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Pursuant to Sixth Circuit I.O.P. 32.1(b)

File Name: 21a0260p.06

UNITED STATES COURT OF APPEALS

FOR THE SIXTH CIRCUIT

BREEZE SMOKE, LLC,

Petitioner,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondent.

No. 21-3902

On Emergency Motion for Administrative Stay.

Petition for Review of an Order of the United States Food and Drug Administration; Agency Case No. PM0000983.

Decided and Filed: November 12, 2021

Before: MOORE, GILMAN, and KETHLEDGE, Circuit Judges.

COUNSEL

ON EMERGENCY MOTION FOR ADMINISTRATIVE STAY AND REPLY: Brian T. Burgess, Andrew Kim, GOODWIN PROCTER LLP, Washington, D.C., for Petitioner. **ON RESPONSE:** Kathleen B. Gilchrist, Hilary K. Perkins, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C., for Respondent. **ON MOTION TO FILE AMICUS BRIEF AND ON BRIEF:** Jacquelyn A. Klima, KERR, RUSSELL, AND WEBER, PLC, Detroit, Michigan, for Amicus Curiae.

The court delivered an order. KETHLEDGE, J., (pg. 11), delivered a separate dissenting opinion.

ORDER

Breeze Smoke, LLC petitions for review of a Food and Drug Administration ("FDA") order denying its Premarket Tobacco Product Applications for certain of its electronic nicotine

delivery systems ("ENDS"). Breeze Smoke moves for a stay of the FDA's order. In addition, several parties—the American Academy of Pediatrics, American Cancer Society Cancer Action Network, American Heart Association, American Lung Association, Campaign for Tobacco-Free Kids, Parents Against Vaping E-Cigarettes, and Truth Initiative—move to file an amicus brief in support of the FDA's position.

"A petitioner must ordinarily move first before the agency for a stay pending review of its decision or order." Fed. R. App. P. 18(a)(1). Thus, a party first moving for relief in this court must "show that moving first before the agency would be impracticable" or "that, a motion having been made, the agency denied the motion or failed to afford the relief requested . . . ." Fed. R. App. P. 18(a)(2)(A)(i)–(ii). Under the Family Smoking Prevention and Tobacco Control Act ("TCA"), however, "any person adversely affected by" the denial of a Premarket Tobacco Product Application may seek judicial review of the denial, 21 U.S.C. § 387*l*(a)(1)(B), and "the court shall have jurisdiction to review the regulation or order . . . and to grant appropriate relief, including interim relief," *id.* § 387*l*(b). Breeze Smoke contends that seeking a stay from the FDA of its marketing-denial order would have been impracticable because the order takes effect immediately and the FDA can take months to consider an agency-level request for a stay. We agree. *See Wages & White Lion Invs., LLC v. FDA*, — F.4th —, No. 21-60766, 2021 WL 4955257, at *2 n.1 (5th Cir. Oct. 26, 2021).

A stay is "an exercise of judicial discretion" dependent on the case's facts. *Nken v. Holder*, 556 U.S. 418, 433 (2009) (quotation omitted). The party seeking "a stay bears the burden of showing that the circumstances justify an exercise of [our] discretion." *Id.* at 433–34. We consider four factors in determining whether to grant a stay: (1) "whether the stay applicant has made a strong showing that [it] is likely to succeed on the merits"; (2) the likelihood that "the applicant will be irreparably injured absent a stay"; (3) "whether issuance of the stay will substantially injure" other interested parties; and (4) "where the public interest lies." *Hilton v. Braunskill*, 481 U.S. 770, 776 (1987). The first two factors "are the most critical." *Nken*, 556 U.S. at 434.

"The FDA's administrative decisions are subject to review under the Administrative Procedure Act ('APA'), 5 U.S.C. § 706, which requires the reviewing court to set aside an

agency action that is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.'" *ISTA Pharms. v. FDA*, 898 F. Supp. 2d 227, 230 (D.D.C. 2012) (citation omitted); *see also* 21 U.S.C. § 387*l*(b). We therefore "must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Or. Nat. Res. Council*, 490 U.S. 360, 378 (1989) (quotation omitted). Although "[j]udicial review under [the arbitrary or capricious] standard is deferential, and a court may not substitute its own policy judgment for that of the agency," we must "ensure[] that the agency has acted within a zone of reasonableness and, in particular, has reasonably considered the relevant issues and reasonably explained the decision." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021).

Breeze Smoke has not made a strong showing that it would likely succeed on its claim that the FDA's review of its application was arbitrary or capricious. Nor has Breeze Smoke made a strong showing that the FDA's denial of its application contradicted the FDA's nonbinding 2019 guidance because that guidance contemplated more rigorous scientific data than Breeze Smoke's application contained.

Administrative agencies are generally required to provide "fair notice" of requirements. *See Golden Living Ctr. – Mountain View v. Sec'y of Health & Human Servs.*, 832 F. App'x 967, 975–76 (6th Cir. 2020) (citing the fair-notice doctrine). The fair-notice requirement extends to informal guidance. *PHH Corp. v. Consumer Fin. Prot. Bureau*, 839 F.3d 1, 48 (D.C. Cir. 2016), *reinstated in relevant part*, 881 F.3d 75, 83 (D.C. Cir. 2018) (en banc), *abrogated on other grounds sub nom. Seila Law, LLC v. Consumer Fin. Prot. Bureau*, 140 S. Ct. 2182 (2020). Courts must review agency action based on the justifications given at the time, not post hoc litigation rationales. *Dep't Homeland Sec. v. Regents of Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020). Finally, although agencies must consider reliance interests when they "change[] course," *id.* at 1913, the fact that a regulated entity has relied on an agency decision does not bar the agency from reconsidering that decision, *Belville Mining Co. v. United States*, 999 F.2d 989, 999 (6th Cir. 1993).

The TCA subjects certain new tobacco products to the FDA's premarketing review. 21 U.S.C. § 387 *et seq.* All parties agree that the TCA applies to Breeze Smoke's flavored

ENDS products. Under the TCA, the FDA "shall deny" applications for new products if, based on the information submitted to the FDA as part of the application "and any other information before [the FDA] with respect to such tobacco product," the FDA finds "a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health ['APPH']." 21 U.S.C. § 387j(c)(2). To determine whether the marketing of the tobacco product is appropriate for the protection of the public health, the FDA evaluates "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." *Id.* § 387j(c)(4). That requires considering both the "likelihood that existing users of tobacco products will stop using such products," and the "likelihood that those who do not use tobacco products will start using such products." *Id.*

In 2016, the FDA deemed all tobacco products subject to the TCA. 81 Fed. Reg. 28,973 (May 10, 2016). This meant that tens of thousands of products then on the market could not legally be sold without the FDA's approval. The FDA allowed the products to stay on the market while it considered the flood of applications, and after a series of schedule changes implemented by the FDA and federal courts, the deadline fell on September 9, 2020. *Vapor Tech. Ass'n v. FDA*, 977 F.3d 496, 500 (6th Cir. 2020).

In advance of this deadline, the FDA issued nonbinding guidance that sought to help firms comply with this accelerated deadline. Hotly contested here is the FDA's guidance regarding "Valid scientific evidence":

> The FD&C Act states that the finding of whether permitting the marketing of a product would be APPH will be determined, when appropriate, on the basis of well-controlled investigations (section 910(c)(5)(A)). However, section 910(c)(5)(B) of the FD&C Act also allows the Agency to consider other "valid scientific evidence" if found sufficient to evaluate the tobacco product. **Given the relatively new entrance of ENDS on the U.S. market, FDA understands that limited data may exist from scientific studies and analyses. If an application includes, for example, information on other products (e.g., published literature, marketing information) with appropriate bridging studies, FDA intends to review that information to determine whether it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be APPH.** Nonclinical 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. **Nonetheless, in general, FDA does not expect that applicants will need to conduct long-term**

> **studies to support an application. As an example for nonclinical assessments, long-term studies such as carcinogenicity bioassays are not expected to be included in an application**. For clinical assessments, **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 (i.e., why the data used are applicable to the new tobacco product) and extrapolating from short-term studies.** In addition, nonclinical in vitro assays that assess the toxicities that are seen following long-term use of tobacco products may be supportive of these clinical assessments. **These studies, used as a basis to support a[n application], should be relevant to the new tobacco product and address, with robust rationale, acute toxicological endpoints or other clinical endpoints that may relate to long-term health impacts**. In this context, FDA considers long-term studies to be those studies that are conducted over six months or longer.

Premarket Tobacco Product Applications for ENDS: Guidance for Industry, A204–05 (emphasis added) (footnotes omitted). To provide brief context on this language: The FDA acknowledged in 2018 that ENDS products may provide a beneficial alternative to combustible cigarettes because they deliver nicotine without also bombarding the user's lungs with the toxins found in cigarettes. *See Vapor Tech. Ass'n*, 977 F.3d at 499. The FDA has also recognized, however, that ENDS products particularly appeal to children, with high-school-age use of ENDS products increasing by over 75% from 2017 to 2018, and middle-school-age use increasing by almost 50% over that same period. *Am. Acad. of Pediatrics v. FDA*, 379 F. Supp. 3d 461, 467 (D. Md. 2019). Flavored ENDS products especially appeal to children: As of 2020, 84.7% of high school ENDS users and 73.9% of middle school ENDS users reported using flavored products. FDA Review of Breeze Smoke's Application, A12. And according to one study, over 80% of children aged 12-17 said that their first experience with ENDS involved a flavored product. *Id.*

This data brings into focus the problem facing the FDA: e-cigarettes offer potential health benefits, to the extent that they convince combustible-tobacco users to get their nicotine from e-cigarettes instead. But *flavored* e-cigarettes disproportionately appeal to children. The FDA, under a statutory obligation to approve only those products that are "appropriate for the protection of the public health," must determine whether applicants can show that their flavored ENDS product will benefit public health enough to outweigh this public-health detriment to children. *See* FDA Review of Breeze Smoke's Application, A9 (noting the importance of

considering whether "the flavored products have an added benefit relative to that of tobacco-flavored [e-cigarettes] in facilitating smokers completely switching away from or significantly reducing their smoking.").

Turning to this case's facts, Breeze Smoke contends that it followed the FDA's 2019 industry guidelines for submitting its Premarket Tobacco Product Applications. But the FDA denied Breeze Smoke's application, citing the lack of longitudinal cohort studies and randomized controlled trials and the insufficiency of the evidence provided, which included published literature, marketing information on other products, bridging studies, and its marketing plan, all of which Breeze Smoke believed comported with the earlier-issued guidance.

The FDA's denial of Breeze Smoke's application emphasized that the strong appeal of flavored ENDS 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 ENDS product." FDA Review of Breeze Smoke's Application, A16; *see also id.*, A18 n.xxii. The FDA suggested that randomized control trials would present the strongest evidence of appropriateness for the public health. *Id.*, A17. The FDA then acknowledged that applicants theoretically could "rely on, and bridge to," data concerning general ENDS category literature. *Id.* But the FDA concluded that, based on the known risks that flavored ENDS products present to youths, Breeze Smoke's application did not demonstrate health benefits to adult smokers sufficient to overcome flavored products' appeal to youths. *Id.*, A21.

Breeze Smoke identifies four buckets of evidence that it submitted: (1) a literature review showing that ENDS use is less harmful than smoking tobacco combustibles, (2) information "bridging" its products to those evaluated in the literature, (3) a survey that Breeze Smoke conducted of its adult users that purported to show a preference for flavored products, and (4) information concerning Breeze Smoke's plan to avoid marketing its products to youth. Pet'r Br. at 7.

The Breeze Smoke literature review offers mixed findings on flavored ENDS products. *See* Breeze Smoke Lit. Review, A52 ("The use of food flavorings in e-liquids . . . need[s] more scientific study."), A69 (citing a study suggesting that adults who vape flavored e-cigarettes are

more likely subsequently to quit smoking than those who vape unflavored e-cigarettes), A70 (citing a separate study saying that users strongly prefer flavored e-cigarettes). Breeze Smoke argues that the literature review was meant to bridge to materials specifically concerning flavored products. Pet'r Br. at 7. But as the FDA noted in its denial of Breeze Smoke's application, the "clear and consistent patterns of real-world use" showing youth initiation of flavored ENDS products rendered this bridging insufficient. FDA Review of Breeze Smoke's Application, A17–18.

On this record, Breeze Smoke's survey presents methodological issues. The FDA's 2019 guidance suggested that applicants include studies "with robust rationale, acute toxicological endpoints or other clinical endpoints that may relate to long-term health impacts." Premarket Tobacco Product Applications for ENDS: Guidance for Industry, A205. Breeze Smoke's study, submitted via Google Form, contained responses from customers "solicited . . . by request in the retail stores." Breeze Smoke Lit. Review, A70. This suggests biased respondents. *See id.*, A73–77.

Considering all of Breeze Smoke's evidence, we disagree with Breeze Smoke, and with our colleagues on the Fifth Circuit, who say that the FDA orchestrated a "surprise switcheroo." *Wages & White Lion Invs., LLC v. FDA*, No. 21-60766, 2021 WL 4955257, at *5 (5th Cir. Oct. 26, 2021). The FDA said that, in light of the accelerated court-ordered deadline for submission of applications for new tobacco products, it *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 ENDS devices are appropriate for the protection of public health. Premarket Tobacco Product Applications for ENDS: Guidance for Industry, A204 ("FDA intends to review that information"), A205 ("[I]nstead 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 (i.e., why the data used are applicable to the new tobacco product) and extrapolating from short-term studies.") (emphasis added in this and following), A223 ("[I]t is *likely* that applicants will conduct certain investigations themselves and submit their own research findings as a part of their [application]."), A238 ("[I]f there is an established

body of evidence regarding the health impact (individual or population) of your product or a similar product that can be adequately bridged to your product, such as data from the published literature or government-sponsored databases, these data *may be sufficient* to support a[n application]").

The FDA found Breeze Smoke's evidence lacking against this standard. *See* FDA Review of Breeze Smoke's Application, A18 (describing the results from bridging literature studies to flavored ENDS products as "quite mixed"). Breeze Smoke 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. We decline to embrace that claim.

On this record, the FDA's 2019 language and its 2021 order likely did not fail to consider reliance interests, *see Regents*, 140 S. Ct. at 1914, and did not introduce a new standard of review in adjudication such that it likely deprived Breeze Smoke of fair warning, *see Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156–57 (2012). Additionally, the FDA correctly notes that Breeze Smoke's reliance on caselaw where an agency was not afforded deference because it acted contrary to longstanding precedent is inapposite because the FDA's 2019 guidance does not qualify as "longstanding."

The FDA's formulaic consideration of Breeze Smoke's youth marketing plan warrants further scrutiny. The FDA acknowledged in its denial of Breeze Smoke's application that the marketing plan, the strategy that a firm uses to avoid marketing flavored ENDS products to those under 21, "is a critical aspect of product regulation." FDA Review of Breeze Smoke's Application, A17 n.xix. The FDA called it "theoretically possible" that "significant" mitigation efforts could reduce flavored products' appeal to youths "such that the risk for youth initiation would be reduced." *Id.* The FDA then said that, because it had not yet seen an application that showed advertising restrictions that would significantly enough decrease youth use, it would not evaluate Breeze Smoke's proposal "at this stage of review" "for the sake of efficiency." *Id.*

The FDA likely should have more thoroughly considered Breeze Smoke's marketing plan. Agency action must consider "the relevant factors" when reaching a decision, and may not

"entirely fail[] to consider an important aspect" of the relevant regulatory task. *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). The FDA argues that it properly declined to consider Breeze Smoke's marketing strategy because "consideration of the specific marketing measures proposed in petitioner's application would not alter its analysis." FDA Br. at 18. It is not clear how the FDA could have known this. The FDA cites *Butte County v. Chaudhuri* for the proposition that an agency need not explicitly mention each piece of evidence, but there the agency's analysis cited countervailing evidence showing why it had rejected the allegedly ignored evidence. 887 F.3d 501, 509 (D.C. Cir. 2018). Here, by contrast, the FDA ignored the marketing plan entirely because prior marketing plans had not satisfied the agency.

Because Breeze Smoke bears the burden of showing a strong likelihood of success on the merits, and because the FDA likely properly concluded that Breeze Smoke failed to show that its products adequately protected the public health, described above, we still deny Breeze Smoke's motion for stay, even in light of the FDA's possibly insufficient consideration of Breeze Smoke's marketing plan. This oversight has not "permeated the entire [adjudication] process." *See Pub. Citizen v. Fed. Motor Carrier Safety Admin.*, 374 F.3d 1209, 1217 (D.C. Cir. 2004).

The FDA reasonably concluded that Breeze Smoke's application did not meet the TCA's requirements that new tobacco products be appropriate for the protection of the public health. The FDA cited well-developed evidence showing that flavored ENDS products' special appeal to youths harms the public health to a degree not outweighed by the (far-less-supported) effects of adult cigarette smokers switches to e-cigarettes. Breeze Smoke argues that the FDA deployed separate standards of review, considering literature that supported the thesis that flavored ENDS products pose special health risks to children and requiring Breeze Smoke present more than literature reviews to justify its products' public health benefits. Pet'r Br. at 18. But the FDA relied on literature concerning flavored ENDS products' appeal to youths because those risks are understood as a matter of scientific consensus. *See* Breeze Smoke Lit. Review, A66 ("There is **substantial evidence** that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults."); FDA Comm'r Speech, A171 ("we know" that "kid-appealing flavors in products like . . . ENDS . . . are a leading driver of youth smoking");

Enforcement Priorities for ENDS without Premarket Authorization Guidance for Industry, A272–78 (collecting data showing "substantial and increasing initiation of ENDS products by youth, particularly certain flavored, cartridge-based products" (on A278)). This differs sharply from an agency's "raw assertion that [two concepts] are different." *Cincinnati Bell Tel. Co. v. Fed. Commc'ns Comm'n*, 69 F.3d 752, 768 (6th Cir. 1995).

Because Breeze Smoke has not shown a strong likelihood of success on the merits, we need not consider the other stay factors. *Gonzales v. Nat'l Bd. of Med. Exam'rs*, 225 F.3d 620, 632 (6th Cir. 2000). We also need not consider the FDA's argument that, were we to grant a stay, Breeze Smoke would still lack the necessary authorization to market its products.

Accordingly, the motion for a stay is **DENIED**. The motion for leave to file an amicus brief is **GRANTED**.

DISSENT

KETHLEDGE, Circuit Judge, dissenting. I would grant the motion for a stay for substantially the reasons stated by the Fifth Circuit in *Wages & White Lion Invs., L.L.C. v. United States Food & Drug Admin.*, 2021 WL 4955257 (5th Cir. Oct. 26, 2021). The FDA essentially decided these applications *en masse* rather than individually; that case is thus materially identical to this one.

ENTERED BY ORDER OF THE COURT

Deborah S. Hunt, Clerk