PUBLISHED

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 21-2077

AVAIL VAPOR, LLC; BLACKSHIP TECHNOLOGIES DEVELOPMENT, LLC; BLACKBRIAR REGULATORY SERVICES, LLC,

Petitioners,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondent.

AMERICAN VAPING ASSOCIATION, INC.; AMERICAN VAPOR MANUFACTURERS ASSOCIATION, INC.; CONSUMER ADVOCATES FOR SMOKE-FREE ALTERNATIVES ASSOCIATION, INC.; SMOKE-FREE ALTERNATIVES TRADE ASSOCIATION, INC.; UNITED VAPERS ALLIANCE, INC.; ARIZONA SMOKE FREE BUSINESS ALLIANCE, INC.; BREATHE EASY ALLIANCE OF ALABAMA; CONNECTICUT CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION; FLORIDA SMOKE FREE ASSOCIATION, INC.; GEORGIA SMOKE FREE ASSOCIATION, INC.; HAWAII CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION; KANSAS SMOKE FREE ASSOCIATION; KENTUCKY VAPING RETAILERS ASSOCIATION, INC., d/b/a Kentucky Smoke Free Association; INDIANA SMOKE FREE ALLIANCE, INC.; IOWANS FOR ALTERNATIVES TO SMOKE AND TOBACCO, INC.; IOWA VAPE ASSOCIATION, INC.; LOUISIANA VAPE ASSOCIATION, INC.; MARYLAND VAPOR ALLIANCE; MICHIGAN VAPE SHOP OWNERS, INC.; MIDWEST VAPE COALITION, INC.; MINNESOTA SMOKE FREE ALLIANCE; MISSOURI SMOKE FREE, INC.; MONTANA SMOKE FREE ASSOCIATION, INC.; NEBRASKA VAPE VENDORS ASSOCIATION, INC.;

NEVADA VAPING ASSOCIATION, INC.; NEW MEXICO SMOKE FREE ALLIANCE, INC.; NEW YORK STATE VAPOR ASSOCIATION, INC.; NORTH CAROLINA VAPING COUNCIL, INC.; OHIO VAPOR TRADE ASSOCIATION, INC.; ROCKY MOUNTAIN SMOKE FREE ASSOCIATION, INC.; RHODE ISLAND CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION; SMOKE FREE ALTERNATIVES COALITION OF ILLINOIS, INC.; SOUTH CAROLINA VAPOR ASSOCIATION, INC.; TEXAS CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION; TENNESSEE SMOKE FREE ASSOCIATION, INC.; VIRGINIA SMOKE FREE ASSOCIATION, INC.; WASHINGTON SMOKE FREE ASSOCIATION, INC.; WEST VIRGINIA SMOKE FREE ASSOCIATION, INC.; DR. DAVID B. ABRAMS; CLIVE D. BATES; PROFESSOR DAVID T. SWEANOR, J.D.,

Amici Supporting Petitioners,

MEDICAL AND PUBLIC HEALTH GROUPS,

Amici Supporting Respondent.

On Petition for Review of an Order of the Food & Drug Administration. (PM0001233)

Argued: October 25, 2022 Decided: December 12, 2022

Before WILKINSON and DIAZ, Circuit Judges, and MOTZ, Senior Circuit Judge.

Petition denied by published opinion. Judge Wilkinson wrote the opinion, in which Judge Diaz and Senior Judge Motz joined.

ARGUED: Eric Nathan Heyer, THOMPSON HINE LLP, Washington, D.C., for Petitioners. Antonia Marie Konkoly, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C., for Respondent. **ON BRIEF:** Joseph A. Smith, Jessica Tierney, THOMPSON HINE LLP, Washington, D.C., for Petitioners. Brian M. Boynton, Principal Deputy Assistant Attorney General, Eric B. Beckenhauer, Assistant Branch Director, Cormac A. Early, Federal Programs Branch, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C.; Daniel J. Barry, Acting General Counsel, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, Washington, D.C.; Wendy S. Vicente, Acting Deputy Chief Counsel for Litigation, Seth I. Heller, Associate Chief Counsel, Office of the Chief Counsel, UNITED STATES FOOD AND DRUG

ADMINISTRATION, Washington, D.C., for Respondent. J. Gregory Troutman, TROUTMAN LAW OFFICE, PLLC, Louisville, Kentucky, for Amici 38 National and State Electronic Nicotine Delivery System Product Advocacy Associations. Mary G. Bielaska, ZANICORN LEGAL PLLC, New York, New York, for Amici Dr. David B. Abrams, Clive D. Bates, and Professor David T. Sweanor, J.D. William B. Schultz, Andrew N. Goldfarb, ZUCKERMAN SPAEDER LLP, Washington, D.C.; Dennis A. Henigan, Connor Fuchs, CAMPAIGN FOR TOBACCO-FREE KIDS, Washington, D.C., for Amici Medical and Public Health Groups.

WILKINSON, Circuit Judge:

The Family Smoking Prevention and Tobacco Control Act requires manufacturers of new tobacco products to obtain authorization from the United States Food & Drug Administration (FDA) prior to marketing their products. *See* Pub. L. 111-31, § 910, 123 Stat. 1776, 1807–12 (2009) (codified at 21 U.S.C. § 387j(a)). In reviewing a manufacturer's Premarket Tobacco Product Application, FDA must determine that the marketing of the product is "appropriate for the protection of the public health." § 910(c)(4), 123 Stat. at 1810. The agency denied Avail Vapor LLC's application for its flavored electronic cigarettes, chiefly on the grounds that its products posed a serious risk to youth without enough offsetting benefits to adults. We now uphold that decision and deny Avail's petition for review.

I.

A.

Congress enacted the Tobacco Control Act (TCA) in 2009. It found that "[t]he use of tobacco products by the Nation's children" was "a pediatric disease of considerable proportions that result[ed] in new generations of tobacco-dependent children and adults." § 2(1), 123 Stat. at 1777. Further, "[v]irtually all new users of tobacco products are under the minimum legal age to purchase such products," and "[t]obacco advertising and marketing contribute significantly to the use of nicotine-containing tobacco products by adolescents." §§ 2(4), 2(5), 123 Stat. at 1777. Congress's previous attempts to curb adolescent tobacco use had failed, and thus the TCA sought "to address comprehensively the public health and societal problems caused by the use of tobacco products." § 2(7), 123

Stat. at 1777. Congress entrusted the FDA with this important task, finding that it "possesses the scientific expertise needed to implement effectively all provisions of the [TCA]." § 2(45), 123 Stat. at 1781.

The TCA authorizes the FDA to regulate tobacco products including "cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco," as well as "any other tobacco products that the [FDA] by regulation deems to be subject" to the TCA. § 901(b), 123 Stat. at 1786. Relevant here, the TCA requires manufacturers of "new tobacco products" to submit Premarket Tobacco Product Applications (PMTAs) and receive authorization from the FDA prior to releasing their products on the market. *See* § 910(a)(2)(A), 123 Stat. at 1807. A "new tobacco product" is any tobacco product that was not "commercially marketed in the United States as of February 15, 2007." § 910(a)(1)(A), 123 Stat. at 1807.

The FDA must deny a PMTA if it finds that "there is a lack of showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." § 910(c)(2)(A), 123 Stat. at 1809. Whether a product is "appropriate for the protection of the public health" is "determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." § 910(c)(4), 123 Stat. at 1810. As part of this inquiry, the TCA explicitly requires the FDA to consider "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." § 910(c)(4)(A)–(B), 123 Stat.

at 1810. Thus, the FDA is required to weigh the benefits of "cessation" associated with a new tobacco product against the risks of "initiation."

Finally, the TCA states that "whether permitting a tobacco product to be marketed would be appropriate for the protection of the public health shall, when appropriate, be determined on the basis of well-controlled investigations." § 910(c)(5)(A), 123 Stat. at 1810. However, if FDA "determines that there exists valid scientific evidence" other than well-controlled investigations "which is sufficient to evaluate the tobacco product," FDA may issue a marketing order based on that evidence. § 910(c)(5)(B), 123 Stat. at 1810.

B.

The petition before us involves the public health debate surrounding the novel use of an ancient product. Electronic nicotine delivery systems (ENDS), also known as e-cigarettes, were introduced widely in the United States since Congress passed the TCA. In contrast to traditional cigarettes, ENDS heat a liquid that includes nicotine, chemicals, and flavors until it generates an aerosol or vapor, which can then be inhaled by the user. *See Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 270 (D.C. Cir. 2019). These products have the potential to benefit adult smokers if used as a complete substitute for combustible tobacco smoking, *i.e.*, if adult smokers "switch" to ENDS products, as they are less likely to cause disease and death. *See* U.S. Dep't of Health and Hum. Servs., *E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General* 186 (2016). These products still contain nicotine, however, which is an addictive substance known to harm the developing brain. *Id.* at 100–07.

Two of the most common ENDS systems have "pods" or "cartridges" that hold nicotine-containing liquid known as "e-liquid." "Closed systems," or cartridge-based systems, use pods or cartridges that are sold pre-filled with e-liquid. Those cartridges are discarded and replaced after the e-liquid within them runs out. "Open systems" have cartridges that can be refilled with e-liquid by the user. Thus, the open system user mostly buys e-liquid bottles to refill his product.

Although the TCA banned the sale of cigarettes with a characterizing flavor (e.g., fruit), *see* § 907(a)(1)(A), 123 Stat. at 1799, this ban did not apply to ENDS products. Therefore, ENDS products not only came in traditional flavors reminiscent of a combustible cigarette, like tobacco and menthol, but also had other flavors derived from fruit, candy, dessert, and other sweets. This distinction between "tobacco-flavored" and other "flavored" products is important for this petition, as the FDA has found that other flavored ENDS products appeal to youth more than traditional tobacco-flavored ENDS products. *See* J.A. 27. This is commonsensical: young people have an age-old proclivity toward sweets.

Sales of e-cigarettes in the United States rose rapidly from 2007 onward. *See Report of the Surgeon General*, *supra*, at 10. After 2010, there was a marked increase in e-cigarette use by both adults and youth. In 2011, an estimated 1.5% of high school students were e-cigarette users. *Id.* By 2015, 16% of high school students used ENDS, surpassing the rate of combustible cigarette use. *Id.* These trends led to substantial concern among public health communities. *Id.* Unlike combustible cigarettes, however, ENDS products had

limited regulatory oversight, as the TCA did not give the FDA immediate jurisdiction over these products. *Id.* at 15.

To close this gap, FDA asserted regulatory jurisdiction over ENDS products in May 2016 in accordance with its authority to "deem" new products subject to the strictures of the TCA. *See* 21 U.S.C. § 387a(b); 81 Fed. Reg. 28,974 (May 10, 2016) ("Deeming Rule"). It noted that the Deeming Rule was necessary in substantial part due to "the continued dramatic rise in youth and young adult use of tobacco products such as e-cigarettes." *Id.* at 29,894. However, the FDA also recognized that this new rule meant that most ENDS products were already on the market without manufacturers having submitted a PMTA, a violation of the TCA. Thus, the FDA decided not to act on a product's lack of premarket authorization for two to three years while manufacturers prepared, and FDA reviewed, marketing applications. *Id.* at 28,977–78. After the Deeming Rule, FDA made a series of public announcements relevant to the matter at hand, which we examine below.

In the summer of 2017, FDA announced that it did not intend to initiate enforcement regarding PMTAs for newly regulated ENDS products for five years, *i.e.*, until 2022. J.A. 94. The extension reflected nationally representative data that suggested youth use of e-cigarettes had declined beginning in 2016. *Id.* The decline, however, did not last long. Whereas the downward trend in youth e-cigarette use in 2016 moved FDA toward more lenient regulation of the ENDS industry, new information caused the FDA to change course. By late 2017, FDA started to see an explosion in complaints about ENDS products, and new data indicated an alarming increase in the use of ENDS products by middle and high school students. J.A. 94–95. Between 2017 and 2018, studies showed that e-cigarette

use had increased by 78% in high school students and 48% in middle school students. J.A. 97. Considering this new data, FDA's then-Commissioner characterized the situation as a "youth vaping epidemic" in 2018. J.A. 75. The FDA began to use its enforcement discretion, issuing over 6,000 warning letters to manufacturers and more than 1,000 civil monetary complaints to retailers for the marketing and sale of ENDS products to minors. J.A. 97.

C.

While FDA was reckoning with the new and evolving information on youth ENDS use, it also issued guidance on PMTAs for ENDS manufacturers. FDA, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems*, *Guidance for Industry* (June 12, 2019) ("2019 Final PMTA Guidance"); *see* J.A. 220–74. The final compliance date was simultaneously moved up from 2022 to September 9, 2020, in response to a suit initiated by a group of pediatric physicians. *See Am. Acad. of Pediatrics v. Food & Drug Admin.*, 379 F. Supp. 3d 461(D. Md. 2019); J.A. 94–95. FDA stated that in reviewing PMTAs, it "weighs all of the potential benefits and risks from the information contained in [a] PMTA to make an overall determination of whether the product should be authorized for marketing." J.A. 234. Further, the FDA stated that while "[n]onclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health," there are some cases where it "may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies," such as when there was "an established body of evidence regarding the health impact . . . of [a manufacturer's] product

or a similar product that can be adequately bridged to [the manufacturer's] product." J.A. 234, 268.

Rapidly accumulating evidence about the danger of ENDS products to youth again shifted FDA's priorities. After the agency issued the 2019 Final PMTA Guidance, two national surveys measuring tobacco habits among youth found that e-cigarette use hit the highest levels ever recorded, underscoring the magnitude of the problem. J.A. 97. In response, in April 2020, FDA issued a final enforcement guidance with the changing landscape in mind. FDA, *Enforcement Priorities for Electronic Nicotine Delivery System (ENDS) and Other Deemed Products on the Market Without Premarket Authorization, Guidance for Industry* (Apr. 29, 2020) ("2020 Enforcement Guidance"); *see* J.A. 89–140. In a departure from its previous policy of deferring enforcement until manufacturers submitted PMTAs, FDA decided to immediately exercise its enforcement authorities with respect to certain products that attracted youth. J.A. 98. At the head of its list were flavored cartridge-based ENDS products, as evidence showed that youth were particularly attracted to these devices. J.A. 108. FDA also intended to prioritize enforcement against all other ENDS products either marketed to youth or for which the manufacturer had failed to take adequate steps to prevent youth access. J.A. 107.

Notwithstanding these specific priorities, FDA made clear that it would "make enforcement decisions on a case-by-case basis" and that it "is continuously evaluating new information and adjusting its enforcement priorities in light of the best available data[.]" J.A. 92, 100. Importantly, FDA found that "evidence continues to accumulate, further confirming that youth are particularly attracted to flavored ENDS products." J.A. 103. New

studies showed that flavors drove both initiation and continued regular use by youth. *Id.* Further, FDA noted that its previous attempts at restricting youth access to ENDS products had fallen flat, finding that "youth have continued access to these products in the face of legal prohibitions and even after voluntary actions by some manufacturers." J.A. 110. As for marketing access restrictions, FDA told manufacturers that it "believes that age verification alone is not sufficient to address this issue, given the most recent data that youth use of ENDS products continues to increase." J.A. 133.

After FDA implemented its 2020 Enforcement Guidance, the percentage of youth using e-cigarettes decreased. J.A. 29. But despite this decline, ENDS remained the most popular tobacco product among youth, "with youth use at levels comparable to what originally led FDA to declare a youth vaping epidemic in 2018." *Id.* Moreover, there was a substantial rise in youth use of yet another type of flavored e-cigarettes, this time a system designed to be discarded after a single use. *Id.* These products were largely excluded from the 2020 Enforcement Guidance, and thus they remained on the market as a flavored option. *Id.* This fast product switching underscored the important role that flavors have in driving youth use, in whatever form or device the flavored e-cigarette is available. Up to and through the PMTA deadline, FDA received applications for over 6 million vaping products. *See* FDA, *Deemed Product Review: A Conversation with the Center for Tobacco Products Office of Science* (June 11, 2021). While the regulatory path may be a winding one, its constants are the persistence of youth use of flavored ENDS products and the obligation of FDA to incorporate new public health data into an evolving regulatory framework.

D.

Avail Vapor is a Richmond, Virginia company which sells, researches, and contracts for ENDS products. Avail submitted its PMTAs to the FDA for approval on September 8, 2020, right before the court-imposed deadline. Avail's PMTAs focused on various fruit- and dessert-flavored e-liquids. These included flavors like "Aphrodite X," a blend of "perfectly ripened strawberries bursting with natural flavor, a touch of juicy melon to add contrast, and just a hint of pillowy marshmallow to balance out the tartness of the strawberry." Gov't Response Br. at 15–16. Avail also included an application for "Golden Dawn," which is a "deliciously balanced dessert vape" featuring "the taste of crunchy, savory waffle cone." *Id.* at 16.

Avail included the results of four behavioral studies to support its PMTAs: 1) a two-week online diary study that assessed vaping habits and attitudes associated with Avail's e-liquids; 2) data from a series of focus groups with a total of 39 participants, which evaluated perceptions and experiences with e-cigarettes and vaping in general; 3) a national survey of adults that measured attitudes towards, and intentions to use tobacco products; and 4) a "human factors summative protocol," which surveyed 18 adults about the usability and safety of one of Avail's e-liquid flavors in four nicotine strengths.

Avail also filed its marketing plan with its PMTAs, which outlined measures designed to prevent underage use. Such measures consisted of naming its flavored e-liquids with "non-descriptive and non-characterizing names" that do not identify the product flavor to prevent appealing to youth. *See* J.A. 293. Avail believed its age-gated brick-and-mortar stores and independent age-verification services in Avail's point-of-sale system would

prevent youth access to its products. *See* J.A. 295–97. Avail also required its distributors to submit a written policy on their age-verification procedures and a record of compliance with these policies. J.A. 314. While some other ENDS manufacturers were exploring innovative "access restriction" technology, whereby, for example, an ENDS product is tied to the thumb print of the purchaser, Avail's marketing plan included only garden variety restrictions that the FDA had previously found wholly inadequate in preventing youth use. Oral Arg. at 34:09; *see* 2020 Enforcement Guidance, J.A. 131–36.

On September 15, 2021, the FDA rejected Avail's PMTAs and issued a marketing denial order for its products. *See* J.A. 11–16. It listed the following as the "key basis" for the denial:

> 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 and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS.
>
> 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 contained four protocols for [randomized controlled trials]….to address the new products' abuse liability, the study reports were not submitted…; therefore, this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s). . . .
>
> 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.

J.A. 11–12. The FDA also provided Avail with a separate Technical Project Lead Review explaining its reasoning for the denial. *See* J.A. 25–45.

Avail administratively appealed this order, requesting that FDA re-review its applications and rescind the marketing denial order. FDA agreed and granted an administrative stay, allowing Avail's products to remain on the market during the re-review process. On February 23, 2022, FDA concluded that recission was not warranted, reiterating its determination that petitioners' evidence did not "demonstrate a sufficient potential benefit to adult smokers" when weighed against the known risk to youth. J.A. 56. In the re-review, FDA looked to each of the four behavioral studies submitted by Avail as part of its PMTAs. *See* J.A. 46–60. The evidence from each behavioral study was found lacking because it did not "demonstrat[e] the benefit to adult users of the applicant's flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes." J.A. 56.

E.

Avail timely petitioned this court for review of FDA's marketing denial order. This court has jurisdiction over Avail's petition pursuant to the TCA. *See* 21 U.S.C. § 387*l*(a)(1)(B) (providing jurisdiction for federal court review of a marketing denial order for the circuit in which a company has its "principal place of business").

Avail raises a flurry of objections to the FDA's marketing denial order. Avail's chief complaint is that the FDA arbitrarily imposed a new "comparative efficacy" standard, which asked applicants to demonstrate through certain long-term studies that their fruit- and dessert-flavored products better promote smoking cessation than tobacco-flavored

products. This standard, Avail complains, was adopted with no explanation to applicants and without consideration of their reliance interests. Avail also raises a substantive objection, arguing that FDA's imposition of this comparative efficacy standard exceeded its statutory authority under the TCA.

All of Avail's objections founder on common ground. First, Avail attempts to tie the hands of the FDA to certain forms of evidence and kinds of studies in what is a rapidly evolving field. Second, in focusing upon procedural points, Avail encourages us to neglect the forest for the trees. Avail essentially argues that "the FDA's willingness to consider some forms of evidence, explicitly phrased as such, required the FDA to accept that evidence as meeting a statutory requirement even where the FDA found the evidence unsatisfactory." *Breeze Smoke, LLC v. U.S. Food & Drug Admin.*, 18 F.4th 499, 507 (6th Cir. 2021) (denying a judicial stay from a substantially similar marketing denial order). Avail's proposed restrictions simply run counter to FDA's broad statutory mandate to determine from the totality of the evidence before it whether marketing of new tobacco products is "appropriate for the protection of the public health." Tobacco Control Act, § 910(c)(2)(A), 123 Stat. at 1809.

II.

We proceed in accord with well-settled principles of administrative law. The TCA incorporates by reference the customary Administrative Procedure Act standard of review. *See* 21 U.S.C. § 387*l*(b) (citing 5 U.S.C. § 706(2)(A)). Under this standard, we are instructed to "hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with

law." 5 U.S.C. § 706(2)(A). Agency action is arbitrary and capricious "if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

Arbitrary and capricious review, however, comes "with a presumption in favor of finding the agency action valid." *Ohio Valley Env't Coal. v. Aracoma Coal Co.*, 556 F.3d 177, 192 (4th Cir. 2009). Further, in reviewing agency action, "due account shall be taken of the rule of prejudicial error," 5 U.S.C. § 706, which is an administrative law "harmless error rule." *Shinseki v. Sanders*, 556 U.S. 396, 406 (2009) (internal quotations omitted). Avail carries the burden of showing that any procedural error by the FDA is harmful. *Id.* at 409.

A.

We shall first set forth why the agency did what it did. We shall then discuss Avail's challenges to its actions.

We must initially review the evidence FDA considered in making its determination that allowing Avail to market its products would not be "appropriate for the protection of the public health." Tobacco Control Act, § 910(c)(2)(A), 123 Stat. at 1809. The TCA requires FDA to make this inquiry by weighing the risk of tobacco product initiation by nonsmokers, including youth, against the benefit of cessation by current smokers. § 910(c)(4), 123 Stat. at 1810.

FDA straightforwardly applied that statutory mandate in reviewing the PMTAs, and it found Avail's applications wanting against that standard. In short, FDA "examined the relevant data and provided an explanation of its decision that includes a rational connection between the facts found and the choice made." *Aracoma*, 556 F.3d at 192 (internal quotations omitted). The care taken by the agency in this review undermines any argument by Avail that FDA acted arbitrarily and capriciously.

In reviewing Avail's PMTAs, FDA began with the same concern that motivated Congress's passage of the TCA: "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." J.A. 29–30. FDA then reviewed a litany of scientific evidence definitively showing the relationship between flavors and youth use of ENDS products. To start, ENDS products are the most used tobacco product among youth, and "[t]he majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time." J.A. 30. Further, youth ENDS users were more likely to use flavored products than adult ENDS users. *Id.*

FDA next examined studies which showed that flavors drove youth initiation of ENDS use, with most users reporting that their first experience with ENDS was with a flavored product. *Id.* And beyond initiation, flavors promoted regular ENDS use: nationally representative studies indicated that youth users consistently cited the availability of desirable flavors as the reason behind their use. J.A. 31. Further, "[r]esearch show[ed] that flavored ENDS are rated as more satisfying than tobacco-flavored ENDS, such that participants will work harder for and take more puffs of flavored ENDS compared to non-

flavored ENDS." *Id.* Evidence also indicated that flavors can actually increase nicotine exposure by "potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use." *Id.* Thus "this evidence suggests flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth[.]" J.A. 31.

Particularly striking, FDA found that although "there is variability in the popularity of device types among youth," the role of flavor is consistent across all of them. *Id.* Across all device types, "fruit was the most commonly used flavor type among youth." *Id.* Further, "the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace." J.A. 32. Ergo, where flavors were only available in certain device types, youth tended to gravitate toward them. *Id.* This was illustrated by the substantial migration of youth towards single-use ENDS, which remained on the market as a flavored option after the 2020 Enforcement Guidance cracked down on other flavored products popular with youth. *Id.*

To FDA, the crux of the issue was that youth use of ENDS products was driving nicotine dependency, a matter of substantial public health concern. *Id.* "[N]icotine exposure during adolescence enhances the rewarding and reinforcing effects of nicotine in adulthood, and can induce short and long-term deficits in attention, learning, and memory." *Id.* The agency, having been tasked by Congress with preventing youth use of tobacco products that "are inherently dangerous and cause cancer, heart disease, and other serious adverse health effects," *see* Tobacco Control Act, § 2(2), 123 Stat. at 1777, noted that "there is a growing body of evidence showing a link between ENDS use and subsequent

smoking among youth." J.A. 33. Other studies showed as well that there is an association between ENDS use and respiratory issues in young adults. *Id.*

Notwithstanding the substantial risks of youthful addiction and associated health issues, FDA considered the possibility that flavored ENDS may help promote smoking cessation or switching to a less detrimental product as required by the statute. FDA noted scientific evidence that ENDS are healthier for tobacco users than combustible cigarettes. J.A. 34. But "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." *Id.* For flavored ENDS, which pose a massive risk of addicting a new generation to nicotine, "the magnitude of the likely benefit would have to be substantial enough to overcome the significant risk . . . ." *Id.*

In contrast to the role that flavors play in promoting ENDS use by youth, FDA found that "the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive." J.A. 36. The literature was conflicting and inconclusive on whether flavors actually promoted switching or cessation by adult smokers. J.A. 35–36.

FDA did not use an "evidentiary double standard" when reviewing petitioners' applications. *See* Pet'rs' Opening Br. at 39. Whereas the evidence on the role of flavors in promoting youth use of ENDS products was established as a matter of scientific consensus, there was no comparable showing of the benefits that flavored ENDS have for adult smokers in promoting switching or cessation. Moreover, evidence showed that "tobacco-flavored ENDS may offer the same type of public health benefits as flavored ENDS," in encouraging adult cigarette smokers to switch to ENDS products and decreasing the use of

combustible cigarettes. J.A. 27. Such tobacco-flavored products, however, "do not pose the same degree of risk of youth uptake" as fruit or dessert-flavored products. *Id.* As such, FDA required Avail to provide strong, product-specific evidence demonstrating its products would provide an extra benefit to current smokers over that of other lower-risk products. J.A. 38–39.

Avail did not do so. For example, as part of its application, Avail included survey data. FDA, however, determined that single-point-in-time data "does not enable reliable evaluation of behavior change over time," which is crucial to determine whether a new product encourages switching or cessation. J.A. 36–37. Avail also presented protocols for randomized controlled trials submitted as part of the PMTAs. FDA acknowledged that data from these studies could potentially meet the statutory standard. J.A. 19. However, since Avail failed to present *any* evidence from these studies, they could not be considered. J.A. 23. Considering the entire population, FDA determined that marketing Avail's flavored products would not be appropriate for the protection of the public health. This judgment, of course, was one the TCA envisioned the FDA could make.

B.

Despite this thorough review, Avail argues that FDA pulled a "surprise switcheroo" on regulated parties by requiring certain types of evidence that FDA had previously represented were unnecessary for a successful PMTA, namely comparative efficacy evidence presented through randomized controlled trials or longitudinal cohort studies. *Wages & White Lions Invs., LLC v. U.S. Food & Drug Admin.*, 16 F.4th 1130, 1138 (5th Cir. 2021) (granting stay of marketing denial order); *but see Wages & White Lions Invs.,*

LLC v. Food & Drug Admin., 41 F. 4th 427, 430 (5th Cir. 2022) (merits panel denying the petition for review). Petitioners contend that, in rejecting its applications, "FDA focused solely on whether PMTAs for flavored ENDS products contained particular long-term studies on the products' effectiveness at promoting smoking cessation—studies that FDA had previously represented were not expected or necessary for PMTAs . . . ." Pet'rs' Opening Br. at 1.

We are unpersuaded by this argument, and we join the majority of our sister circuits in finding that FDA neither changed the standard nor the types of evidence required. *See Prohibition Juice Co. v. U.S. Food & Drug Admin.*, 45 F.4th 8, 20–21 (D.C. Cir. 2022); *Liquid Labs LLC v. U.S. Food & Drug Admin.*, 52 F.4th 533, 539–43 (3d Cir. 2022); *Wages and White Lion Invs.*, 41 F.4th at 438–39; *Gripum, LLC v. U.S. Food & Drug Admin.*, 47 F.4th 553, 559–60 (7th Cir. 2022); *see also Breeze Smoke*, 18 F.4th at 505–07 (denying a judicial stay of a marketing denial order). Our review of the record shows that FDA did not reject Avail's application because it failed to include certain long-term studies, but rather due to a lack of *any* "valid scientific evidence" substantial enough to outweigh the known risks to youth of flavored products. *See* Tobacco Control Act, § 910(c)(5)(B), 123 Stat. at 1810.

It is a bedrock principle of administrative law that "agencies should provide regulated parties fair warning of the conduct [a regulation] prohibits or requires." *Romero v. Barr*, 937 F.3d 282, 295 (4th Cir. 2019) (internal quotations omitted) (alteration in original). This means that an agency may not change its policy *sub silentio* or without fair notice to regulated entities. *See, e.g.*, *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502,

515 (2009). And further, "[w]hen an agency changes course . . . it must be cognizant that longstanding policies may have engendered serious reliance interests that must be taken into account." *Dep't of Homeland Sec. v. Regents of the Univ. of Calif.*, --- U.S. ----, 140 S. Ct. 1891, 1913 (2020) (internal quotations omitted). The agency, however, did not traduce these principles here. FDA told manufacturers about the type and quality of evidence required to be included with their PMTAs. Avail failed to include this evidence and this failure, rather than the absence of certain studies in its PMTAs, resulted in FDA issuing a marketing denial order.

1.

FDA never guaranteed that manufacturers could carry their evidentiary burden under the TCA without providing long-term data *See Prohibition Juice*, 45 F.4th at 21. Instead of looking to the overall context of the FDA's public statements, Avail highlights isolated statements which allegedly show that FDA "switched" the evidence it required in a PMTA. Avail makes a fuss about the 2019 Final PMTA Guidance, which stated, "in general, FDA does not expect that applicants will need to conduct long-term studies to support an application." Pet'rs' Opening Br. at 8; *see also* J.A. 235. Avail argues that it relied on this sentence in drafting its PMTAs, and thus FDA failed to consider its reliance interests when it switched the evidentiary standard along the way. It is not, however, the fault of FDA that petitioners failed to look at the 2019 guidance in any depth. If it had, it would have found "a more complicated story." *Gripum,* 47 F.4th at 559.

The 2019 Final PMTA Guidance made clear that FDA required "valid scientific evidence" under which the FDA could evaluate the health risks of the new ENDS products.

J.A. 234. In that same document, FDA noted that "[n]onclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health." *Id.* However, FDA recognized that due to the relative novelty of ENDS, "in some cases, it *may* be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies," such as if there was "an *established body of evidence* regarding the health impact . . . of your product or a similar product that can *be adequately bridged* to your product." J.A. 268. (emphases added). FDA further warned manufacturers that "[p]ublished literature reviews . . . or reports may be acceptable to support a PMTA, but are considered a less robust form of support for a PMTA." J.A. 269.

The FDA also "recommend[ed] an applicant *compare* the health risks of its product to both products within the same category and subcategory, as well as products in different categories as appropriate." J.A. 235 (emphasis added). This is because "FDA reviews the health risks associated with changes in tobacco use behavior (e.g., initiation, switching, dual use, cessation) that are likely to occur with the marketing of the new tobacco product." *Id.* In other words, FDA said that "it *might* accept evidence other than long-term studies," but only "if that evidence had sufficient scientific underpinnings" to enable the FDA to weigh the risks of initiation against the benefits of switching and cessation. *Breeze Smoke*, 18 F.4th at 506–07 (emphasis in original). To the extent that Avail is suggesting that the willingness to accept other evidence meant that "long-term studies were likely unnecessary," it is "over-read[ing]" this guidance. *Prohibition Juice*, 45 F.4th at 22–23; *see also Liquid Labs,* 52 F.4th at 542 n.11.

Moreover, regarding long-term studies, FDA found that "instead of conducting clinical studies that span months or years to evaluate potential clinical impact, applicants could demonstrate possible long-term health impact by including existing longer duration studies in the public literature with the appropriate bridging information . . . and extrapolating from short-term studies." J.A. 235. The agency made quite clear that it was interested in receiving information about long-term *impact*, even if that information did not necessarily come from a long-term *study*. Avail, however, "conflate[s] 'long-term' studies with studies examining behavior 'over time,'" essentially arguing that it need not have provided the latter because FDA suggested the former was not strictly necessary for a PMTA. *Liquid Labs*, 52 F.4th at 541 n.10. While the 2019 Final PMTA Guidance "broadened the types of evidence it would consider" beyond "the two types of evidence it usually requires," "the agency made clear it would not relax the scientific rigor of the requisite public health demonstration." *Prohibition Juice*, 45 F.4th at 21. FDA did not, in other words, abandon its statutory obligation to consider whatever evidence was necessary to make a sound determination of a new tobacco product's impact upon public health.

2.

Avail's argument with respect to two FDA internal memoranda is even weaker. Petitioners point to these documents as proof that FDA denied its applications solely because they lacked randomized controlled trials and longitudinal cohort studies. *See* Pet'rs' Opening Br. at 15–17; *see also* J.A. 61–87 (text of internal memoranda dated July 9, 2021 and August 17, 2021). What Avail fails to recognize, however, is that these internal documents were just that: internal. Not only are internal documents unlikely to create

reliance interests, but the record also makes clear that each was rescinded prior to or superseded by FDA's marketing denial order issued on September 15, 2021. *See* J.A. 88. In fact, the Technical Project Lead Review accompanying FDA's marketing denial order made clear that long-term studies are not required by looking to "any acceptably strong evidence" in Avail's applications. J.A. 27.

Agencies are customarily given latitude in their internal discussions and debates when they do not become agency policy. *See City of Virginia Beach v. U.S. Dep't of Com.*, 995 F.2d 1247, 1252–53 (4th Cir. 1993) (noting that action by agencies should be judged "on the basis of their final decisions" and not "for matters they considered before making up their minds"). That latitude needs to be broad in the case of a statutory charge as general as this one, where internal discussions involve "complex predictions within the [FDA's] area of special expertise." *Nat'l Audobon Soc'y v. U.S. Army Corps of Eng'rs*, 991 F.3d 577, 583 (4th Cir. 2021). Petitioners not only wish to restrict FDA's consideration of certain forms of evidence, but also to locate a point where agency deliberations become frozen in time. The result would be gridlock, an agency decisional process robbed of the value of ongoing dialogue.

3.

As part of their arbitrary and capricious review, courts must examine the care and thoroughness of agency action. A careful approach to a problem inspires more judicial confidence than some back-of-the-hand dismissal. An agency must thus address the issues such that a reviewing court "can understand enough about the problem confronting the agency to comprehend the meaning of the evidence relied upon and the evidence discarded;

the questions addressed by the agency and those bypassed; the choices open to the agency and those made." *Aracoma*, 556 F.3d at 192–93 (internal quotations omitted), The carefulness of FDA's review is nowhere better illustrated than in its administrative re-review of Avail's PMTAs. As part of this process, FDA looked thoughtfully at each of Avail's four behavioral studies, the nature of which we discussed above. *See* Section I.D, *supra*. FDA's re-review is part of the administrative record before this court. *See* J.A. 46–60. We find it particularly telling that Avail itself asked for this administrative re-review. *See* J.A. 47. FDA's decision on re-review forms part of "the grounds that the agency invoked when it took the action," which was ultimately the issuance and continuing validity of its marketing denial order. *Michigan v. EPA*, 576 U.S. 743, 758 (2015).

FDA discussed in-depth the deficiencies of Avail's four behavioral studies. The two-week online diary study did not collect data specific to the products in petitioners' applications, and therefore could not present the proper comparative efficacy data necessary to offset the known risks to youth associated with flavored ENDS products. J.A. 56–57. As for the evidence submitted from a series of focus groups, Avail did not provide information showing that the small focus groups were representative of current adult users of tobacco products *other* than e-cigarettes. J.A. 57. Without representative data on adult smokers of traditional cigarettes, the focus groups could not measure switching or cessation. The evidence from Avail's "perceptions and intent to use study" similarly did not stratify its results by participants' tobacco-use status, and therefore did not "support conclusions on current adult smokers' behavioral intentions to try, or switch to, Avail's products." *Id.* Finally, petitioners' data from a "human factors summative protocol," which

surveyed 18 adults about the usability and safety of one Avail flavor in four nicotine strengths "did not examine behavior change or use of ENDS," in general or with Avail's products. *Id.* Such information was necessary to demonstrate a benefit to adult smokers under the TCA. *Id.* Since none of these studies were scientifically rigorous, FDA could not rely on them in determining whether Avail's products were "appropriate for the protection of the public health."

III.

Avail's other main argument involves the marketing plan included with its PMTAs, which highlighted how Avail would limit youth access and exposure to its products. The FDA declined to consider this marketing plan in its initial review of Avail's applications, since it had yet to find marketing plans or access restrictions that truly decreased the appeal of flavored ENDS products to youth or stopped them from accessing those products. J.A. 35, n.xix. On re-review, FDA again did not consider the marketing plan in determining whether to rescind its marketing denial order of Avail's products. Avail argues that the failure to consider its marketing plan was arbitrary and capricious, as "FDA repeatedly stressed the importance of marketing plans and applicants' efforts to restrict youth exposure to marketing and youth access" in its public guidance. Pet'rs' Opening Br. at 34.

A.

The FDA did not act arbitrarily and capriciously in declining to review Avail's marketing plan. As noted by the agency in oral argument, a PMTA is like a driver's test, in that it has two components: First, valid scientific evidence showing that a product is appropriate for the protection of the public health, like the "written test," and second, a

determination that the totality of the evidence supports a marketing authorization, like the "road test." A marketing plan, which includes youth access restrictions, comes in at the road test phase to support the final determination that an application is appropriate for the protection of the public health.

Like a driver's test, both components are necessary, and neither is sufficient. An applicant who fails the written test does not proceed to the road test. So too here: FDA determined that Avail could not show its products were appropriate for the protection of the public health, and no marketing plan could rectify that baseline infirmity. As the Fifth Circuit said, "FDA stating that marketing plans would help FDA determine whether the new tobacco product meets the [statutory] standard is *not* the same as FDA stating that *if* marketing plans exist *then* market authorization was a step away." *Wages & White Lion*, 41 F.4th at 440 (internal quotations omitted) (emphasis in original).

B.

But even assuming, purely arguendo, that it was error not to review Avail's marketing plan, that error is harmless. "Administrative adjudications are subject to the same harmless error rule that generally applies to civil cases," thus "[r]eversal on account of error is not automatic but requires a showing of prejudice." *Sea "B" Mining Co. v. Addison*, 831 F.3d 244, 253 (4th Cir. 2016). This standard requires us to consider "'the likelihood that the result would have been different,' as well as how the error might impact the public perception of such proceedings." *Id.* (quoting *Sanders*, 556 U.S. at 407). This doctrine "prevents reviewing courts from becoming 'impregnable citadels of technicality'

and preserves the relative roles of courts and agencies in implementing substantive policy." *Id.* (quoting *Sanders*, 556 U.S. at 407).

Avail was on notice that youth access restrictions and run-of-the-mill marketing plans were inadequate in the fight against the youth vaping epidemic. *See id.* at 440–41. The 2020 Enforcement Guidance clearly highlighted that "focusing on *how* the product was sold would not appropriately address youth use" as "youth have continued to access [popular ENDS] products in the face of legal prohibitions and even after voluntary actions by some manufacturers." J.A. 110. In that same guidance, FDA found that while it "vigorously enforces the age verification requirements in its compliance check program," it "believes that age verification alone is not sufficient to address this issue." J.A. 133.

In the face of these warnings, Avail's marketing plan might have aided its application by presenting novel access restrictions beyond those that the FDA previously determined were not working. Instead, Avail's plan focused solely on age verification and avoiding marketing that would make its products attractive to youth. This was insufficient. *See Prohibition Juice*, 45 F.4th at 25 (explaining that "self-verification of age at the point of sale and . . . less vibrant marketing unappealing to youth" "track measures the FDA in its 2020 guidance deemed inadequate"); *Wages & White Lion*, 41 F.4th at 442 (noting the "FDA had already explained" that limiting products to "age-gated vape and specialty tobacco shops and through age-gated online sales" "do *not* work"); *Liquid Labs*, 52 F.4th at 544 (finding that "age verification measures, a mystery shopper program . . . and a prohibition on marketing material that could be perceived to be targeting individuals below

the legal vaping age . . . are similar, if not identical to the kinds of approaches the FDA found did not address this serious problem") (internal quotations omitted).

In short, even if FDA had reviewed Avail's marketing plan, it still would have issued a marketing denial order on petitioners' products. As the agency notes, nowhere did Avail identify *how* its marketing plan would provide "substantial mitigation efforts" which would "decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns" of marketing its products. J.A. 35, n.xix (Technical Project Lead Review). Whereas other manufacturers submitted unique access restriction plans designed to address this high burden, *see* Gov't Response Br. at 36, Avail did not. Thus, any error here was harmless. *See Prohibition Juice*, 45 F.4th at 25 (concluding petitioner failed to show that the consideration of its marketing plan "could have changed the agency's decision on their applications"); *Wages & White Lion*, 41 F.4th at 442 (finding that even if it was error to ignore an applicant's marketing plans, it was harmless because petitioners failed to "show that they would have received authorization had [the] FDA considered the[] plans"); *Liquid Labs*, 52 F.4th at 543 (declining to review an applicant's marketing plan "does not change the result because there is no indication that the plan would have made up for the deficiencies the FDA identified in [petitioner's] applications").

Finally, Avail errs in encouraging us to follow the Eleventh Circuit's decision in *Bidi Vapor LLC v. U.S. Food & Drug Administration*, which found arbitrary and capricious the FDA's decision not to review certain applicants' marketing plans. 47 F.4th 1991, 1195 (11th Cir. 2022). But petitioners in that case submitted novel marketing restrictions "not specifically mentioned in the 2020 Guidance" which merited a closer look by the agency.

Id. at 1205 (identifying a unique "Trace/Verify technology" and an "authentication system designed to prevent counterfeit products from becoming accessible to youth"). Avail nowhere identified truly novel restrictions beyond age verification and "nondescriptive" marketing that would tip the scales in its favor. And in all events, the sequencing of review by the FDA can hardly be termed arbitrary. Considering marketing questions before verifying the underlying safety of the product to be marketed is to put the cart before the horse.

IV.

A.

We see no merit in Avail's remaining arguments that FDA acted arbitrarily and capriciously in reviewing petitioners' PMTAs. Avail argues that the FDA was required to consider the distinction between open and closed systems when adjudicating its PMTAs. According to Avail, FDA's 2020 Enforcement Guidance focused on cartridge-based flavored ENDS products, and thus signaled to industry that open-system products, and the bottled e-liquids which accompany them, would be entitled to different treatment. As an initial matter, FDA *did* acknowledge the differences between products in its denial order, stating that "there may be differential appeal of certain product styles." J.A. 31; *see also Prohibition Juice*, 45 F.4th at 26. But even with these distinctions in mind, FDA determined that the scientific evidence shows that "the role of flavor is consistent" between open and closed systems. J.A. 31. It is not our job as a reviewing court to redo an agency's evaluation of relevant evidence. Indeed, we cannot "second guess an agency's reasonable choice of methodology." *American Whitewater v. Tidwell*, 770 F.3d 1108, 1116 (4th Cir.

2014). FDA's original focus on *enforcement* against cartridge-based ENDS products did not foreclose it from denying a marketing order for Avail's e-liquids, especially in light of the growing evidence that the role of flavors in driving youth initiation was consistent across products.

B.

We turn last to Avail's substantive challenge to the FDA's statutory authority. Petitioners argue that "FDA exceeded its statutory authority by imposing a new comparative efficacy standard that requires applicants seeking authorization to market flavored ENDS products to demonstrate that those products better promote smoking cessation than the appellant's otherwise identical tobacco flavored products." Pet'rs' Opening Br. at 2. We disagree and join the Third, Fifth, and D.C. Circuits in determining that FDA acted within its statutory mandate when it required applicants to submit such "comparative efficacy" evidence. *See Liquid Labs*, 52 F.4th at 542–43; *Wages and White Lion*, 41 F.4th at 434–35; *Prohibition Juice*, 45 F.4th at 19–20.

The TCA explicitly contemplates that FDA must embark on a comparative inquiry before allowing any marketing of a new tobacco product. First, as part of any PMTA, a manufacturer must include "full reports of all information . . . concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents *less risk* than other tobacco products." *See* Tobacco Control Act, § 910(b)(1), 123 Stat. at 1808 (emphasis added). Then, considering the information presented in the application, the FDA must "deny an application . . . if, upon the basis of the information submitted to the Secretary as part of the application . . . 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." § 910(c)(2)(A)., 123 Stat. at 1809. "In other words, the statute not only allows but expressly instructs the FDA to consider evidence regarding just the comparison that the manufacturers say the FDA lacks statutory authority to make." *Prohibition Juice*, 45 F.4th at 19.

And as part of the ultimate inquiry into whether an application is appropriate for the public health, the Secretary must also "tak[e] into account . . . the *increased or decreased likelihood* that existing users of tobacco products will stop using such products" on the one hand and "the *increased or decreased likelihood* that those who do not use tobacco products will start using such products" on the other. *See* Tobacco Control Act, § 910(c)(4)(A)–(B), 123 Stat. at 1810 (emphasis added). It would seem apparent that "nothing can 'increase' or 'decrease' in a vacuum" and thus this phrase "necessarily implies a comparative analysis." *Wages and White Lion*, 41 F. 45h at 434.

V.

Under the TCA, the FDA has the daunting task of ensuring that another generation of Americans does not become addicted to nicotine and tobacco products. The TCA gives FDA the flexibility to determine whether marketing of a new tobacco product is appropriate for the protection of public health, taking into account evolving science and an ever-changing market. FDA made the determination that Avail's flavored ENDS products, seeking in all respects to mimic those sweet treats to which youth are particularly attracted, pose a substantial risk of youth addiction without enough offsetting benefits to adult smokers. FDA could not allow young adults to perceive e-cigarettes as another Baby Ruth

or Milky Way, only to find themselves in the grip of a surreptitious nicotine addiction. This was hardly arbitrary. Substantial evidence supports the assertion that "[t]here is an epidemic of youth use of e-cigarette products, and flavored products like petitioners' are at the center of that problem." Gov't Response Br. 22. For the foregoing reasons, we deny Avail's petition.

DENIED