446.
14. Rostron BL, Cheng YC, Gardner LD, Ambrose BK. Prevalence and Reasons for Use of Flavored Cigars and ENDS among US Youth and Adults: Estimates from Wave 4 of the PATH Study, 2016-2017. *Am J Health Behav.* 2020;44(1):76-81.
15. Ambrose BK, Day HR, Rostron B, et al. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. *JAMA.* 2015;314(17):1871-1873.

16. Tsai J, Walton K, Coleman BN, et al. Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2018;67(6):196-200.
17. Audrain-McGovern J, Strasser AA, Wileyto EP. The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug Alcohol Depend.* 2016;166:263-267.
18. St Helen G, Dempsey DA, Havel CM, Jacob P, 3rd, Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug Alcohol Depend.* 2017;178:391-398.
19. Morean ME, Butler ER, Bold KW, et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PLoS One.* 2018;13(1):e0189015.
20. Leventhal AM, Goldenson NI, Cho J, Kirkpatrick MG, McConnell RS, Stone MD, Pang RD, Audrain-McGovern J, Barrington-Trimis JL. Flavored E-cigarette Use and Progression of Vaping in Adolescents. *Pediatrics.* 2019 Nov;144(5):e20190789.
21. Audrain-McGovern J, Rodriguez D, Pianin S, Alexander E. Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents. *Drug Alcohol Depend.* 2019;202:149-155.
22. Villanti AC, Johnson AL, Halenar M, et al. Menthol and mint cigarettes and cigars: Initiation and progression in youth, young adults and adults in Waves 1 - 4 of the PATH Study, 2013 - 2017. *Nicotine Tob Res.* 2020.
23. Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: tobacco marketing strategies. *Health Aff (Millwood).* 2005;24(6):1601-1610.
24. Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tobacco Control.* 2016;25(Suppl 2):ii62.
25. Camenga DR, Morean M, Kong G, Krishnan-Sarin S, Simon P, Bold K. Appeal and Use of Customizable E-cigarette Product Features in Adolescents. *Tob Regul Sci.* 2018;4(2):51-60.
26. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Prev Med Rep.* 2017;5:33-40.
27. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. *Jama.* 2019;322(21):2095-2103.
28. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine Tob Res.* 2015;17(2):186-192.
29. Yingst J, Foulds J, Veldheer S, et al. Measurement of Electronic Cigarette Frequency of Use Among Smokers Participating in a Randomized Controlled Trial. *Nicotine Tob Res.* 2020;22(5):699-704.
30. Vogel EA, Prochaska JJ, Ramo DE, Andres J, Rubinstein ML. Adolescents' E-Cigarette Use: Increases in Frequency, Dependence, and Nicotine Exposure Over 12 Months. *J Adolesc Health.* 2019;64(6):770-775.
31. Slotkin TA. Nicotine and the adolescent brain: insights from an animal model. *Neurotoxicol Teratol.* 2002;24(3):369-384.
32. Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *J Physiol.* 2015;593(16):3397-3412.
33. Bava S, Tapert SF. Adolescent brain development and the risk for alcohol and other drug problems. *Neuropsychol Rev.* 2010;20(4):398-413.
34. Bernheim A, Halfon O, Boutrel B. Controversies about the enhanced vulnerability of the adolescent brain to develop addiction. *Front Pharmacol.* 2013;4:118.
35. Casey BJ, Jones RM. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. *J Am Acad Child Adolesc Psychiatry.* 2010;49(12):1189-1201; quiz 1285.
36. Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain Cogn.* 2010;72(1):114-123.

37. Shulman EP, Smith AR, Silva K, et al. The dual systems model: Review, reappraisal, and reaffirmation. *Dev Cogn Neurosci.* 2016;17:103-117.
38. Kota D, Sanjakdar S, Marks MJ, Khabour O, Alzoubi K, Damaj MI. Exploring behavioral and molecular mechanisms of nicotine reward in adolescent mice. *Biochem Pharmacol.* 2011;82(8):1008-1014.
39. Shram MJ, Lê AD. Adolescent male Wistar rats are more responsive than adult rats to the conditioned rewarding effects of intravenously administered nicotine in the place conditioning procedure. *Behav Brain Res.* 2010;206(2):240-244.
40. Natividad LA, Torres OV, Friedman TC, O'Dell LE. Adolescence is a period of development characterized by short- and long-term vulnerability to the rewarding effects of nicotine and reduced sensitivity to the anorectic effects of this drug. *Behav Brain Res.* 2013;257:275-285.
41. de la Peña JB, Ahsan HM, Tampus R, et al. Cigarette smoke exposure during adolescence enhances sensitivity to the rewarding effects of nicotine in adulthood, even after a long period of abstinence. *Neuropharmacology.* 2015;99:9-14.
42. Conner M, Grogan S, Simms-Ellis R, et al. Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study. *Tob Control.* 2017;27(4):365-372.
43. Holliday ED, Gould TJ. Chronic Nicotine Treatment During Adolescence Attenuates the Effects of Acute Nicotine in Adult Contextual Fear Learning. *Nicotine Tob Res.* 2017;19(1):87-93.
44. Counotte DS, Spijker S, Van de Burgwal LH, et al. Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. *Neuropsychopharmacology.* 2009;34(2):299-306.
45. Fountain SB, Rowan JD, Kelley BM, Willey AR, Nolley EP. Adolescent exposure to nicotine impairs adult serial pattern learning in rats. *Exp Brain Res.* 2008;187(4):651-656.
46. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr.* 2017;171(8):788-797.
47. Aleyan S, Cole A, Qian W, Leatherdale ST. Risky business: a longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users in Canada. *BMJ Open.* 2018;8(5):e021080.
48. Berry KM, Fetterman JL, Benjamin EJ, et al. Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths. *JAMA Netw Open.* 2019;2(2):e187794.
49. Hammond D, Reid JL, Cole AG, Leatherdale ST. Electronic cigarette use and smoking initiation among youth: a longitudinal cohort study. *Cmaj.* 2017;189(43):E1328-e1336.
50. Loukas A, Marti CN, Cooper M, Pasch KE, Perry CL. Exclusive e-cigarette use predicts cigarette initiation among college students. *Addict Behav.* 2018;76:343-347.
51. Treur JL, Rozema AD, Mathijssen JJP, van Oers H, Vink JM. E-cigarette and waterpipe use in two adolescent cohorts: cross-sectional and longitudinal associations with conventional cigarette smoking. *Eur J Epidemiol.* 2018;33(3):323-334.
52. Kintz N, Liu M, Chou CP, et al. Risk factors associated with subsequent initiation of cigarettes and e-cigarettes in adolescence: A structural equation modeling approach. *Drug Alcohol Depend.* 2020;207:107676.
53. Lozano P, Barrientos-Gutierrez I, Arillo-Santillan E, et al. A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents. *Drug Alcohol Depend.* 2017;180:427-430.
54. Stanton CA, Bansal-Travers M, Johnson AL, et al. Longitudinal e-Cigarette and Cigarette Use Among US Youth in the PATH Study (2013-2015). *J Natl Cancer Inst.* 2019;111(10):1088-1096.
55. Best C, Haseen F, Currie D, et al. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tob Control.* 2017;27(4):373-378.
56. Bold KW, Kong G, Camenga DR, et al. Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics.* 2018;141(1).

57. National Academies of Sciences Engineering Medicine. Public Health Consequences of E-Cigarettes. In. Washington, DC: National Academies Press; 2018.
58. Edwards KC, Sharma E, Halenar MJ, et al. Longitudinal pathways of exclusive and polytobacco cigar use among youth, young adults and adults in the USA: findings from the PATH Study Waves 1-3 (2013-2016). *Tob Control.* 2020;29(Suppl 3):s163-s169.
59. Gentzke AS, Creamer M, Cullen KA, et al. Vital Signs: Tobacco Product Use Among Middle and High School Students - United States, 2011-2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(6):157-164.
60. Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. Tobacco Product Use Among Middle and High School Students - United States, 2011-2017. *MMWR Morb Mortal Wkly Rep.* 2018;67(22):629-633.
61. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association Between E-Cigarette Use and Chronic Obstructive Pulmonary Disease by Smoking Status: Behavioral Risk Factor Surveillance System 2016 and 2017. *Am J Prev Med.* 2020;58(3):336-342.
62. Osei AD, Mirbolouk M, Orimoloye OA, et al. The association between e-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS) 2016 & 2017. *BMC Pulm Med.* 2019;19(1):180.
63. Giovanni SP, Keller TL, Bryant AD, Weiss NS, Littman AJ. Electronic Cigarette Use and Chronic Respiratory Symptoms among U.S. Adults. *Am J Respir Crit Care Med.* 2020;201(9):1157-1160.
64. Chang JT, Anic GM, Rostron BL, Tanwar M, Chang CM. Cigarette Smoking Reduction and Health Risks: A Systematic Review and Meta-analysis. *Nicotine Tob Res.* 2021;23(4):635-642.
65. Vyncke T, De Wolf E, Hoeksema H, et al. Injuries associated with electronic nicotine delivery systems: A systematic review. *J Trauma Acute Care Surg.* 2020;89(4):783-791.
66. Rossheim ME, Livingston MD, Soule EK, Zeraye HA, Thombs DL. Electronic cigarette explosion and burn injuries, US Emergency Departments 2015–2017. *Tobacco Control.* 2019;28(4):472.

Drug Use Trends Among U.S. Teens

Monitoring the Future 2020 Survey Results

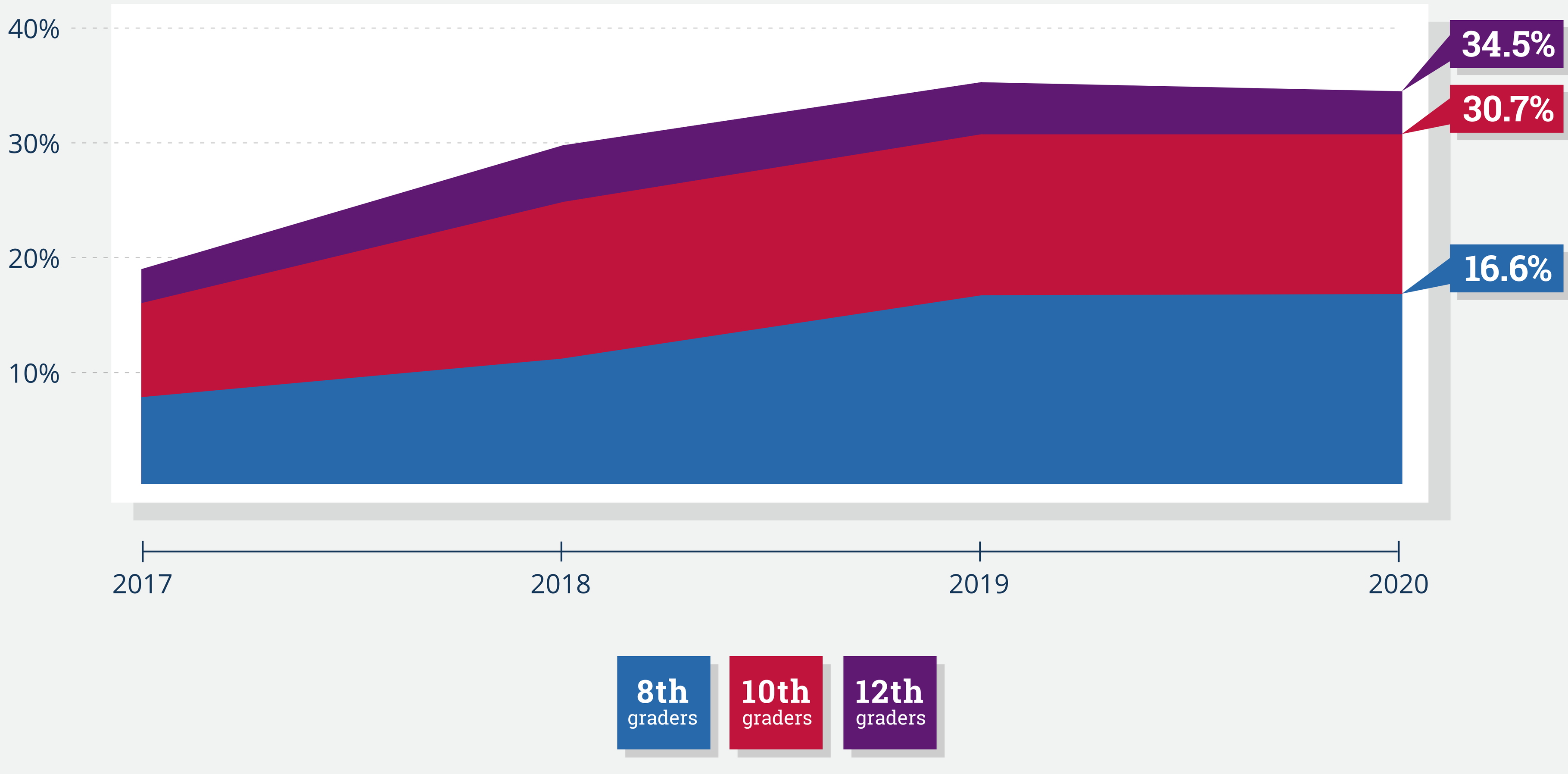
Monitoring the Future is an annual drug use survey of eighth, 10th and 12th grade students conducted by researchers at the University of Michigan, Ann Arbor, and funded by the National Institute on Drug Abuse.

[More than 11,800 students from 112 schools across the United States participated in the 2020 survey.*]

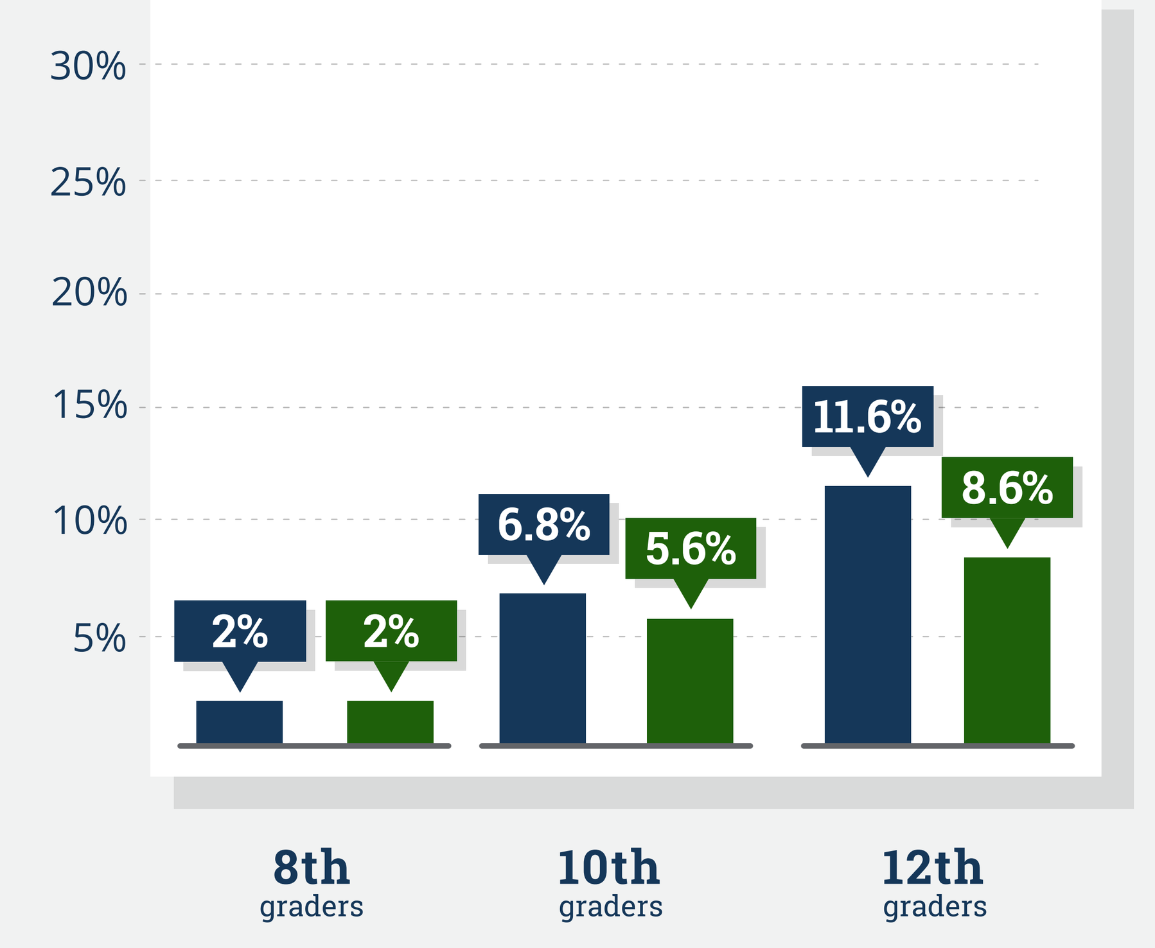
*Data collection stopped prematurely due to the COVID-19 pandemic. Completed surveys represent about 25% of the size of a typical year's data collection. However, results were gathered from a broad geographic range and were statistically weighted to be nationally representative.

Surge of Nicotine Vaping Levels Off, but Remains High

Past-Year Nicotine Vaping Held Steady



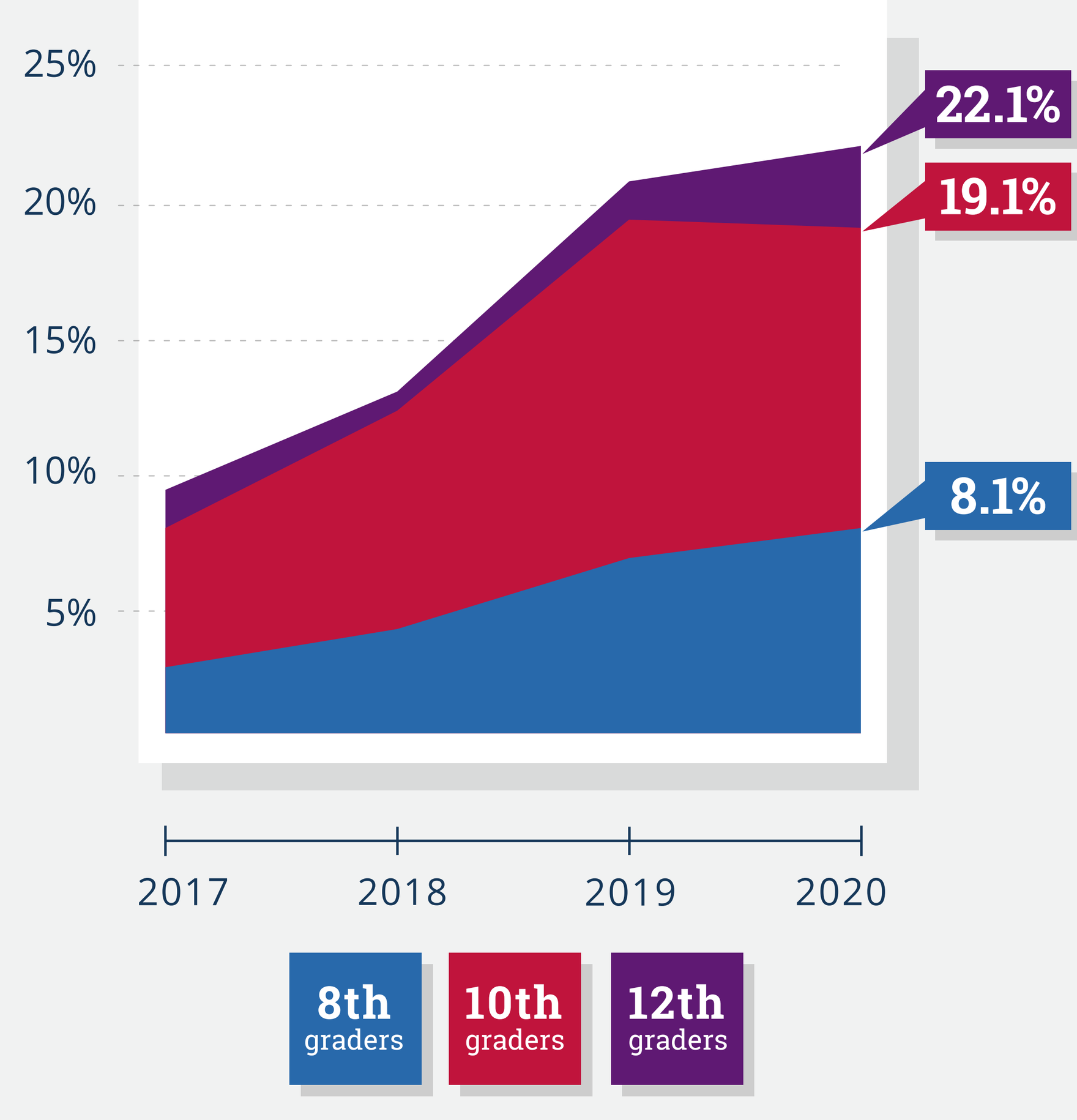
Daily or Near-Daily Nicotine Vaping



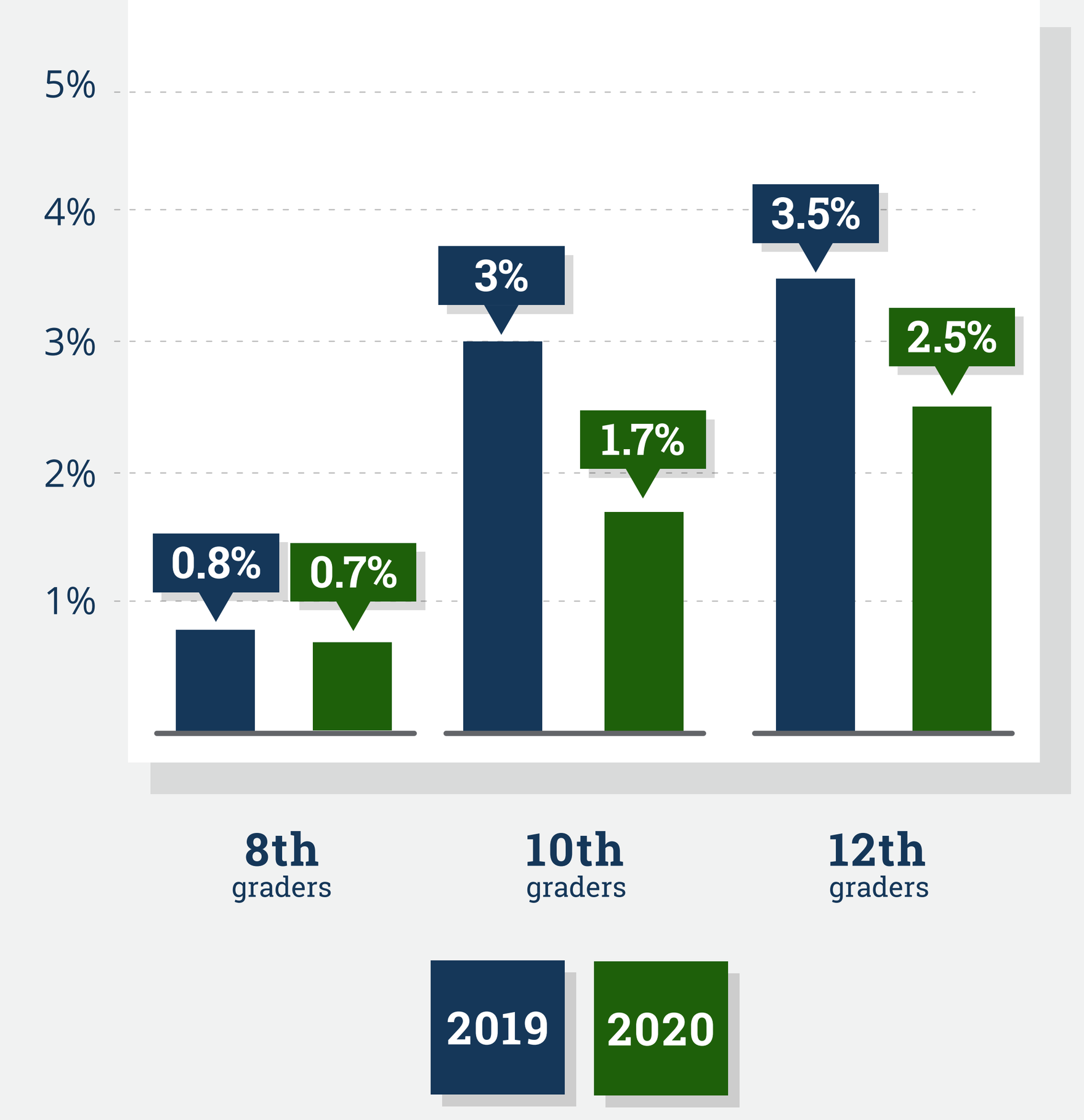
Past-Year JUUL Use Dropped Significantly Among Older Grades

Past-Year Marijuana Vaping Holds Steady

Past-Year Marijuana Vaping

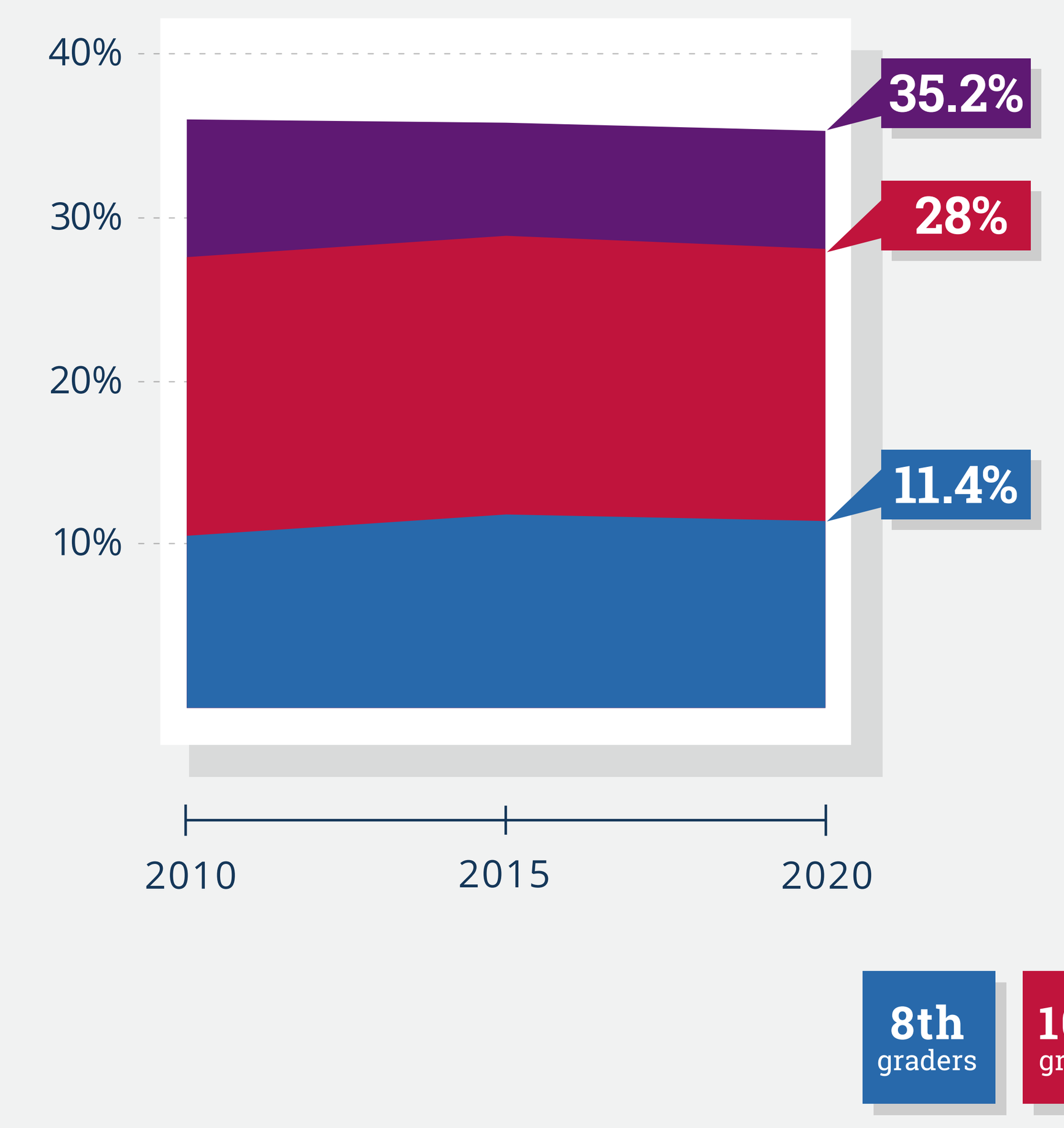


Daily or Near-Daily Marijuana Vaping Decreases Significantly Among 10th Graders

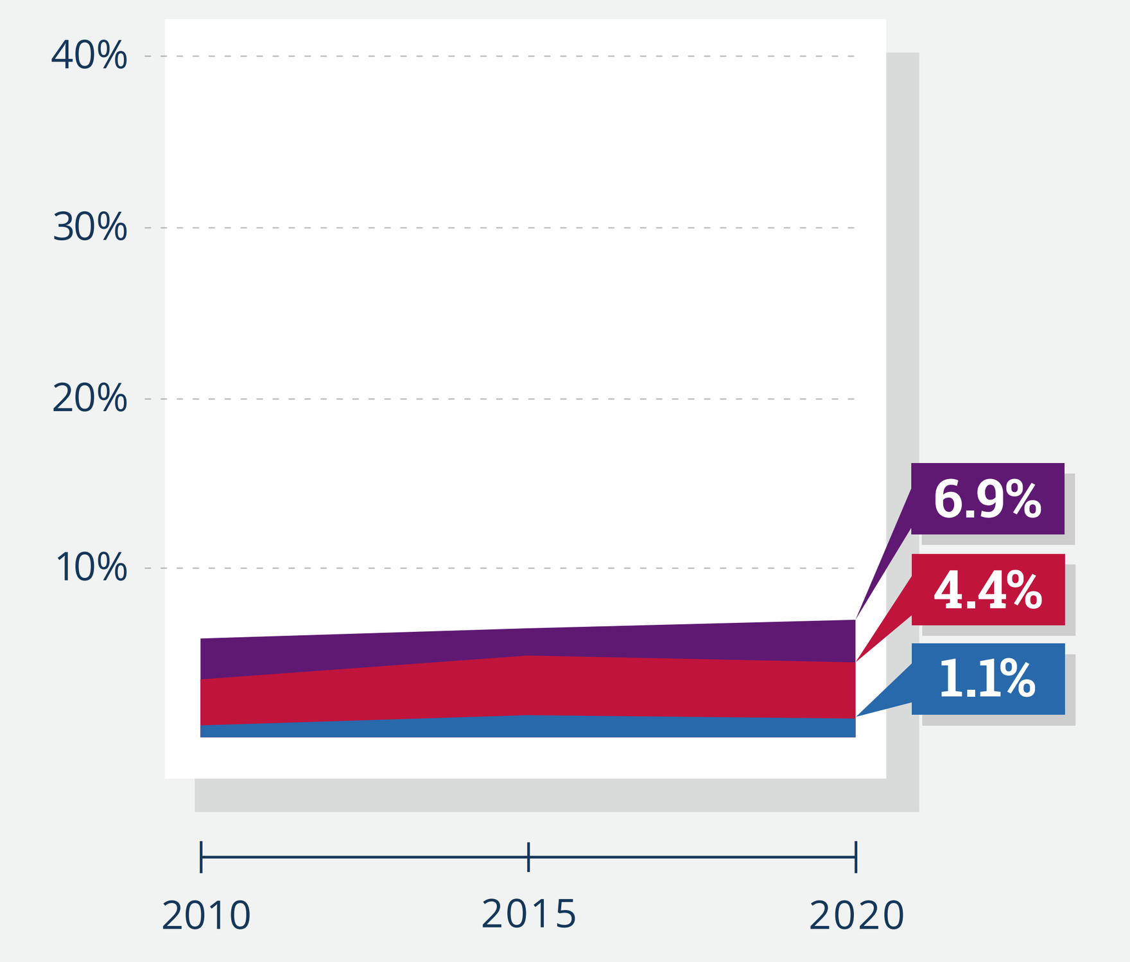


Marijuana Use Remains Steady

Past-Year Marijuana Use



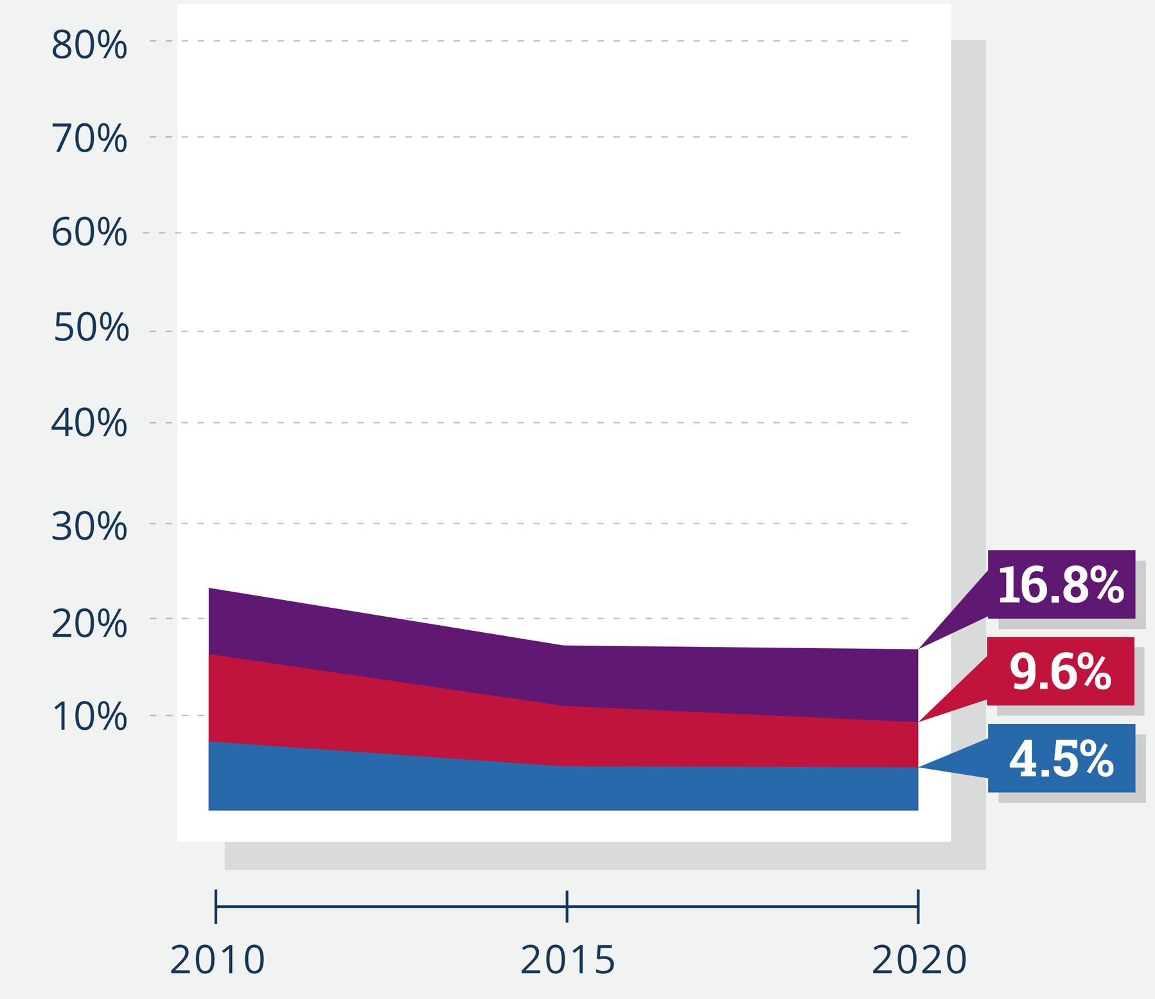
Daily Marijuana Use



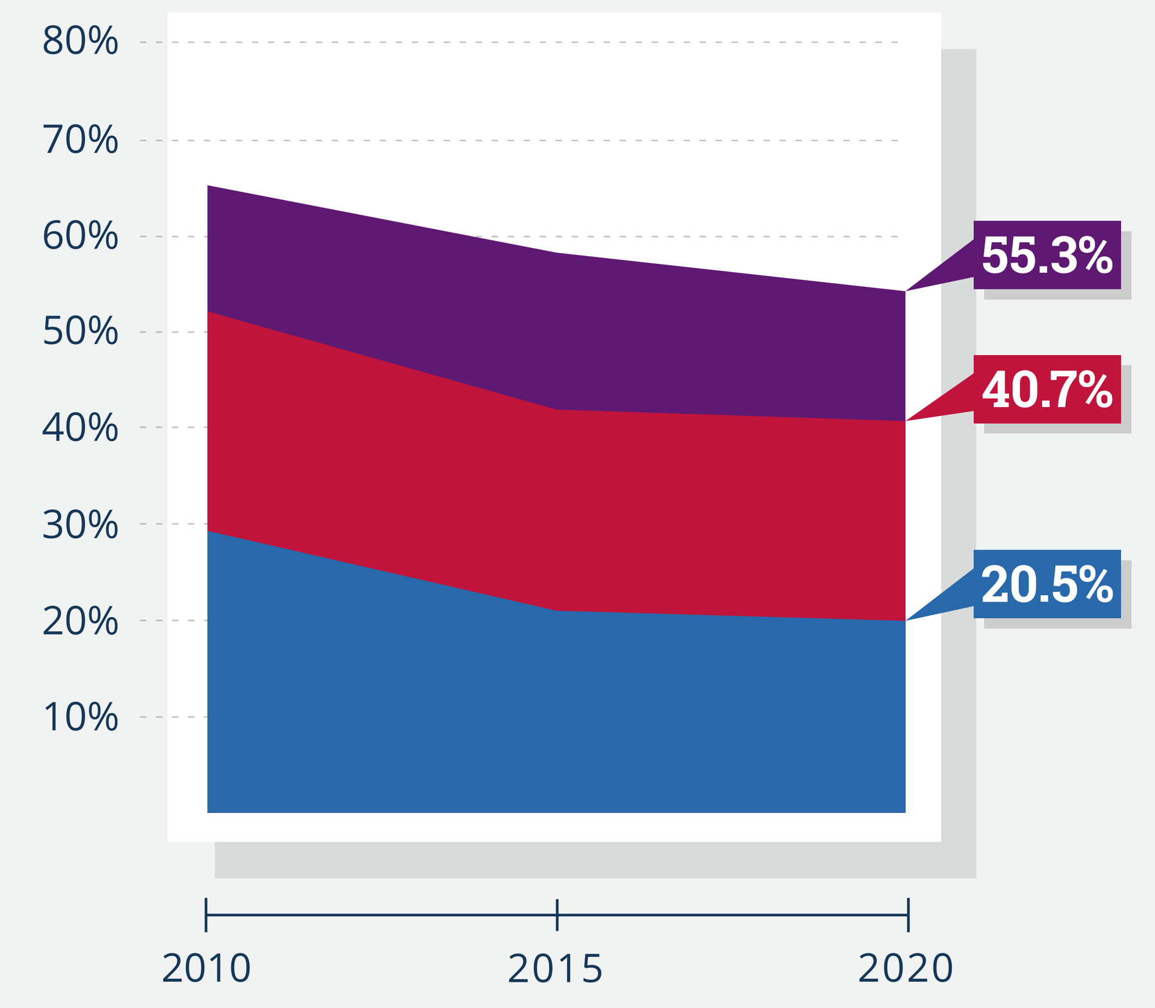
Gradual Decline in Alcohol Use Slows

Long-term trend of decreasing alcohol use among all grades levels off.

Binge Drinking*



Past-Year Alcohol Use

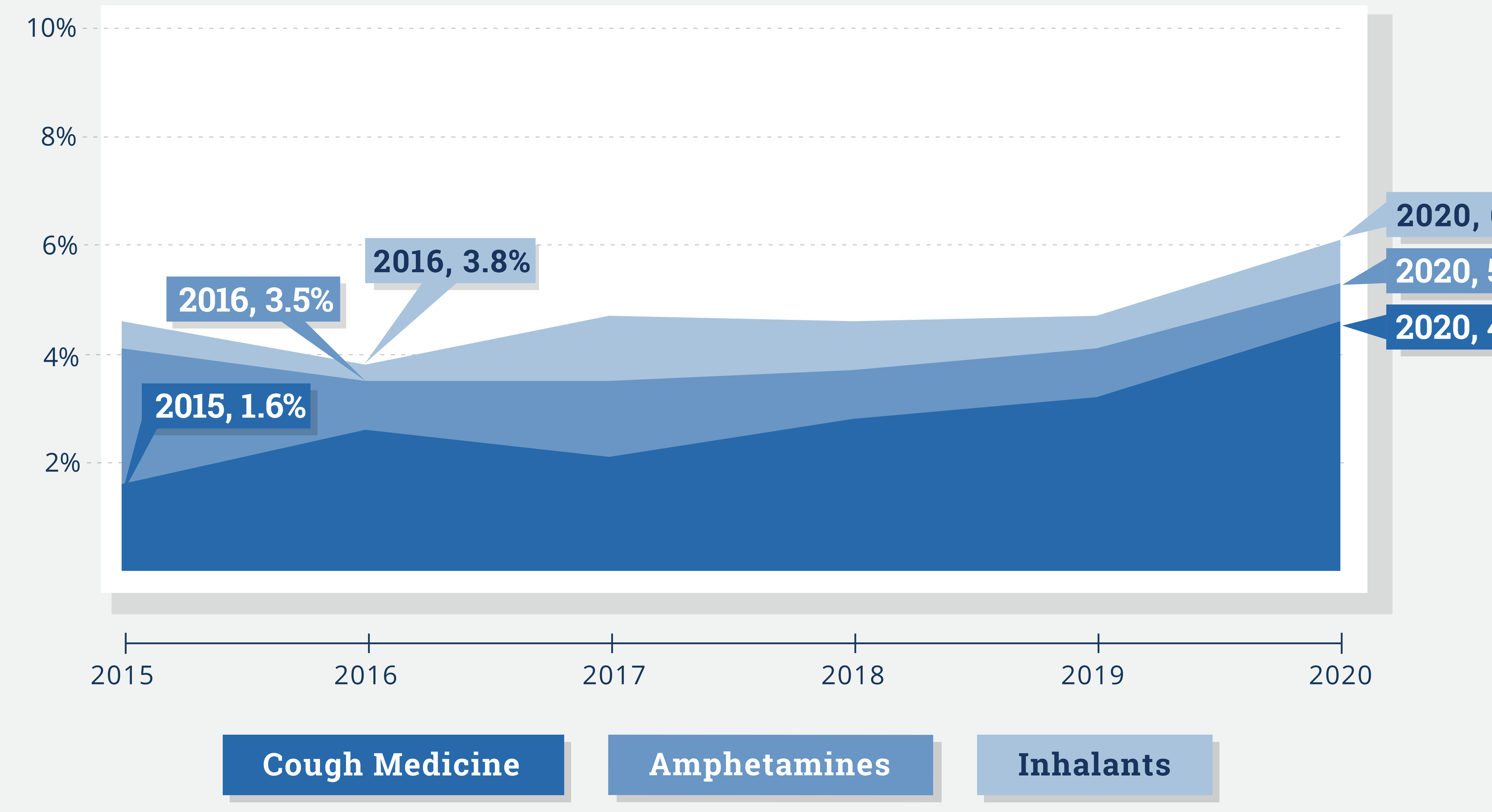


*5 or more drinks in a row in the past two weeks

8th graders | 10th graders | 12th graders

Amphetamine, Inhalant & Cough Medicine Misuse Trending Upward Among Eighth Graders

Past-Year Substance Misuse Among Eighth Graders

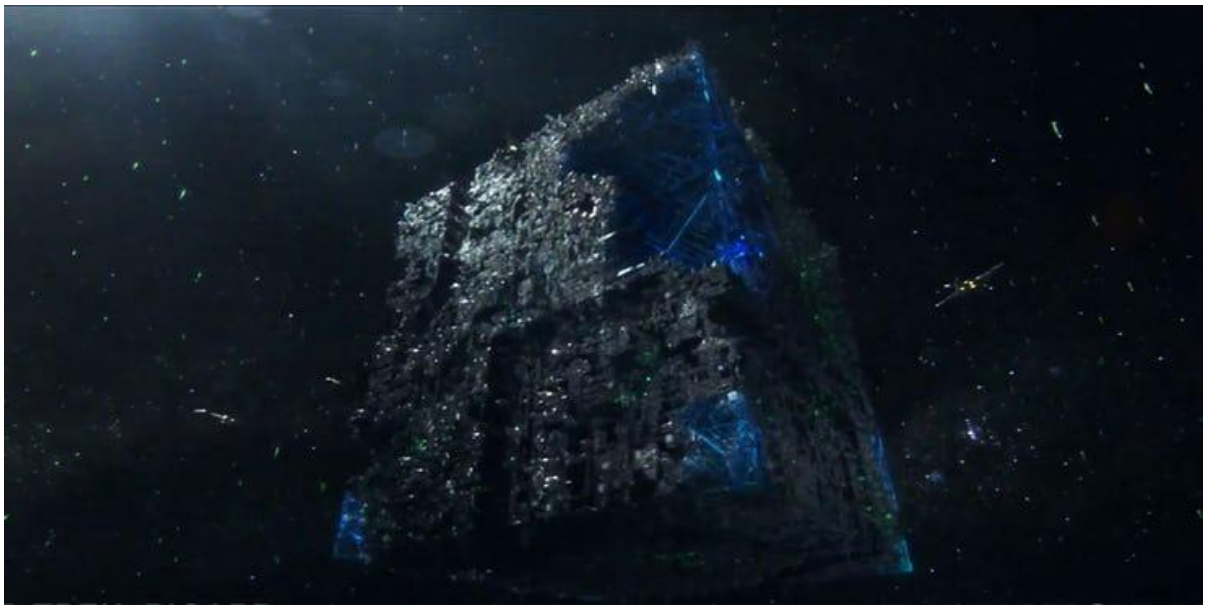


STAR TREK

RESISTANCE IS FUTILE: A HISTORY OF STAR TREK'S THE BORG

by Eric Diaz
Aug 13 2019 • 9:00 AM

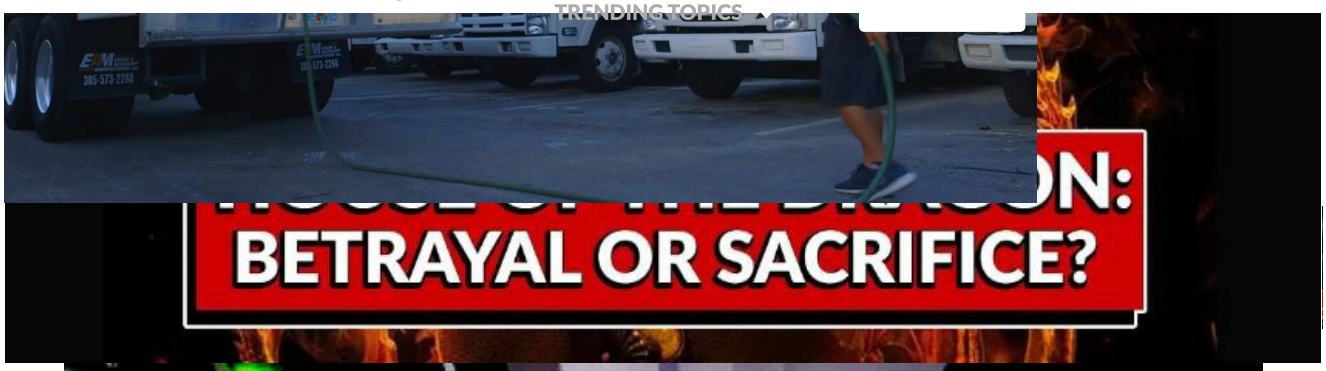
Although we still have to wait several months for *Star Trek: Picard* to drop its first episode, the recently released SDCC trailer gave us some tantalizing teases about what to expect. And it looks like we can expect the Federation's biggest menace, the Borg, to make their return. Not only are two of the most famous Borg characters part of the series (Seven of Nine and Hugh), but we also see a Borg cube. But just who and what are the Borg, and why are they such an ever present threat to the life of one Jean-Luc Picard?



CBS

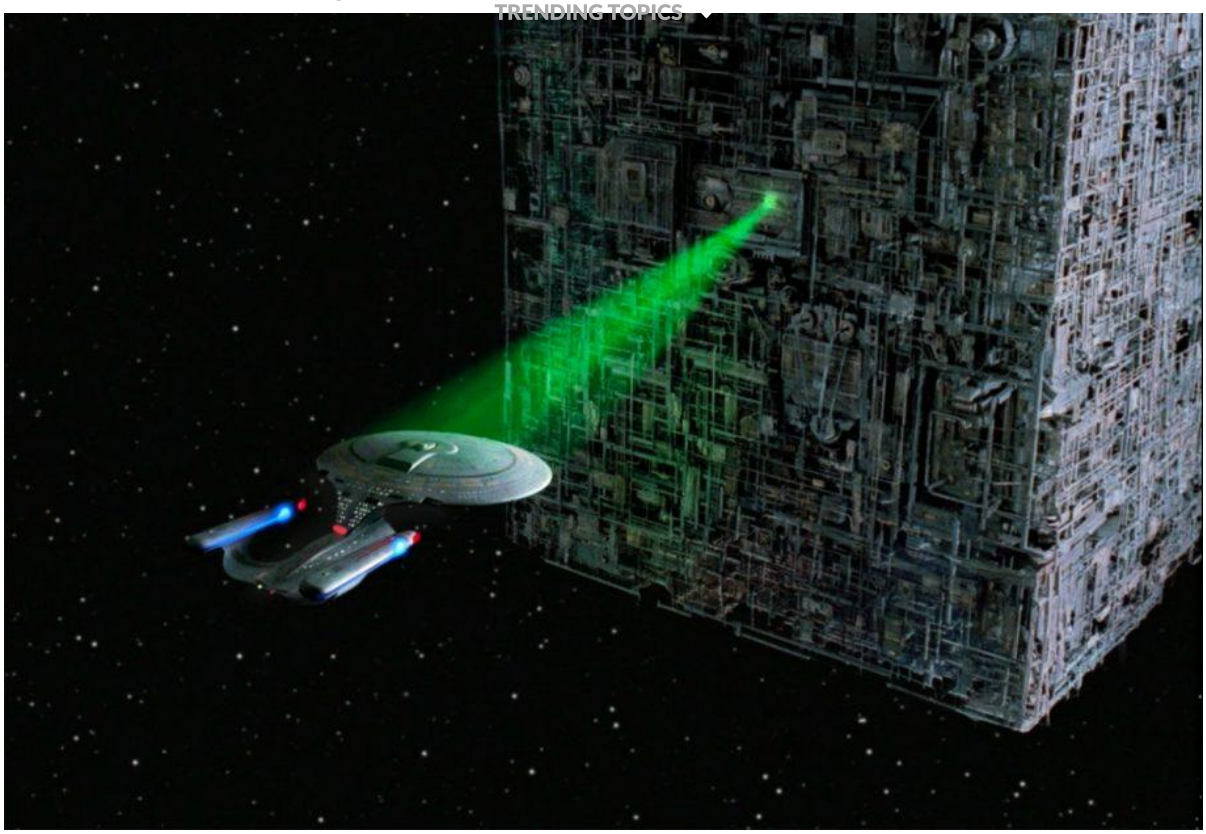
Resistance is Futile

After hints of a technologically superior race were dropped in *The Next Generation's* first season finale "The Neutral Zone," the Borg made their first actual appearance in the second season *TNG* episode "Q Who." After season one failed to make any new alien races



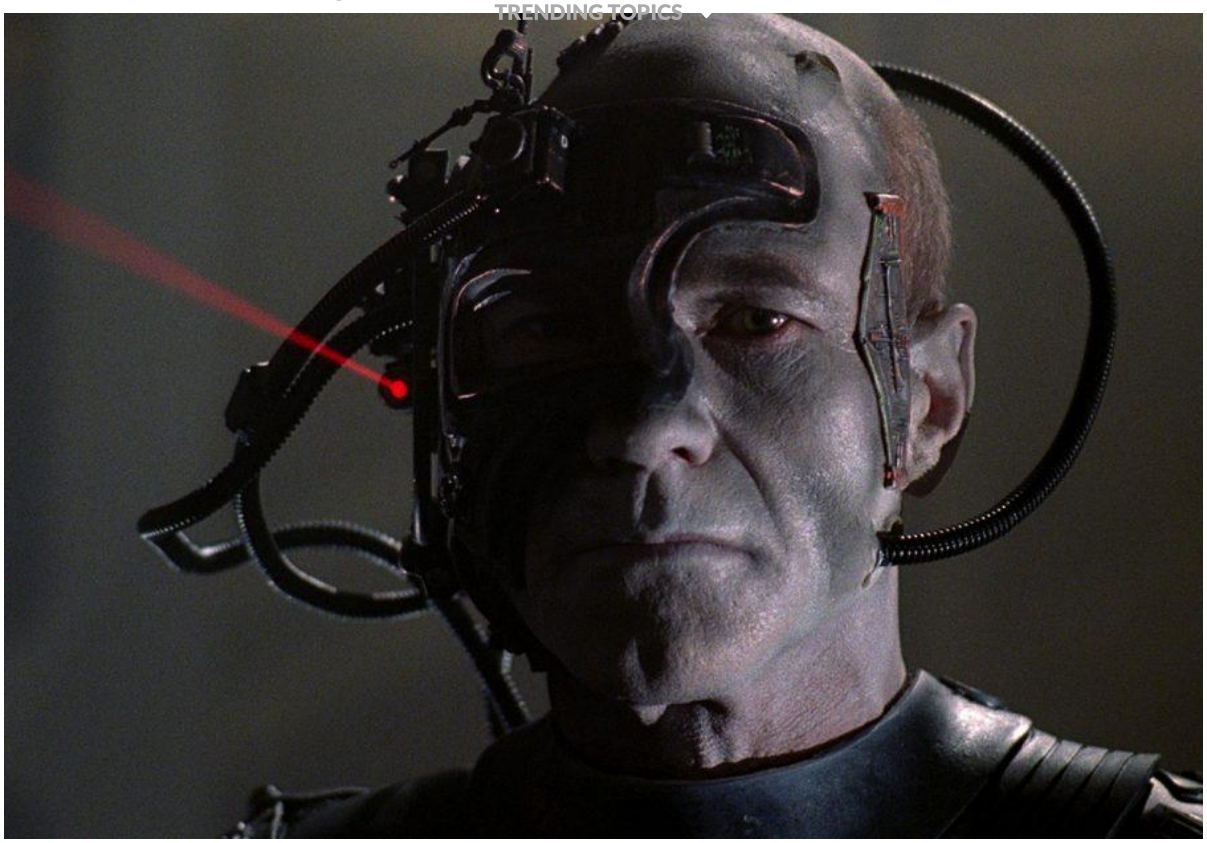
CBS

As a way of testing Picard's ability to deal with unknowns, the omnipotent Q sent the *Enterprise* millions of light years away to an area of space unexplored by the Federation. There, the Borg had a presence, and almost instantly tried to assimilate the *Enterprise*. Far



CBS

Over a year later in the TNG season 3 finale "The Best of Both Worlds," the Borg made their presence known in Federation space when they assimilated an entire human colony. In the cliffhanger finale episode, the Borg assimilated Jean-Luc Picard and made him into a sort of representative of their conquest of the Federation. Unlike most Borg, he had a name: Locutus. The majority of Starfleet mobilized to defend themselves from the Borg. In total, the Borg wiped out 39 ships in the battle of Wolf 359. Among the destroyed vessels was the ship of future *Deep Space Nine* commander Benjamin Sisko.

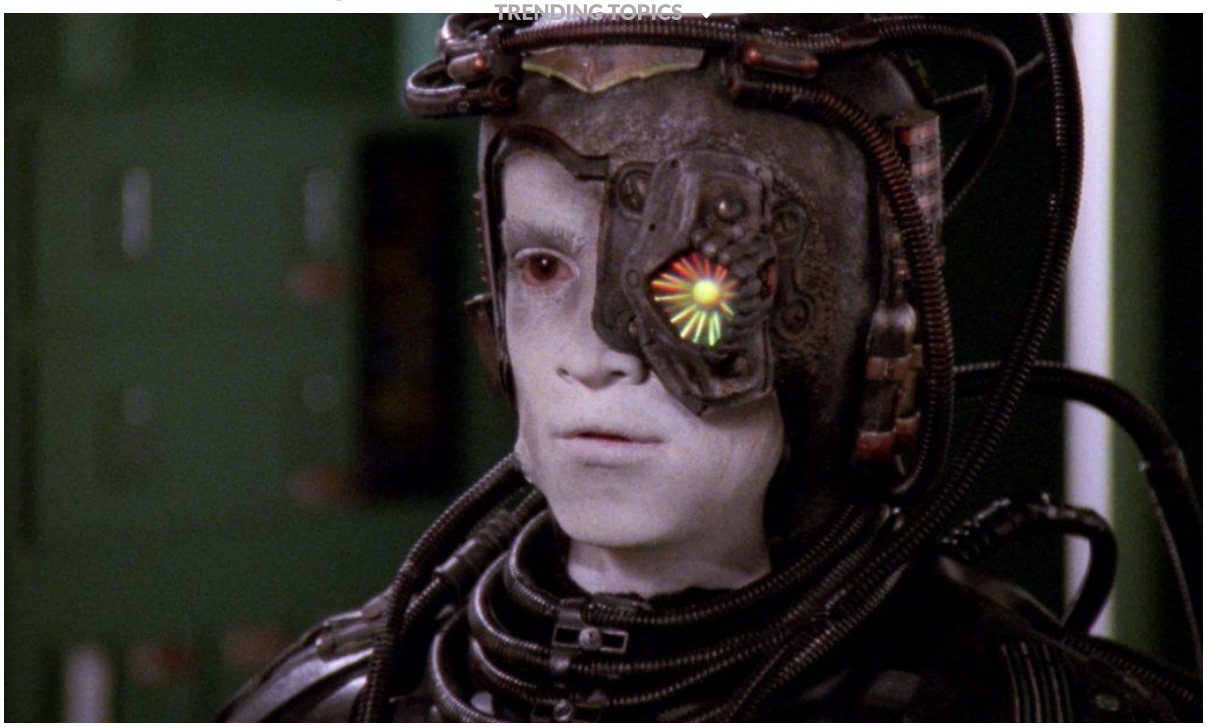


CBS

Luckily for the Alpha Quadrant, Commander Data was able to retrieve Picard from the clutches of the Borg and un-assimilate him in "The Best of Both Worlds Part II." Using the knowledge of their inner workings, the *Enterprise* was able to destroy the Borg cube. It saved the Federation, but that was all just the beginning. In many ways, the worst was yet to come.

The Borg 2.0

In the season 5 episode of *TNG* titled "I, Borg," the *Enterprise* encountered a downed Borg scout vessel. The ship had only one survivor, a teenage boy named "Third of Five." His name was derived from the fact that there were five drones in his unit all together. In an act of mercy, Doctor Crusher saved the injured Borg. Under the *Enterprise* crew's care, the drone began to exhibit a personality, and started to become an individual. He was given a name by the crew, who called him "Hugh." And he befriended Lt. Geordi La Forge.



Picard initially dismissed the notion of an individualized Borg, harboring intense resentment for how they kidnapped and used him years before. He intended to plant a disabling virus within Hugh, hoping that when they returned him to the collective, the virus would contaminate the entire collective and destroy them. Essentially, they were committing genocide. Despite their destructive capability, Picard couldn't bring himself to perform such an act. But the hopes were that when they returned Hugh to the collective, his newly found sense of individuality spread. It worked. But the *Enterprise* crew would come to wish it hadn't.

Several Borg ended up becoming "infected" with Hugh's newfound sense of individuality, and became a sort of splinter race of Borg. Being too individualistic for the collective, but still too Borg for the universe at large, these newly emotional beings became a lost tribe in space. They fell under the sway of Data's identical twin android brother Lore, who served as a sort of cult leader for them. Although they were ultimately released from Lore's thrall in the two part episode "Descent," not much has been heard from this particular group of Borg since.

Enter: The Borg Queen

But the *Enterprise* crew also went back in time and managed to stop them, allowing history to unfold as it should. It was during the events of this move that we learned that although they were a hive mind, much like insects, there was a queen. The Borg Queen (Alice Krige) retained her personality, and was revealed as the main guiding force behind the collective's actions. Although she was destroyed in the movie's climactic battle, we would learn later of other Borg Queens. This revelation changed the fundamental dynamic of what we knew about the Borg.

The Voyager Years

times than the *TNG* crew ever did. They discovered something called Unimatrix Zero, a sort of collective unconscious that assimilated drones could visit mentally. It is ultimately destroyed, which leads to an uprising within the collective once again.

CBS

After taking on several Borg children freed from the collective, *Voyager* has many more run ins with a different Borg queen. During this time, we learn that the Borg use transwarp technology to travel nearly anywhere in the galaxy, giving them an advantage over almost every other species. But in *Voyager's* final episode titled "Endgame," Captain Janeway manages to destroy one of their most important transwarp hubs. On top of that, Janeway introduces a pathogen into the Borg collective that disrupts their mental communication with one another, effectively crippling them.

What became of the Borg collective after the events of *Voyager* is unknown. The *Star Trek: Picard* trailer shows us a Borg cube, so we know that even without the transwarp hubs, they found their way back into Federation space at some point over the past twenty years. And a much more human Seven of Nine shows that her remaining Borg tendencies seem to be removed. One thing is certain: the Borg are nearly impossible to defeat completely, and they will be a thorn in the side of the Federation for years to come.

Picard premieres January 23, 2020 on CBS All Access.

MUSIC

Rick Astley Recreates 'Never Gonna Give You Up' ...

GAMES

MAGIC: THE GATHERING Heads to Middle-earth with LORD OF THE...

More by Eric Diaz

SPIDER-MAN

Uncle Ben's Gravestone Is a New Mod in SPIDER-MAN REMA...

HORROR

'JAWN of the Dead' Craft Beer Honors George A. R...

MOVIES

SAMARITAN Clip Sees Sylvester Stallone Grumpily Reveal Super...

MARVEL

Every Easter Egg We Spotted in the SHE-HULK Premiere

RINGS OF POWER

20 Posts

SHE-HULK

25 Posts

THE SANDMAN

24 Posts

TAGGED: STAR TREK: VOYAGER, PATRICK STEWART, STAR TREK: FIRST CONTACT, STAR TREK THE NEXT GENERATION, THE BORG, STAR TREK: PICARD

YOU MIGHT ALSO LIKE...

STAR TREK

Trailblazing STAR TREK Actress Nichelle Nichols Has Died at Age 89

Tai Gooden 3 min read

STAR TREK

STAR TREK's Science Advisor Works on All the Franchise's Current Shows

Melissa T. Miller 7 min read

SCI-FI

Astronaut Cosplays as Starbuck from BATTLESTAR GALACTICA

Melissa T. Miller 2 min read

STAR TREK

STAR TREK: STRANGE NEW WORLDS' Finale Gives New Meaning to Classic Episode

Eric Diaz 6 min read

MARVEL

Professor X Has a High Flying MCU Adventure in a DOCTOR STRANGE Fan Edit

Rotem Rusak 2 min read

SEE MORE

The wild history of vaping, from a 1927 'electric vaporizer' to today's mysterious lung injury crisis

Hilary Brueck Nov 12, 2019, 2:33 PM

Women dressed as nuns have a cigarette break during the Walmer Castle pageant in Kent circa 1931. Fox Photos/Getty Images

People have been coming up with inventive ways to get high on nicotine for near a hundred years.

But it wasn't until Chinese inventor Hon Lik invented his e-cigarette in 2003 that modern vaping was born.

Today, as the vaping lung injury crisis worsens, people are still coming up with new smoking alternatives. One is a salt-based formulation.

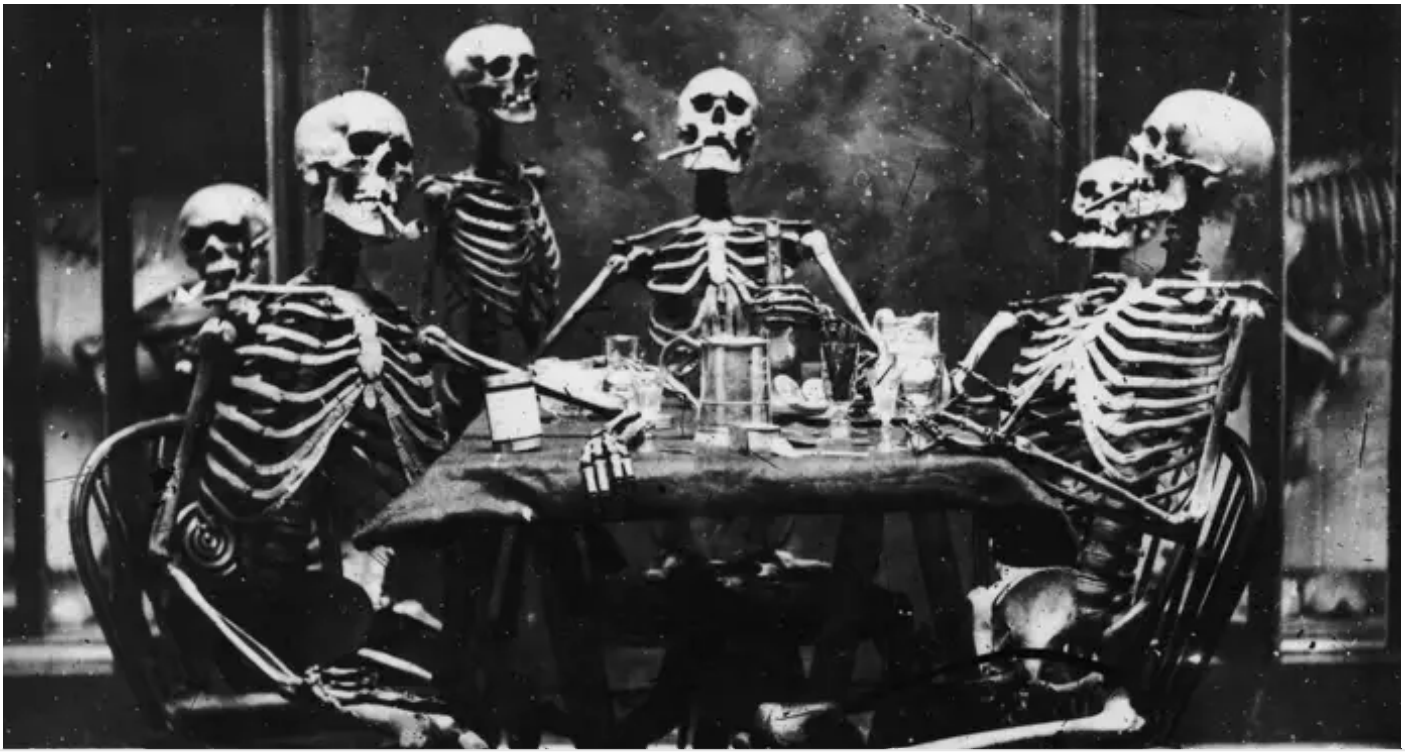
Visit Insider's homepage for more stories.

For thousands of years, people have been enjoying the subtle rush that smoking tobacco leaves, thereby ingesting nicotine, can provide.

But it wasn't until about 220 years ago that doctors started realizing how harmful smoking can be. Dr. Benjamin Rush was one of the first to point this out, in 1798, calling smoking "offensive" and a-moral, while also suggesting, correctly, that it can prompt "incurable diseases" and cancers.

nicotine high, without the stinky cigarettes. Here's a look at how vaping came to be, and where the industry's steam might be headed next.

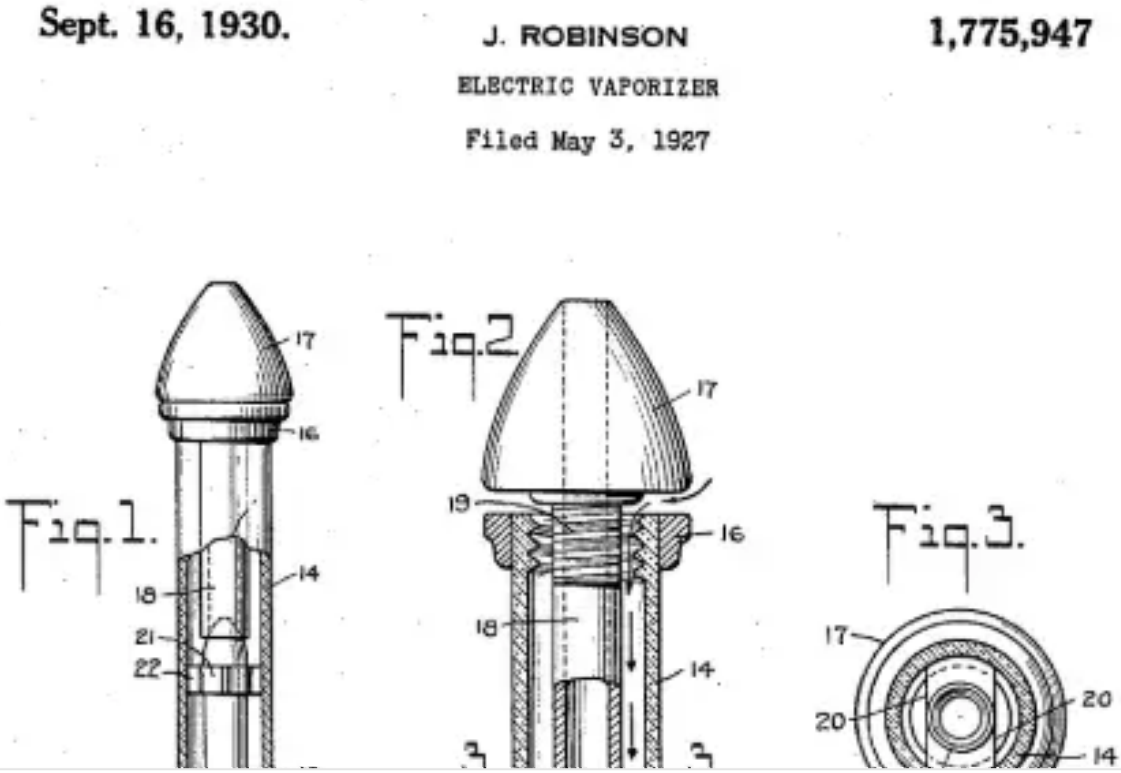
Concerns about smoking go back more than 200 years.



Six skeletons smoking around the dinner table, in an image taken around 1865. London Stereoscopic Company/Hulton Archive/Getty Images

In the 1800s, doctors started seeing lip cancer cases in smokers. Shortly after, some of the first reports of lung cancer began surfacing, with nearly 1,000 cases reported by the 1920s.

In 1927, Joseph Robinson dreamed up what might be the very first "electric vaporizer," a device he said was for "medicinal compounds."


Sept. 16, 1930. J. ROBINSON 1,775,947

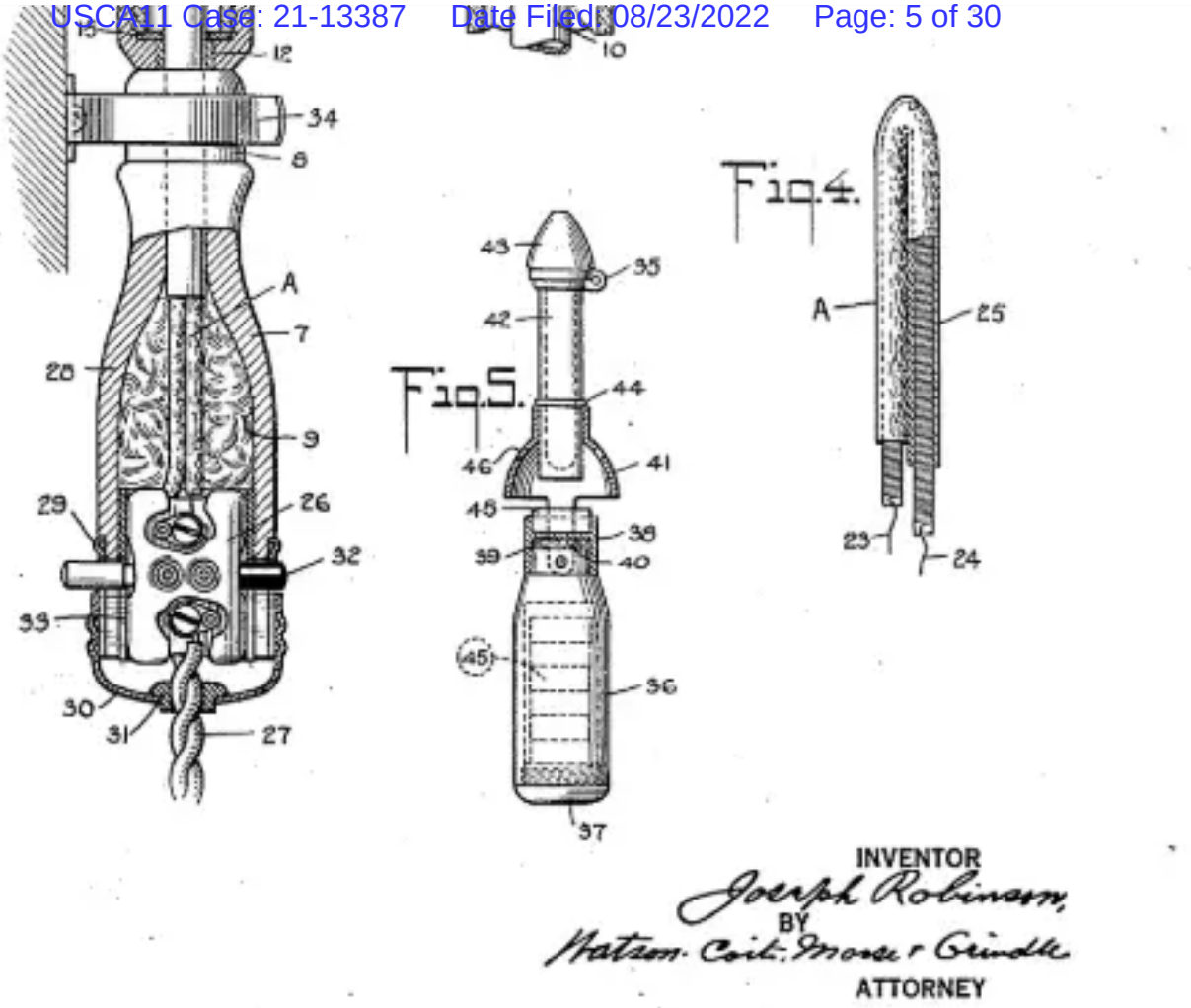
ELECTRIC VAPORIZER

Filed May 3, 1927

Fig. 1.

Fig. 2

Fig. 3.



What may be the very first US patent for an "electric vaporizer" was filed on May 3, 1927. US Patent via Google Patents

He dreamt the device would make it easier to inhale vapors "without any possibility of being burned."

But people kept on smoking. It wasn't until the 1950s and 60s that most people started becoming concerned about the health effects of cigarettes.

Two women lighting cigarettes on a tennis court in Essex, England circa 1930's. Keystone View/FPG/Getty Images

Source: *Cancer Medicine, 6th edition*

making the process

Herbert Gilbert filed a patent for this "smokeless non-tobacco cigarette" on April 17, 1963. US Patent and Trademark Office

Source: *Smithsonian*

There were other attempts at early e-cigarettes over the years. Jed Rose, who invented the first nicotine patch, experimented with something called "distilled smoke" in his lab at UCLA in the 1980s.

Jed Rose and Frederique Behm experimenting with early e-cigarettes in the 1980s. Jed Rose and Frederique Behm

Source: *Insider*

Source: *Insider*

In 2000, a tabletop "Volcano" vaporizer entered the market. It was not really designed for tobacco, though.

Patients at Cannabis Therapeutics in Colorado Springs Tyrone Ennis 40, and Ryan Niell 19, watch Sarah Harris 23, fill a bag with marijuana vapor from a volcano vaporizer. Joe Amon/The Denver Post via Getty Images

"How Rich People Smoke Pot" is how The Daily Beast referred to it.

The e-cigarette as we know today didn't show up until Chinese smoker and pharmacist Hon Lik invented it in 2003.

Hon Lik smokes his invention in Beijing on May 25, 2009. Frederic Brown/AFP via Getty Images

Lik, who at one point was downing up to three packs of cigarettes a day, says he was galvanized to invent a new device after his own father, also a smoker, died of lung cancer.

"I believed that if I could use vapor to simulate cigarette smoke, this could help me," Lik said.

Hon Lik, the Chinese inventor who dreamed up the electronic cigarette in a nicotine-induced vision, smokes one in his Beijing office on September 23, 2013. Wang Zhao/AFP via Getty Images

Source: *Reuters*

But Lik, like many others, has become a dual user. He still smokes cigarettes.

vm / Getty Images

Researchers suspect that for some cigarette users like Lik, e-cigs only "perpetuate nicotine addiction," providing "more access to nicotine."

But there is some evidence that e-cigs can help people quit smoking, if they're part of a larger cessation program with counseling, support, and anti-smoking drugs on board.

Around 2006, vaping was first introduced in Europe, and it wasn't long before it made its way into the US too.

Jamie Laing vaping a bespoke blu e-cigarette on April 21, 2015 in London. Neil Mockford/Getty Images for Blu eCIGs

Source: *US Customs and Border Protection*

World health authorities were puzzled by the new devices.

Indonesian teen sucking fumes from e-cigarettes in Medan, North Sumatra, Indonesia on December 5, 2014.
Ivan Damanik/NurPhoto via Getty Images

"As far as WHO is aware, no rigorous, peer-reviewed studies have been conducted showing that the electronic cigarette is a safe and effective nicotine replacement therapy," the World Health Organization wrote in 2008.

As vapers inhale, they heat up a liquid.

John Keeble/Getty Images

It's usually a mix of propylene glycol and/or vegetable glycerin (called PG-VG), which vaporizes and delivers drugs, along with any chosen flavors.

N'Joy, founded in 2007, was one of the first major e-cigarette brands in the US.

Britany Nola attends the N'JOY King Launch at The Jane Hotel on December 6, 2012 in New York City. Eugene Gologursky/WireImage

The company once filed for bankruptcy in 2016, as it struggled to find enough customers interested in using its devices.

But other companies have had no problems attracting new customers.

In 2015, JUUL chose one magazine to launch their advertising campaign: VICE. Vice marketed itself to advertisers as the "#1 youth media company." From the collection of Stanford Research Into the Impact of Tobacco Advertising

Juul has recently come under fire for its early-day marketing techniques, which Stanford physician Robert Jackler called "patently youth-oriented."

At least a quarter of teens in the US today say they've tried vaping, while about 6% of high schoolers vape regularly.

Pips Taylor at the official UK launch of blu eCigs, and the start of the brand's forthcoming UK music tour on May 8, 2014. David Benett/Getty Images for blu eCigs

Source: *Insider*

Some teens are now suing Juul, saying they became addicted to their nicotine products and never smoked before.

Melia Robinson/Business Insider

Source: *Insider*

"It's really not wonderful," President Trump said of vaping in September. "People are dying from vaping."

President Donald Trump talks about a plan to ban most flavored e-cigarettes, in the Oval Office of the White House, Wednesday, September 11, 2019, in Washington. AP Photo/Evan Vucci

So far, at least 37 people across the US have died after vaping nicotine, THC, or (usually) some combination of the two.

Skye Gould/Business Insider

across the country.

A former Juul executive filed a lawsuit earlier this week, saying that company knowingly sold tainted Juul pods to customers and stores.

Because the e-cigarettes industry is largely unregulated at the federal level, it's difficult to know exactly what's in any single vape.

Rainer Jensen/picture alliance via Getty Images

Source: *US Food and Drug Administration*

Many experts suspect there could be dangerous chemicals lurking in some vapes.

Child-proof refill bottles of liquid nicotine on display at Salt Lake Vapors, in Salt Lake City. AP Photo/Rick Bowmer

Vitamin E acetate has recently been found in the lungs of sick vapers nationwide.

"When vitamin E acetate is inhaled, it may interfere with normal lung function," Centers for Disease Control and Prevention (CDC) principal deputy director Anne Schuchat said.

President Trump promised in September that his administration would be pushing for a ban on flavored e-cigarettes soon, but nothing's happened yet

Chairman Raja Krishnamoorthi (D-IL) points to a poster showing similarities between Marlboro cigarette ads and JUUL vaping paraphernalia, during a House Economic and Consumer Policy Subcommittee hearing that heard testimony on JUUL's role in the youth nicotine epidemic, on July 25, 2019 in Washington, DC. Mark Wilson/Getty Images

"When has a ban really worked for anything?" Lawyer Rick Meadow, whose firm is handling one teenager's lawsuit against Juul, told Insider. "If there's a market for it, somebody's going to come through with it."

Research on vaping is still scant, but some preliminary studies are starting to trickle out, suggesting that (like smoking) there may be serious health consequences to vaping.

Model Frances Richards smokes a pack of cigarettes all on one cigarette holder. Jacobsen/Getty Images

"I think there's an emerging consensus that the immune cells of the lung are a little bit upset by vaping," Professor Robert Tarran, who studies vaping at the University of North Carolina Marisco Lung Institute, previously told Insider.

"As a consumer product, they're a disaster," Stanton Glantz, who directs the UCSF Center for Tobacco Research Control and Education, told Insider.

Cigarette giants are already experimenting with some new e-cig alternatives.

Sea salt. Shutterstock

One that Rose sold to cigarette giant Philip Morris International isn't heated above room temperature at all, and involves mixing a nicotine salt with acid.

He called the system "literally cool," compared to vaping.

KEEP READING

More: Features Vaping vapes volcano vape