21-2840

IN THE UNITED STATES COURT OF APPEALS
FOR THE SEVENTH CIRCUIT

GRIPUM, LLC,

Petitioner,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondent.

On Petition for Review of a Final Marketing Denial Order
by the U.S. Food and Drug Administration

BRIEF FOR RESPONDENT

BRIAN M. BOYNTON
Principal Deputy Assistant Attorney General
Civil Division

ERIC B. BECKENHAUER
Assistant Branch Director

KATE TALMOR
Trial Attorney
Civil Division
Federal Programs Branch
U.S. Department of Justice
1100 L Street, NW
Washington, DC 20005
(202) 305-5267
kate.talmor@usdoj.gov

Of Counsel:

DANIEL J. BARRY
Acting General Counsel
Dep't of Health and Human Services

WENDY S. VICENTE
Acting Deputy Chief Counsel for Lit.
Food and Drug Administration

MARCI B. NORTON
Senior Counsel
Office of the Chief Counsel
Food and Drug Administration

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Cases: **Page(s)**

Statutes:

Other Authorities:

STATEMENT REGARDING ORAL ARGUMENT

Petitioner challenges an order of the U.S. Food and Drug Administration (FDA) denying its application for authorization to market certain "e-cigarette" products in flavors that are particularly attractive to youth, such as candy and fruit. After this Court granted petitioner's motion for a stay pending review, *see* Doc. 18 (Nov. 4, 2021), and the Fifth Circuit granted a stay pending review in a similar case, *see Wages & White Lion Invs., L.L.C. v. FDA*, 16 F.4th 1130 (5th Cir. 2021), the Sixth Circuit denied another manufacturer's analogous stay motion, *see Breeze Smoke, LLC v. FDA*, 18 F.4th 499 (6th Cir. 2021). That manufacturer then filed a stay application with the Supreme Court which, after considering FDA's response, denied the application without recorded dissent. *See Breeze Smoke, LLC v. FDA*, 142 S. Ct. 638 (2021). The Eleventh Circuit has since granted stays pending review in several similar cases, *see, e.g.*, *Bidi Vapor LLC v. FDA*, No. 21-13340 (Feb. 1, 2022).

Given the importance of the issues presented, the government respectfully requests oral argument.

INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act (TCA or Act) makes it unlawful for a manufacturer to market a "new tobacco product"—defined as a product that was not on the market as of February 15, 2007—without authorization from the U.S. Food and Drug Administration (FDA). The TCA requires FDA to deny an application to market a new tobacco product unless FDA finds that marketing the product would be "appropriate for the protection of the public health," taking into account the impact on both nonusers and existing users of tobacco products. 21 U.S.C. § 387j(c)(2), (4). Under this standard, an applicant must show a net benefit to public health based upon the risks and benefits to the population as a whole. In evaluating applications, FDA, among other things, weighs the risk that youth will start using a new tobacco product against the product's potential to help adults significantly reduce or cease their use of combustible cigarettes.

There is no dispute that electronic nicotine delivery systems—often referred to colloquially as "e-cigarettes"—are new tobacco products within the meaning of the TCA. FDA has granted applications to market certain tobacco-flavored e-cigarettes based on evidence that youth use of tobacco-

flavored products is limited and that such products may help adults switch from combustible cigarettes. But for e-cigarettes with flavors other than tobacco, "the risk of youth initiation and use is substantial" and well-documented. Appx. 17. To support a finding that the marketing of a flavored e-cigarette product is nonetheless appropriate for the protection of the public health, "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." *Id.*

Petitioner seeks to market flavored e-cigarettes that present a significant risk to youth. FDA reasonably concluded that petitioner had failed to adduce evidence establishing that the benefits of its products outweigh the well-documented risks. "FDA's denial of [petitioner's] application emphasized that the strong appeal of flavored [e-cigarette] products to youths required a showing of a 'substantial enough' 'magnitude of the likely benefit . . . to overcome the significant risk of youth uptake and use posed by the flavored [e-cigarette] product.'" *Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 506 (6th Cir. 2021) (third alteration in original).

There is no merit to petitioner's arguments that FDA's denial of petitioner's application announced a new evidentiary standard, failed to

consider relevant evidence, or was otherwise arbitrary and capricious or inconsistent with the TCA. FDA applied the standard articulated in the TCA and in prior and subsequent agency rules and guidance and reasonably concluded that petitioner's evidence failed to show that the marketing of these flavored e-cigarettes would be appropriate for the protection of the public health. Appx. 20-22; *Breeze Smoke*, 18 F.4th at 506-07.

STATEMENT OF JURISDICTION

On October 8, 2021, petitioner filed a timely petition for review of FDA's September 8, 2021, order denying petitioner's application to market certain new tobacco products. Short App. 8. This Court has jurisdiction under 21 U.S.C. § 387*l*(a)(1)(B).

STATEMENT OF THE ISSUE

Petitioner applied for FDA authorization to market certain e-cigarette products in flavors attractive to youth. The question presented is whether FDA properly denied petitioner's application because the evidence did not show that the serious risk that such products pose to youth is outweighed by a benefit to adults seeking to stop or significantly reduce smoking combustible cigarettes, and petitioner thus failed to demonstrate that the

marketing of the products would be appropriate for the protection of the public health.

STATEMENT OF THE CASE

I. Statutory Background

The Family Smoking Prevention and Tobacco Control Act established a comprehensive scheme for the regulation of tobacco products. Pub. L. No. 111-31, div. A, 123 Stat. 1776 (2009). The Act was predicated on Congress's finding that use of tobacco products by youth "is a pediatric disease of considerable proportions." TCA § 2(1), 123 Stat. at 1777. The TCA applies to products such as cigarettes and smokeless tobacco, as well as to other products made or derived from tobacco that FDA by regulation deems to be subject to the Act. 21 U.S.C. § 387a; *see also id.* § 321(rr)(1).

The TCA provision at issue here makes it unlawful for a manufacturer to introduce in interstate commerce any "new tobacco product" unless the manufacturer obtains premarket authorization from FDA. 21 U.S.C. § 387j(a)(1)-(2). The statute defines a "new tobacco product" as one that was not commercially marketed in the United States as of February 15, 2007, or that was modified after that date. *Id.* § 387j(a)(1).

The TCA requires that FDA "shall deny" a manufacturer's application to market a new tobacco product "if, upon the basis of the information submitted to [FDA] as part of the application and any other information before [FDA] with respect to such tobacco product," the agency "finds that . . . 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." 21 U.S.C. § 387j(c)(2). The TCA specifies that, in making that determination, FDA must evaluate "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product," taking into account 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." *Id.* § 387j(c)(4). Because "[v]irtually all new users of tobacco products are under the minimum legal age to purchase such products," TCA § 2(4), 123 Stat. at 1777, FDA (among other things) weighs the risk that a new tobacco product will promote youth initiation and use against the product's potential for helping adults who smoke combustible cigarettes switch to a less-dangerous alternative. In order to obtain

marketing authorization, an applicant must demonstrate a net benefit to public health taking such risks and benefits into account.[1]

II. Regulatory Background

1. E-cigarettes deliver nicotine, which is "among the most addictive substances used by humans," "by vaporizing a liquid that includes other chemicals and flavorings." *Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 270 (D.C. Cir. 2019). "The device heats the liquid until it generates an aerosol—or 'vapor'—that can be inhaled." *Id.*

The term "e-cigarettes" encompasses a variety of devices. Some devices have "pods" or "cartridges" that hold nicotine-containing liquid known as the "e-liquid." *See* Eunice Park-Lee et al., *Notes from the Field: E-Cigarette Use Among Middle and High School Students – National Youth Tobacco Survey, United States, 2021*, 70 Morbidity & Mortality Wkly. Rep. 1387, 1387 n.* (2021).[2] Some pods or cartridges (known as closed systems) come pre-filled with e-liquid and are replaced after the e-liquid is used up, while others

[1] The TCA provides a separate premarket authorization pathway for tobacco products that are substantially equivalent to products that were commercially marketed in the United States as of February 15, 2007. 21 U.S.C. § 387j(a)(2)(A)(i)(I). That pathway is not at issue here.

[2] https://go.usa.gov/xeGq5.

(known as open systems) can be refilled by the user. *Id*. Tank or "mod" (short for "modifiable") devices can also be refilled by users and are also usually customizable. *Id*. Petitioner sells bottled e-liquid products for use in open systems. Br. 6.

In 2016, FDA exercised its statutory authority to deem e-cigarettes and other products made or derived from tobacco to be subject to the TCA's requirements. 81 Fed. Reg. 28,974 (May 10, 2016). Most e-cigarettes were not on the market as of February 15, 2007, and thus meet the TCA's definition of a "new tobacco product" and became unlawful to market without FDA authorization after the rule's August 8, 2016, effective date. As a policy matter, however, FDA decided against immediate enforcement of that statutory prohibition for products on the market as of the rule's effective date. *Id.* at 28,977-78; *see also id.* at 29,011 n.13.

Through enforcement policies that FDA has revised over time, the agency has sought to strike a balance between the serious risk that e-cigarettes pose to youth and their potential benefit in helping adults quit or significantly reduce smoking combustible cigarettes. FDA has "repeatedly emphasized that the availability of non-combustible options should not come at the expense of addicting a generation of children to

nicotine through these same delivery vehicles." FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry* 38 (Apr. 2020) (2020 Guidance).[3] Moreover, FDA has "consistently informed industry that its compliance policies will be responsive to changed circumstances," *id*. at 35, and that "manufacturers cannot have settled expectations to market unlawful products, especially in the face of evolving public health concerns," *id*. at 36.

2. Initially, FDA announced that, for e-cigarettes already on the market as of the 2016 rule's effective date, the agency generally would not take enforcement action based on a product's lack of premarket authorization for a two-to-three-year period while manufacturers prepared, and FDA reviewed, marketing applications. 81 Fed. Reg. at 28,978. In 2017 guidance, FDA extended that period until 2022. *See* 2020 Guidance 5. Prior to that announcement, nationally representative data suggested that youth use of e-cigarettes had declined beginning in 2016. *Id*.

[3] https://go.usa.gov/xeG3C.

By late 2017, however, FDA began to see an alarming increase in the use of e-cigarettes by middle and high school students. 2020 Guidance 6. FDA therefore stepped up enforcement actions against products marketed to youth and against retailers that sold e-cigarettes to minors, *id.* at 6-7, and the agency sent letters directing manufacturers with significant market share to submit plans to help restrict minors' access to e-cigarettes, *id.* at 7. In response, manufacturers proposed safeguards such as age-verification technology for online sales, enhanced monitoring of retailer compliance with age-verification and sales restrictions, contractual penalties for retailers that failed to comply with such requirements, and limits on the quantity of e-cigarettes that a customer could purchase within a particular period of time. *Id.*

Nonetheless, in 2019, youth e-cigarette use hit the highest levels ever recorded. 2020 Guidance 8. FDA thus revised its enforcement policy. Although FDA continued to enforce sales restrictions, it concluded that "age verification alone is not sufficient to address this issue, given the most recent data that youth use of [e-cigarette] products continues to increase." *Id.* at 44. "The reality," FDA explained, "is that youth have continued access to [e-cigarette] products in the face of legal prohibitions and even

after voluntary actions by some manufacturers." *Id*. In part because many youth obtain their e-cigarette products from friends or other sources in their social networks, *id*. at 45, FDA determined that sales restrictions alone would "not be sufficient to address youth use of these products," *id*. at 44.

Instead of focusing solely on how an e-cigarette product is sold, FDA's 2020 policy prioritized enforcement against the types of products that were, at that time, especially popular among youth: flavored, cartridge-based e-cigarettes (other than tobacco-flavored or menthol-flavored products). 2020 Guidance 10. FDA emphasized the "extraordinary popularity" of flavored e-cigarette products with youth, *id*. at 13, noting that 93% of e-cigarette users aged 12-17 reported that their first e-cigarette was a flavored product, and that 71% of youth users indicated they used e-cigarettes "because they come in flavors I like," *id*. at 14. FDA also explained that the leading e-cigarette brand at that time (JUUL) was a cartridge-based product that commanded 70% of the market and that features of cartridge-based products made them especially easy to use and conceal, and thus particularly attractive to youth. *Id*. at 15-16. And while FDA focused its concern at that point on particular types of cartridge-based products, it made clear that it would "make enforcement decisions on a

case-by-case basis" and that it "retains discretion to pursue enforcement action at any time against any deemed new tobacco product marketed without premarket authorization." *Id.* at 11.

Although the 2020 enforcement policy led to the removal of many flavored products from the market and contributed to a decline in youth use, use of e-cigarettes by children and adolescents has remained at levels comparable to those that originally led FDA to declare a youth vaping epidemic. *See* Appx. 12. The market exit of flavored, cartridge-based e-cigarettes led to a substantial rise in youth use of disposable e-cigarettes, which had largely been excluded from the 2020 enforcement policy because, at the time that policy was developed, those products were not commonly used by youth. Appx. 14-15. As FDA recognized, "[t]his trend illustrates that the removal of one flavored product option" can prompt "youth to migrate to another [e-cigarette] type that offer[s] the desired flavor options, underscoring the fundamental role of flavor in driving appeal." Appx. 15.

3. Shortly before September 9, 2020, FDA received a large volume of applications to market e-cigarette products. That influx resulted in part from a court-ordered deadline in an action brought by public-health

organizations. *See American Acad. of Pediatrics v. FDA*, 399 F. Supp. 3d 479 (D. Md. 2019), *appeal dismissed sub nom. In re Cigar Ass'n of Am.*, 812 F. App'x 128 (4th Cir. 2020). That court observed that, "however laudable the FDA's intended regulatory response is, the record before me shows a purposeful avoidance by the industry of complying with the premarket requirements despite entreaties from the FDA." *Id.* at 485. The court thus directed FDA to require manufacturers to submit applications for premarket authorization within ten months of its order—a date later extended to September 9, 2020, as a result of the pandemic—and provided that products for which timely applications had been submitted could remain on the market without being subject to FDA enforcement action for up to a year. *Id.* at 487.[4]

FDA has acted on many of those applications. To date, the applications that FDA has granted have been for tobacco-flavored e-cigarette products. *See* FDA, *Technical Project Lead Review for Applications Submitted by R.J.*

[4] The court later clarified that its order did not restrict FDA from taking enforcement action during the application review period. Order, *American Acad. of Pediatrics v. FDA*, No. 18-883 (D. Md. Aug. 12, 2019), Doc. No. 132.

Reynolds Vapor Company (Oct. 12, 2021).[5] In authorizing the marketing of those products, FDA determined that youth interest in tobacco flavors is low. *Id*. at 17 (citing a 2020 nationwide survey finding that the prevalence of tobacco-flavored e-cigarette use was 2.9% among 10th and 12th graders). FDA also found evidence that established cigarette users had the "highest purchase intent" for tobacco-flavored products under review. *Id*. FDA thus concluded that the applicant had demonstrated that current adult smokers are particularly interested in the new tobacco-flavored products to assist in intended switching from combustible cigarettes, and that those products have the potential to benefit that group as compared to continued exclusive use of combustible cigarettes. *Id*. at 4. After conducting a scientific review, FDA found that permitting the marketing of those tobacco-flavored products would be appropriate for the protection of the public health. *Id*.

In contrast to tobacco-flavored e-cigarettes, FDA has explained that e-cigarettes in other flavors, such as fruit or dessert, present a significant risk to youth that is well documented by nationally representative studies. *See, e.g.*, Appx. 13. Thus, for FDA to find that the marketing of such

[5] https://go.usa.gov/xef5N.

products is appropriate for the protection of the public health, applications to market flavored products must show that this significant risk to youth is outweighed by likely benefits to existing users of tobacco products "substantial enough such that the net impact to public health would be positive." Appx. 16-17. "[A]s the known risks [of a product] increase, so too does the burden of demonstrating a substantial enough benefit" to support the finding of a net positive effect. *Id.* FDA has denied applications to market e-cigarette products on the ground that certain manufacturers have failed to submit evidence that satisfies the statutorily required showing.

III. FDA's Denial Of Petitioner's Application To Market Flavored E-Cigarette Products

Since 2013, petitioner has manufactured and distributed flavored liquids for use with e-cigarette products. Br. 6. On September 7, 2020, petitioner submitted its application to market hundreds of flavored e-liquids, including "Peanut Butter Milk Pie," "Sugar Cookie," and "Lemon Muffin Cupcake." *Id.*; Short App. 3-5. In reviewing petitioner's application, FDA first determined that flavored e-cigarette products of this type present a significant and well-documented risk to youth, Appx. 12-16, and reiterated the determination made in the 2020 guidance that the agency is "not aware

of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use [e-cigarettes]," Appx. 18 n.xix. FDA then considered whether petitioner provided robust and reliable evidence showing that its products would provide a benefit to adult smokers by facilitating switching or significantly reducing their use of combustible cigarettes. Appx. 17-20. In particular, the agency looked for evidence demonstrating that petitioner's specific products would provide an added benefit to adult smokers relative to tobacco-flavored products, which do not present the same risk to youth. *Id.*

In its application petitioner relied on a literature review summarizing scientific studies on the use of e-cigarettes generally, *see* Appx. 39-110 (providing excerpts of submitted materials), and surveys collecting consumer intentions, perceptions, and patterns of use regarding e-cigarette products. *Id.*; Appx. 21. Neither the studies nor the surveys tested, discussed, or in any way referenced petitioner's products.

FDA concluded that petitioner's evidence, as well as other evidence reviewed by the agency, did not support a finding that petitioner's flavored products would provide a sufficient benefit to adult users relative to their risk to youth. FDA noted that, although the application referenced

randomized controlled trials and longitudinal cohort studies, those studies did not evaluate petitioner's products or compare them to tobacco-flavored products. Appx. 21. Indeed, the trials "did not sufficiently demonstrate the relative effect of the flavored products as compared to a tobacco-flavored product" or include results "assessing switching or cigarette reduction" from petitioner's products. *Id.* Petitioner's data was thus "insufficient to evaluate the magnitude of the potential benefit to adult users that is needed" to meet the statutory standard. *Id.*

FDA also reviewed a significant body of literature concerning studies and surveys of e-cigarette use and abuse. Based on this review, FDA concluded that "the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive," and "the literature does not establish that flavors differentially promote switching amongst [e-cigarette] users in general." Appx. 18. FDA thus denied petitioner's application because the evidence failed to show that the marketing of its flavored products would be appropriate for the protection of the public health. Appx. 21-22.

IV. Manufacturers' Requests For Emergency Relief

Petitioner sought review in this Court on October 8, 2021 and, nine days later, filed an emergency motion for a stay pending review. Doc. 5 (Oct. 17, 2021). FDA timely opposed petitioner's motion and, on November 4, 2021, this Court entered an order (without separate opinion) granting petitioner's request for a stay pending review. Doc. 18.

Both the Supreme Court and other courts of appeals have considered analogous stay motions. On October 26, 2021, the Fifth Circuit granted a stay pending review, concluding that the petitioner was likely to succeed on the merits. *Wages & White Lion Invs., L.L.C. v. FDA*, 16 F.4th 1130 (5th Cir. 2021). But several weeks later the Sixth Circuit reached a contrary result, concluding in a published opinion that the petitioner "ha[d] not made a strong showing" that FDA failed to consider relevant factors. *Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 503 (6th Cir. 2021). In particular, the court determined that FDA had not departed from its prior statements regarding the evidence required to support a marketing application: FDA's 2019 guidance explained that the agency "*might* accept evidence other than long-term studies, if that evidence had sufficient scientific underpinnings to meet the TCA's statutory mandate of demonstrating that flavored

[e-cigarettes] are appropriate for the protection of public health." *Id.* at 506-07. And FDA reasonably "found [the] evidence lacking against this standard," *id.* at 507, because neither the literature nor petitioner's survey data provided evidence of potential benefits sufficient to overcome FDA's finding of "clear and consistent patterns of real-world use showing youth initiation of flavored [e-cigarettes] products," *id.* at 506 (quotation marks omitted).[6] The unsuccessful manufacturer then filed a stay application with the Supreme Court, which, after considering FDA's opposition, denied the application without recorded dissent. *See Breeze Smoke, LLC v. FDA*, 142 S. Ct. 638 (2021). That petitioner subsequently moved to dismiss its petition for review, and the Sixth Circuit granted the motion. Motion to Voluntarily Dismiss, *Breeze Smoke, LLC v. FDA*, No. 21-3902 (6th Cir. Feb. 10, 2022), Doc. 39; Order Granting Dismissal, Doc. 40-1. The Eleventh Circuit has entered a summary order (over the dissent of one panel member) granting several requests for stays pending review, *see, e.g.*, *Bidi Vapor LLC v. FDA*, No. 21-13340 (Feb. 1, 2022).

[6] A dissenting judge would have granted a stay for the reasons provided by the Fifth Circuit. *Breeze Smoke*, 18 F.4th at 508-09 (Kethledge, J., dissenting).

SUMMARY OF ARGUMENT

I. There is an epidemic of youth use of e-cigarettes, and flavored products like petitioner's are at the center of that problem. While measures to restrict youth access to e-cigarettes are important and have been required in granting marketing authorization for certain other tobacco products, FDA's experience has shown such restrictions alone to be insufficient to reduce youth initiation and use. 2020 Guidance 44. Many youth obtain their e-cigarettes through friends, *id.* at 45, and youth e-cigarette use has reached record levels despite industry efforts to restrict access and rigorous FDA enforcement of such measures, *id.* at 7-8. Against the backdrop of that experience demonstrating the limitations of sales access restrictions, FDA reasonably determined that petitioner's proposed sales restrictions would not be sufficient to tip the balance between adult benefit and youth risk.

II. Because the risks of flavored e-cigarettes are well established, the showing needed to demonstrate that the marketing of these products is appropriate for the protection of the public health is demanding. FDA examined petitioner's application for evidence that its specific flavored e-cigarette products would provide a countervailing benefit to adult

smokers greater than the benefit provided by other, lower-risk products, and it found petitioner's evidence wanting. FDA explained that the materials submitted by petitioner and the literature it reviewed did not suffice to make the required showing 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." Appx. 18. Taking into account the risks and benefits to the population as a whole, FDA determined that petitioner had not carried its burden of establishing that marketing its flavored products would be appropriate for the protection of the public health, as required by the TCA.

Contrary to petitioner's contentions, FDA was not required to promulgate regulations before adjudicating e-cigarette marketing applications, and FDA did not announce a new evidentiary standard in reviewing petitioner's evidence. On the contrary, FDA's approach in denying petitioner's application was consistent with the agency's 2021 final rule and earlier statements of policy. As another court of appeals recently observed, a 2019 FDA guidance explained that the agency "*might* accept evidence other than long-term studies, if that evidence had sufficient

scientific underpinnings to meet the TCA's statutory mandate of demonstrating that flavored [e-cigarettes] are appropriate for the protection of public health." *Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 506-07 (6th Cir. 2021). And FDA reasonably "found [petitioner's] evidence lacking against this standard," *id.* at 507, because the literature submitted by petitioner did not provide evidence specific to its products of potential benefits sufficient to overcome FDA's finding of "clear and consistent patterns of real-world use showing youth initiation of flavored [e-cigarette] products," *id.* at 506 (quotation marks omitted). Because FDA did not change course with respect to its interpretation of the TCA's public-health standard, there was no prior interpretation on which manufacturers might have relied, and the agency therefore was not obligated to consider any such reliance.

FDA likewise did not adopt a new "tobacco product standard" that required notice-and-comment rulemaking pursuant to 21 U.S.C. § 387g(a)(3). Congress specifically directed FDA to adjudicate marketing applications to determine whether they meet the public-health standard established in § 387j(c), and FDA did so here. The process that Congress established—and that FDA followed—for adjudicating marketing

applications is distinct from the authority granted to FDA to promulgate tobacco product standards.

STANDARD OF REVIEW

FDA's denial of an application to market a new tobacco product is reviewed under the familiar, deferential standards established by the Administrative Procedure Act and may be held unlawful and set aside only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2); *see* 21 U.S.C. § 387*l*(b). Review under that standard "is narrow and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

ARGUMENT

Notably absent from petitioner's brief is any reference to Congress's command that FDA "shall deny" an application to market new tobacco products absent a showing that they are appropriate for the public health. 21 U.S.C. § 387j(c)(2). Far from the "amorphous concept" petitioner suggests, Br. 18, Congress set forth in the TCA a sensible scheme that places the burden on manufacturers to marshal evidence demonstrating that a product's risks outweigh its benefits, "taking into account" both "the

increased or decreased likelihood that existing users . . . will stop" using tobacco products and "the increased or decreased likelihood that those who do not use tobacco products will start." 21 U.S.C. § 387j(c)(4). FDA found that petitioner's application to market e-cigarettes in flavors attractive to children failed to contain such evidence; petitioner's challenges to that determination are meritless.

I. FDA Reasonably Determined That Flavored E-Cigarettes Pose A Serious Risk To Youth That Is Not Adequately Mitigated By Marketing Restrictions Of The Type Petitioner Proposed

A. There is an epidemic of youth use of e-cigarettes

Because the TCA requires FDA to consider a new tobacco product's effect on the population as a whole, taking into account 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," 21 U.S.C. § 387j(c)(4), FDA reasonably began its analysis by considering the risks of flavored e-cigarettes to nonusers, particularly youth. FDA explained that the "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," and that

"almost 90 percent of adult daily smokers started smoking by the age of 18." Appx. 12; *see also* Appx. 15 (explaining that "[y]outh and young adult brains are more vulnerable to nicotine's effects than the adult brain due to ongoing neural development").

FDA further explained that significant long-term health consequences are associated with youth-initiated e-cigarette use. The nicotine in e-cigarettes can have permanent effects on the developing adolescent brain and can "induce short and long-term deficits in attention, learning, and memory." Appx. 15. Studies also have shown associations between e-cigarette use and "asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease." Appx. 16. Moreover, those who use e-cigarettes during childhood or adolescence are significantly more likely to begin using combustible cigarettes, raising concerns that, over time, the "trend of declining cigarette smoking could slow or even reverse." *Id.* Given the scientific consensus on the risks of flavored e-cigarettes and the "lifelong implications" of e-cigarette use by youth, FDA determined that "preventing tobacco use initiation in young people is a central priority for protecting population health." Appx. 13.

Despite these risks, youth use of e-cigarettes has exploded. From 2017 to 2018, the number of high-school-age youth reporting use of e-cigarettes rose by more than 75%, and use among middle-school-age youth increased nearly 50%. FDA, *Results From 2018 National Youth Tobacco Survey Show Dramatic Increase in E-Cigarette Use Among Youth Over Past Year* (Nov. 15, 2018);[7] *see* Appx. 16 (noting the "exponential growth in youth [e-cigarette] use observed from 2017 to 2019"). While this use declined somewhat following FDA's 2020 enforcement efforts, youth e-cigarette use remains at epidemic levels.[8] *See* Appx. 12 & n.ix. In 2020, approximately 19.6% of U.S. high school students and 4.7% of middle school students—roughly 3.6 million children and adolescents—were current users of e-cigarettes, making e-cigarettes "the most widely used tobacco product among youth by far." Appx. 13.

[7] https://perma.cc/9C3U-XSXT?type=image.

[8] Petitioner asserts that youth use "hardly approaches the 'epidemic' which FDA . . . perceive[s]," claiming that recent data "shows that only 3.1% of high school students and 0.2% of middle school students were '*daily users*' of" e-cigarettes. Br. 57-58 (emphasis added). Even putting aside that petitioner cites an extra-record industry-trade publication as support, youth use of e-cigarettes may appropriately be measured by use within the past 30 days or other usage patterns aside from *daily* use.

FDA found that flavors play a significant role in driving youth e-cigarette use. There is strong evidence that flavors encourage youth to begin experimenting with e-cigarettes and also promote more frequent and sustained use. Appx. 13-14. In a 2016-2017 study, "93.2% of youth and 83.7% of young adult [e-cigarette] users reported that their first [e-cigarette] was flavored," and 71% said they used e-cigarettes "because they come in flavors I like." Appx. 13. Similarly, in 2020, 84.7% of high school e-cigarette users and 73.9% of middle school users reported using a flavored product. *Id.* The majority of middle and high school users (over 70%) reported using fruit-flavored e-cigarettes, while others used flavors including "candy, dessert, or other sweets." *Id.*

FDA also considered studies showing that "[t]he role of flavors in increasing the appeal of tobacco products to youth—across tobacco product categories—is well-established in the literature." Appx. 14.[9] The

[9] Deepa R. Camenga et al., *Appeal and Use of Customizable E-Cigarette Product Features in Adolescents*, 4 Tobacco Reg. Sci. 51-60 (Mar. 2018); M.B. Harrell et al., *Flavored E-Cigarette Use: Characterizing Youth, Young Adult, and Adult Users*, 5 Preventive Med. Rep. 33-40 (2017); J.K. Pepper et al., *Adolescents' Interest in Trying Flavoured E-Cigarettes*, 25 Tobacco Control ii62-ii66 (Sept. 15, 2016); Carrie M. Carpenter et al., *New Cigarette Brands with Flavors That Appeal to Youth: Tobacco Marketing Strategies*, 24 Health Affairs 1601-10 (2005).

2020 National Youth Tobacco Survey—a large, cross-sectional survey of middle and high school students—shows that, "within the [e-cigarette] category, there is variability in the popularity of device types among youth" but, "across these different device types, the role of flavor is consistent." *Id.* While it appears "that the preference for device types . . . is likely fluid," such that "the removal of one flavored product option prompt[s] youth to migrate to another [device] type that offer[s] the desired flavor options," Appx. 14-15, youth preference for flavors is consistent across device types, Appx. 14. These studies "underscor[e] the fundamental role of flavor in driving appeal." Appx. 15. For example, when pod-based flavored e-cigarettes became less readily available, there was a substantial rise in youth use of disposable flavored e-cigarettes. *Id.*

B. FDA reasonably determined that sales access restrictions do not sufficiently reduce youth use of flavored e-cigarettes

Petitioner brushes aside the voluminous evidence linking youth e-cigarette initiation to flavored-product availability, claiming that the data on which FDA relied is inapplicable because petitioner sells only open-system e-liquids in age-limited retail establishments. *See, e.g.*, Br. 55-56. But FDA reasonably concluded that youth-access restrictions of this type could

not tip the scale in favor of petitioner's application. FDA made that determination against the backdrop of the agency's 2020 guidance, which details efforts by FDA and manufacturers to reduce youth access to e-cigarettes and documents the inadequacy of such measures. The 2020 guidance, which is discussed in FDA's review of petitioner's application, *see* Appx. 11-12, explains that, from April 2018 to August 2019, the agency sent more than 6,000 warning letters and more than 1,000 civil money penalty complaints to online and brick-and-mortar retailers for illegal sales of e-cigarettes to minors. 2020 Guidance 8. FDA also asked manufacturers to propose measures they could implement to help restrict youth access to e-cigarettes. The proposed measures included the use of age-verification technology for online sales, enhanced monitoring of retailer compliance with age-verification requirements, and contractual penalties for retailers that failed to comply with sales restrictions. *Id.* at 7.

Youth e-cigarette use continued to increase notwithstanding these efforts. 2020 Guidance 8, 22. Evidence from this period shows that the vast majority of youth do not buy e-cigarettes themselves but instead obtain them from others. The 2018 National Youth Tobacco Survey found that 72.6% of youth e-cigarette users reported obtaining e-cigarettes from a

"social source," such as a friend or family member, while only 11.4% of youth users had purchased tobacco products themselves within the past thirty days. *See* Sherry T. Liu et al., *Youth Access to Tobacco Products in the United States, 2016-2018*, 5 Tobacco Reg. Sci. 491-501 (Nov. 2019).[10] This pattern complicates enforcement efforts and shows that sales access restrictions alone do not suffice to stem the tide of youth e-cigarette use. "The reality is that youth have continued access to [e-cigarette] products in the face of legal prohibitions and even after voluntary actions by some manufacturers." 2020 Guidance 44; *see id.* at 21.

Contrary to petitioner's assertions, FDA did not ignore the potential impact of access restrictions in assessing petitioner's application. FDA recognized that 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." Appx. 18 n.xix. And where FDA has granted marketing authorization for other tobacco products, those grants have been conditioned on certain marketing restrictions. But given the magnitude of the problems "regarding youth use" of flavored e-

[10] https://go.usa.gov/xeGZH.

cigarettes, FDA explained in denying petitioner's application that no known "advertising and promotion restrictions" have been identified that would "decrease appeal to youth to a degree significant enough to address and counter-balance" such "substantial concerns." *Id.* Under these circumstances, and in light of FDA's independent determination that petitioner had not submitted sufficient evidence of benefits to adults from its specific products (as discussed below), FDA reasonably determined that advertising and sales access restrictions would not tip the balance between adult benefits and youth risks and therefore would not alter FDA's conclusion as to whether the marketing of petitioner's products would be appropriate for the protection of the public health. *See id.*

Petitioner does not claim to have proposed to FDA any novel or materially improved access restrictions relative to those measures that FDA had indicated in 2020 were inadequate to prevent youth use. Instead, petitioner rests its argument solely on the assertion that there is a "negligible" risk "that youth will acquire Gripum's flavored E-Liquids from the age-restricted retailers who sell its products." Br. 56. Petitioner's assertion lacks evidence and also misses the point—that most youth do not buy e-cigarettes directly and youth access has persisted despite restrictions

of this type. In contrast, other manufacturers have proposed using novel technologies that they claim have the potential to lock devices against underage users, which may significantly reduce youth use of such products. *See* Jennifer Maloney, *Juul Pitches Locked E-Cigarette in Bid to Stay on U.S. Market*, Wall Street J. (Feb. 24, 2020). Petitioner does not assert that its application proposed restrictions of that type.

Given that petitioner does not claim to have proposed access measures different from those that FDA previously found inadequate to "counter-balance" the very serious youth vaping problem, Appx. 18 n.xix, and that petitioner's evidence failed to demonstrate a sufficient benefit to adult smokers, there is no basis to credit petitioner's argument that FDA arbitrarily applied generalized presumptions, rather than an individualized adjudication, to its application, *contra* Br. 54-60.

Petitioner also places significant reliance on its portrayal of FDA's "own retail compliance data" (*i.e.*, enforcement actions), which, according to petitioner, provides "widely accepted evidence that youths use [e-cigarettes] for their nicotine, not their flavors," and "establishes that youths" neither "favor bottled E-Liquids" nor purchase them from age-restricted retailers. Br. 8, 56, 61. FDA's enforcement data is not part of the

administrative record and thus not properly before the Court for consideration.[11] Even were the Court to consider this data, it does not support petitioner's arguments; that petitioner's products may not yet have been the target of FDA enforcement actions says nothing about whether they are appropriate for the protection of public health. And the fact that FDA may have focused its limited enforcement resources on certain types of products or retailers does not bear on the question whether petitioner's products meet the statutory standard. The evidence in any event shows that flavors in e-cigarettes drive youth use across device types, Appx. 14-15, and that most youth obtain e-cigarettes from friends, rather than purchasing them directly, thereby underscoring the reasonableness of FDA's determination.

[11] Petitioner's brief contains copious citations to non-record sources that should not be considered in deciding this petition. *E.g.*, Br. 10 (citing journal publication *from 1976*, proposing "a new approach to safer smoking," for the proposition that "people smoke for the nicotine but die from the tar"); Br. 57-58 (citing vaping-industry trade publication to dispute FDA's finding of a youth vaping epidemic).

II. FDA Reasonably Determined That Petitioner Failed To Submit Robust and Reliable Evidence Sufficient to Outweigh Its Products' Substantial Risk To Youth

A. FDA adequately considered the sufficiency of the evidence of benefits to adult smokers

As discussed above, the TCA directs FDA to deny an application to market a new tobacco product unless the manufacturer demonstrates that marketing the product would be "appropriate for the protection of the public health," taking into account 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." 21 U.S.C. § 387j(c)(2), (4). Consistent with that standard, FDA has "repeatedly emphasized that the availability of non-combustible options" that could potentially benefit existing users of tobacco products "should not come at the expense of addicting a generation of children to nicotine through these same delivery vehicles." 2020 Guidance 38. As FDA explained, "as the known risks" of a product "increase, so too does the burden of demonstrating a substantial enough benefit." Appx. 16-17. "[T]he expectations for scientific evidence related to potential adult benefit" thus "vary based on demonstrated risk to youth," and manufacturers of products that present a particularly

significant risk to youth have to make a stronger showing of benefits to existing users in order to satisfy the statutory standard. Appx. 18.

FDA reasonably determined that the evidence provided did not show that petitioner's flavored e-cigarette products likely provide a sufficient benefit to existing users of tobacco products to outweigh the significant and well-documented risk to youth. "Given the known and substantial risk of flavored [e-cigarettes] with respect to youth appeal, uptake, and use," FDA concluded that petitioner could satisfy its burden of showing that the marketing of its flavored products would be appropriate for the protection of the public health only by providing "reliable and robust evidence of a potential benefit to adult smokers that could justify that risk" to youth. Appx. 10 (. In light of the lower risk to youth posed by tobacco-flavored e-cigarettes, some of which now have marketing authorization, *see* FDA, *FDA Permits Marketing of E-Cigarette Products, Marking First Authorization of Its Kind by the Agency* (Oct. 12, 2021),[12] FDA looked for evidence that petitioner's flavored products would provide a benefit to adult smokers relative to the benefit already provided by these lower-risk products.

[12] https://go.usa.gov/xef5Q.

Although FDA explained that "evidence generated using either a[] [randomized controlled trial] design or longitudinal cohort study design is mostly likely to demonstrate such a benefit," the agency emphasized that "other types of evidence could be adequate if sufficiently reliable and robust, and will be evaluated on a case-by-case basis," Appx. 19, and it considered the strength of petitioner's evidence. Contrary to petitioner's suggestion (Br. 27-29, 42 n.56), FDA denied petitioner's application *not* because it failed to include a randomized controlled trial or longitudinal cohort study but because it failed to include *any* evidence robust enough to carry petitioner's burden under the statute.[13] Appx. 21-22.

There is no merit to the contention that FDA failed to explain why the studies cited in petitioner's application were not sufficiently robust to satisfy the TCA. *See* Br. 29-30. FDA explicitly found that, "although the [application] include[s] a [randomized controlled trial] and longitudinal

[13] Petitioner urges that "[u]ltimately . . . this appeal is also about whether the lives of Gripum's customers—adults who wish to quit smoking—will be sacrificed." Br. 5. This assertion is unfounded: Petitioner has not provided evidence supporting any positive health effects from its products, much less life-saving benefits. And its argument ignores the availability of tobacco-flavored e-cigarettes that have marketing authorization as well as drugs approved for smoking cessation.

cohort study," those studies "did not include the actual use of the new products or compare tobacco-flavored products to other flavored products" and "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." Appx. 21. Petitioner submitted only general academic publications that neither evaluated nor even referenced its specific products,[14] and FDA reasonably concluded that such generic, non-product-specific evidence was insufficient to carry petitioner's statutory burden.

Petitioner cites (Br. 5, 29 n.47, 31) a superseded memorandum in which FDA considered whether, for flavored e-cigarettes, any application that did not contain a randomized controlled trial or a longitudinal cohort study should "likely receive a marketing denial order" because other types of evidence would be insufficient to carry the applicant's burden. Appx. 224.

[14] Elsewhere petitioner disputes FDA's conclusion that a youth vaping epidemic exists and criticizes FDA for relying on studies of youth initiation that did not explicitly state whether children were using Gripum's particular flavored products or those of a competitor. Br. 54, 57-58. As explained *supra* n.16, FDA relied on such studies because they are accepted as a matter of scientific consensus and strongly support the conclusion that youth initiation is driven by the desire for flavored products and fluid between brands.

According to petitioner, FDA "employed a secret 'fatal flaw' inquiry," rather than "an individualized review of the substance of Gripum's [application]," whereby it categorically denied applications without further review solely due to the absence of a randomized controlled trial or a longitudinal cohort study demonstrating a product's benefits over time. Br. 5-6. But FDA rescinded that approach before acting on petitioner's application. *See* Appx. 256. And the record confirms that FDA looked for "other evidence" that petitioner submitted about its products establishing a benefit to adults and found none that sufficed to support the statutorily required showing. Appx. 10 & n.vi (making clear FDA would also "consider evidence from another study design if it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time").

Other portions of the record likewise make clear that FDA's review was not limited to determining whether petitioner submitted a randomized controlled trial or longitudinal cohort study. *See, e.g.*, Appx. 20 (explaining that FDA looked for randomized controlled trials, longitudinal cohort studies, "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 [e-cigarette] over an appropriate comparator tobacco-flavored [e-cigarette]").[15]

FDA also reviewed the published literature regarding e-cigarette benefits and concluded that, "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." Appx. 18. FDA observed that "the findings are quite mixed and as a result the literature does not establish that flavors differentially promote switching amongst [e-cigarette] users in general." *Id.*; *see also Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 506 (6th Cir. 2021) (finding the "literature review offers mixed findings on flavored [e-cigarette] products"). Even assuming

[15] Petitioner likewise urges that FDA "grossly miscalculated the volume of [applications] it expected and was inundated when reality far outpaced its expectancy" and thus decided to "serially rubber-stamp marketing denials." Br. 46. Again, FDA did not follow this approach. Regardless, it is not unlawful for a federal agency to strive to act expediently to fulfill a statutory mandate. *Cf. Allied Local & Reg'l Mfrs. Caucus v. U.S. EPA*, 215 F.3d 61, 78 (D.C. Cir. 2000) (holding that it was "regulatory common sense" for federal agency to consider "'regulatory efficiency and program considerations'" where Congress did not prohibit doing so (quoting 63 Fed. Reg. 48,792, 48,794 (Sept. 11, 1998)).

arguendo that published studies may provide some indication that flavored e-cigarettes in general may promote switching, the scientific literature as a whole is "far from conclusive" in this respect. Appx. 18. FDA reasonably concluded that the "heterogeneity" of this literature is likely due at least in part "to differences in the products studied," meaning that even if some e-cigarettes provide meaningful benefits, others may not, and product-specific evidence is therefore needed to support a marketing application.[16] *Id.* As explained above, petitioner failed to provide *any* such product-specific evidence and thus failed to carry its burden of showing that the marketing of its products would be appropriate for the protection of the public health.

B. FDA did not announce a new standard in denying petitioner's application

Petitioner claims that FDA acted unlawfully by failing to adopt ascertainable standards before adjudicating premarket applications and by

[16] By contrast, "FDA relied on literature concerning flavored [e-cigarette] products' appeal to youths because those risks are understood as a matter of scientific consensus." *Breeze Smoke*, 18 F.4th at 508. FDA also explained why these risks extend to petitioner's products, given that the "preference for device types and popularity of certain styles is likely fluid and affected by the marketplace." Appx. 14.

purportedly adopting new evidentiary standards unsupported by statute. Neither contention has merit.

1. First, FDA was not required to issue a rule setting premarket-application standards and metrics before adjudicating manufacturers' submissions. Petitioner insists that FDA cannot adjudicate its application in a non-arbitrary manner because the agency "never published guidance or a final [premarket tobacco product application] rule which articulated any threshold standards for" meeting the Act's mandate. Br. 35. But the Tobacco Control Act itself prescribes the standards manufacturers must meet before marketing new tobacco products, and nothing in the statute obligates FDA to impose further or more-detailed requirements before reviewing applications.

Although the TCA authorizes FDA to elaborate on the form and manner of premarket-authorization submissions, it imposes no duty on the agency to do so. In contrast, when Congress wanted to require FDA to issue regulations implementing the Act, it used unmistakably clear language directed at the agency, as where it provided in another subparagraph of the same statutory section that FDA "shall issue regulations to implement this paragraph." 21 U.S.C. § 387e(j)(3)(B); *see also id.* § 387k(*l*)(1) (providing that

"the Secretary shall issue regulations or guidance (or any combination thereof) on the scientific evidence required for assessment and ongoing review of modified risk tobacco products").

There is no merit to petitioner's contention that, in the absence of a rulemaking, it "was left to speculate as to exactly what FDA would require when determining the benefits, risks and likelihoods set forth in 21 U.S.C. § 387j(c)." Br. 37. The TCA itself describes the information to be submitted and the substantive showing required. 21 U.S.C. § 387j(c)(4). That other manufacturers successfully have obtained premarket authorization for e-cigarettes and other tobacco products confirms that manufacturers are not stymied by a lack of adequate information to support the preparation and submission of premarket applications. *See American Acad. of Pediatrics v. FDA*, 399 F. Supp. 3d 479, 485 (D. Md. 2019) (rejecting as "disingenuous[]" the cigar industry's related contention "that it cannot complete its applications without further formal guidance" regarding premarket review).[17]

[17] Similarly, petitioner's repeated insistence that FDA's review of flavored-product applications "has resulted in a *de facto* product ban," *e.g.*, Br. 46, is factually inaccurate. Marketing applications for numerous

Contrary to petitioner's assertions (*e.g.*, Br. 35), Congress provided guiding principles when it directed FDA to evaluate "the risks and benefits to the population as a whole, including users and nonusers," weighing "the increased or decreased likelihood that existing users of tobacco products will stop" against "the increased or decreased likelihood that those who do not use tobacco products will start." 21 U.S.C. § 387j(c)(4). FDA need not define precisely "how likely is likely," Br. 37, before effectuating that command because Congress granted the agency flexibility to determine how best to weigh these competing concerns. Equally flawed are petitioner's complaints that FDA failed to indicate "how effective is effective?," whether "the term 'population as a whole' include[s] or exclude[s] those under age 21?,"[18] in which specific devices petitioner's

---

flavored e-cigarette products have moved forward for further scientific review and remain pending before the agency. *See, e.g.*, Motion for Voluntary Dismissal, *Turning Point Brands, Inc. v. FDA*, No. 21-3855 (6th Cir. Oct. 8, 2021), Doc. No. 19 (premising request for dismissal on fact that marketing applications remain under agency review).

[18] Petitioner charges FDA with having "secretly chosen to include those under age 21 when measuring the risks of flavored E-Liquids but then exclude them when measuring a product's benefits." Br. 37 n.51. It is no secret that the "population as a whole," including "those who do not use tobacco products," includes minors. 21 U.S.C. § 387j(c)(4). And surely petitioner is not suggesting FDA should consider benefits of youth using its

e-liquids should be tested and at what concentrations, and "the control and variable parameters for the testing," such as "device temperature ranges." Br. 36-38. FDA's marketing denial order does not mandate the type of granular quantification petitioner anticipates (*i.e.*, a precise number of smokers switching to e-cigarettes); nor is FDA required to design the precise specifications of petitioner's product trials. The statutory standard admits of flexibility both for manufacturers in submitting applications and FDA in reviewing them. The fact remains that petitioner failed to submit *any* product-specific evidence demonstrating benefits of its products.

Even were there some basis to conclude that FDA was required to promulgate a standards-and-metrics rule before adjudicating premarket applications, the proper course would be to seek to compel agency action unlawfully withheld, *see* 5 U.S.C. § 706(1). Petitioner has not brought or briefed such a claim, and its request that the Court order FDA to "reset" and promulgate a rule before adjudicating premarket tobacco applications, Br. 40, should be denied.[19]

---

products, in light of petitioner's agreement that "[n]o rational adult would ever countenance any youth using tobacco products." Br. 59.

[19] Petitioner briefly asserts that the TCA offends due process because it

2. Petitioner's contention that FDA adopted a new evidentiary standard is equally baseless. As explained above, the requirement that applications to market flavored e-cigarettes include evidence showing a benefit to adult users that outweighs their substantial risks to youth flows directly from the TCA. 21 U.S.C. § 387j(c)(2), (4). In applying that standard, FDA reasonably determined that, for products like flavored e-cigarettes that present a particularly significant risk to youth, a manufacturer must provide evidence that the product provides greater health benefits than other products that do not present the same degree of risk.

There is no merit to petitioner's contention (Br. 47) that FDA lacks authority to require manufacturers to show that their flavored e-cigarette products provide greater benefits than lower-risk products in order to

---

is so "vague" as to provide no "ascertainable standards." Br. 41. But petitioner could not be entitled to relief on such a theory because it has not brought a challenge *to the statute* and has not developed argumentation to support any such challenge. "[P]erfunctory and undeveloped arguments, and arguments that are unsupported by pertinent authority, are waived (even where those arguments raise constitutional issues)." *Crespo v. Colvin*, 824 F.3d 667, 674 (7th Cir. 2016) (quotation omitted). Regardless, such a claim would fail for the reasons set forth herein. *See, e.g.*, *Boutilier v. INS*, 387 U.S. 118, 123 (1967) (in the civil context, a statute will not be voided unless it is "so vague and indefinite as really to be no rule or standard at all").

demonstrate that the marketing of their products provides a net benefit to public health. The statutory provision governing new tobacco products expressly contemplates a comparative analysis of risk by requiring applications to include "full reports of all information . . . concerning investigations which have been made to show . . . whether [the new] tobacco product presents less risk than other tobacco products." 21 U.S.C. § 387j(b)(1)(A). FDA reasonably concluded that the statutorily required inquiry into whether a product will have a net benefit to the public health properly takes into account whether other products on the market that present less risk to youth are similarly likely to promote smoking cessation and reduction. If a less risky product provides similar or greater benefits, the public-health benefits of marketing the riskier product generally will not be sufficient to make it "appropriate for the protection of the public health." *Id.* § 387j(c)(2). Because the population-level health risks of flavored products are considerably higher than those of tobacco-flavored e-cigarettes, due to the far greater incidence of youth initiation, FDA reasonably required a greater degree of population-level benefit to users before authorizing the marketing of such products.

Contrary to petitioner's contention (Br. 47-48), FDA's analysis in this

respect was focused on "benefits," not efficacy, and it did not conflate the TCA's public-health requirement with the "safe" and "effective" standard applied in the drug context. 21 U.S.C. § 355(b)(1)(A)(i). Unlike the premarket review standard for drugs, which requires the submission of information showing that a drug is safe and effective for its intended use, the TCA requires premarket tobacco applications to include information regarding the health risks of the tobacco product and whether the product presents less risk than other tobacco products. FDA has not required flavored e-cigarette manufacturers to run complex trials establishing that their products are *effective* at promoting smoking cessation among smokers committed to stopping—only to show that their products better promote switching from combustible cigarettes, including among adults with no desire to cease tobacco use altogether, relative to a comparable tobacco-flavored product. In other words, rather than evaluating safety and effectiveness, FDA in the tobacco-product-authorization context considers whether the product is appropriate for the protection of the public health, which here turns on whether products that pose an acute risk to children and adolescents also provide a countervailing benefit to existing tobacco users greater than the benefit provided by less risky products.

There is likewise no merit to the contention that FDA improperly announced a new "tobacco product standard" without undertaking notice-and-comment rulemaking consistent with 21 U.S.C. § 387g(a)(3). While the TCA gives FDA broad authority to establish tobacco product standards through rulemaking, it also directs FDA to adjudicate marketing applications for new tobacco products to determine whether they meet the public-health standard established in § 387j(c). These are separate sources of authority that entail distinct requirements.

Petitioner incorrectly contends that "FDA's actions unlawfully grafted its comparative efficacy standard onto the TCA § 910 [application] requirements." Br. 51. On the contrary, FDA simply applied the criteria set forth in the TCA to govern the adjudication of marketing applications. The TCA reflects Congress's concern that novel tobacco products could addict a new generation of users and its recognition that it was therefore "essential" that "manufacturers, prior to marketing [tobacco] products, be required to demonstrate that [their] products will meet a series of rigorous criteria, and will benefit the health of the population as a whole." TCA § 2(36), 123 Stat. at 1779. The adjudicative process set forth in § 387j(c) establishes the means through which FDA is to ascertain whether a new tobacco product meets

these "rigorous criteria[] and will benefit the health of the population as a whole." *Id.* The statute itself sets out the information that manufacturers "shall" submit, including "full reports of all information" regarding a product's "health risks" — including whether it "presents less risk than other tobacco products." 21 U.S.C. § 387j(b)(1). Contrary to petitioner's suggestion, that process expressly puts the onus on manufacturers, not FDA, to establish the appropriateness of new products prior to marketing — a burden that petitioner tries to flip by invoking an inapposite provision.[20]

C. FDA's approach in denying petitioner's application is consistent with other agency statements

Contrary to petitioner's contention (*e.g.*, Br. 32, 43), FDA's approach in denying petitioner's application is consistent with the agency's 2021 final rule and earlier statements of policy, which explain that FDA will apply the

[20] Petitioner also insists that FDA denied marketing approval of its flavored products for failure to "pro[ve] that they were more effective at promoting smoking cessation than Gripum's tobacco-flavored E-Liquids." Br. 33. Petitioner misreads the denial order: FDA did not suggest that petitioner's flavored products must be shown more effective for adults switching or reducing cigarette use compared to *its own* tobacco-flavored products, only that they be shown more effective than *a comparator* tobacco-flavored product.

TCA's public-health standard in adjudicating applications for premarket authorization. Elaborating on that standard, these sources explain that long-term clinical studies will sometimes, but not always, be necessary to meet the statutory standard and that the evidence needed to support an application will vary according to a product's risks.

FDA's most recent statement on this subject is found in the final rule on Premarket Tobacco Product Applications and Recordkeeping Requirements. 86 Fed. Reg. 55,300 (Oct. 5, 2021). The rule explains that, consistent with the TCA, whether the marketing of a product is appropriate for the public health "shall, when appropriate, be determined on the basis of well-controlled investigations," but FDA may base its determination on "valid scientific evidence (other than evidence derived from [well-controlled investigations]) which is sufficient to evaluate the tobacco product." *Id.* at 55,387 (alteration in original) (quoting 21 U.S.C. § 387j(c)(5)). The rule states that "FDA does not expect that long-term clinical studies will need to be conducted *for each* [premarket tobacco product application]; instead, it expects that it should be able to rely on other valid scientific evidence to evaluate *some* [applications]" and will "consider whether there are other sources of scientific evidence that

sufficiently demonstrate the potential health risks of the product." *Id.* (emphases added). FDA emphasized, however, that "information from nonclinical studies alone is generally not sufficient to support a determination that permitting the marketing of the product would be [appropriate for the protection of the public health]." *Id.*

FDA's 2019 guidance likewise cautioned that "[n]onclinical studies alone are generally not sufficient to support" the required showing. Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, Guidance for Industry, June 2019, at 12.[21] While "FDA believes that in some cases, it may be possible to support a marketing order for an [e-cigarette] product without conducting new nonclinical or clinical studies," *id.* at 46, the guidance underscores the need to review such evidence to determine whether it supports the required showing. "For example, if there is an established body of evidence regarding the health impact (individual or population) of [a subject] product or a similar product that can be adequately bridged to [the subject] product, such as data from the published literature or government-sponsored databases,

[21] https://www.fda.gov/media/127853/download.

these data may be sufficient to support" an application. *Id.* FDA stated that it "intends to review that information to determine whether it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be [appropriate for the protection of the public health]." *Id.* at 12. The agency's statement that, "in general, FDA does not expect that applicants will need to conduct long-term studies to support an application," *id.* at 13, was made in the context of this broader discussion and cannot reasonably be construed to mean that manufacturers of products that present a particularly significant risk to youth will not need to provide robust evidence demonstrating a countervailing benefit to adult users.

As the foregoing shows, it is not the case that FDA previously made an across-the-board statement that applicants would not need to provide especially robust forms of evidence. FDA's denial of petitioner's application is consistent with prior and subsequent statements that FDA "*might* accept evidence other than long-term studies, if that evidence had sufficient scientific underpinnings to meet the TCA's statutory mandate of demonstrating that flavored [e-cigarette] devices are appropriate for the protection of public health." *Breeze Smoke*, 18 F.4th at 506-07. This Court

should thus follow the Sixth Circuit in "declin[ing] to embrace" petitioner's flawed argument 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." *Id.* at 507 (emphases added).

Contrary to petitioner's contention (Br. 32, 43-44), FDA did not need to consider petitioner's reliance interests in adjudicating its application because FDA "did not introduce a new standard of review in adjudication such that it likely deprived [petitioner] of fair warning." *Breeze Smoke*, 18 F.4th at 507. Petitioner's reliance on *Christopher v. SmithKline Beecham Corp.* is unavailing because that case involved an action contrary to the agency's clear and longstanding view of the law's substantive requirements. *See* 567 U.S. 142, 157-59 (2012) (refusing to defer to Department of Labor's statutory interpretation that contradicted decades of past practice by industry in which the agency had acquiesced). By contrast, here FDA's denial of petitioner's application was not contrary to a clear and longstanding interpretation of the TCA. As explained above, FDA's denial was consistent with its nonbinding 2019 guidance and other statements regarding the TCA's evidentiary requirements. Because FDA did not change course with

respect to its interpretation of the TCA's public-health standard, there was no prior interpretation on which manufacturers might have relied, and the agency therefore was not obligated to consider any such reliance. *Cf. DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913 (2020).

CONCLUSION

For the foregoing reasons, the petition for review should be denied.

Respectfully submitted,

BRIAN M. BOYNTON
Principal Deputy Assistant Attorney General
Civil Division

ERIC B. BECKENHAUER
Assistant Branch Director

/s/ Kate Talmor
KATE TALMOR
Trial Attorney
Federal Programs Branch
U.S. Department of Justice
1100 L Street, NW
Washington, DC 20005
(202) 305-5267
kate.talmor@usdoj.gov

Of Counsel:

DANIEL J. BARRY
Acting General Counsel
Dep't of Health and Human Services

WENDY S. VICENTE
Acting Deputy Chief Counsel for Lit.
Food and Drug Administration

MARCI B. NORTON
Senior Counsel
Office of the Chief Counsel
Food and Drug Administration

CERTIFICATE OF COMPLIANCE WITH FEDERAL RULE OF APPELLATE PROCEDURE 32(a)

I hereby certify that this brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and (6) because it has been prepared in 14-point Book Antiqua, a proportionally spaced font.

I further certify that this brief complies with the type-volume limitation of Rule 32(a)(7)(B) because it contains 10,394 words, excluding the parts of the brief exempted under Rule 32(f), according to the count of Microsoft Word.

/s/ *Kate Talmor*
KATE TALMOR

CERTIFICATE OF SERVICE

I hereby certify that on February 17, 2021, I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the Seventh Circuit by using the appellate CM/ECF system. Participants in the case are registered CM/ECF users, and service will be accomplished by the appellate CM/ECF system.

/s/ Kate Talmor
KATE TALMOR