10-27-2022

Liquid Labs LLC v. FDA

PRECEDENTIAL

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 21-2883

LIQUID LABS LLC,
Petitioner

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION

On Petition for Review of a Final Marketing Denial Order
By the United States Food and Drug Administration
(Agency Nos. PM0003412 & PM0000984)

Submitted Under Third Circuit L.A.R. 34.1(a)
October 3, 2022

Before: CHAGARES, Chief Judge, SHWARTZ and SCIRICA, Circuit Judges.

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Kevin T. Duffy, Jr.
Duffy & Staab
165 West Putnam Avenue
Suite 2B
Greenwich, CT 06903

Gary G. Staab
Duffy & Staab
2 William Street
The Kennedy Building
Suite 302
White Plains, NY 10601

Counsel for Petitioner

Arun G. Rao
Gustav W. Eyler
Hilary K. Perkins
Jonathan E. Amgott
United States Department of Justice
Consumer Protection Branch
450 5th Street, N.W.
Suite 6400 South
Washington, DC 20001

Brian M. Boynton
Joshua Koppel
United States Department of Justice
Civil Division
950 Pennsylvania Avenue, N.W.
Room 7212
Washington, DC 20530

Daniel J. Barry
United States Department of Health & Human Services
200 Independence Avenue, S.W.

Washington, DC 20201

Wendy S. Vicente
Marci B. Norton
Food and Drug Administration
Office of the Chief Counsel
10903 New Hampshire Ave.
Silver Spring, MD 20993

Counsel for Respondent

James G. Troutman
Troutman Law Office
4205 Springhurst Boulevard
Suite 201
Louisville, KY 40241

Counsel for Amicus Petitioners 38 National and State Electronic Nicotine Delivery System Product Advocacy Associations

Mary G. Bielaska
Zanicorn Legal
845 Third Avenue
6th Floor
New York, NY 10022

Counsel for Amicus Petitioners Dr. David B. Abrams,Clive D. Bates, and Professor David T. Sweanor, J.D.

William B. Schultz
Zuckerman Spaeder
1800 M Street, N.W.
Suite 1000
Washington, DC 20036

Counsel for Amicus Respondents Medical and Public Health Groups

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OPINION OF THE COURT

SHWARTZ, Circuit Judge.

Liquid Labs LLC ("Liquid Labs") sought permission from the Food and Drug Administration ("FDA") to market products used in e-cigarettes. The FDA denied the request, and Liquid Labs petitions for review. Because the FDA's order was within its statutory authorities and the Administrative Procedure Act ("APA"), we will deny the petition.

I

A

E-cigarettes are electronic nicotine delivery systems ("ENDS") that vaporize e-liquids and allow for inhalation.[1]

[1] Some e-cigarettes are disposable, while others are reusable. Within the reusable group, some e-cigarettes have "open systems," meaning they are "refillable" and "include[] a reservoir that a user can refill with an e-liquid of their choosing," JA 210; some have "closed systems," meaning, for example, they "use[] e-liquid contained in replaceable cartridges or pods that are not intended to be refillable," JA 210

See, e.g., Big Time Vapes, Inc. v. FDA, 963 F.3d 436, 439 n.11 (5th Cir. 2020), cert. denied, 141 S. Ct. 2746 (2021). Liquid Labs manufactures and sells e-liquids that generally contain nicotine and flavoring.

Liquid Labs' e-liquids qualify as "new tobacco product[s]" under the Family Smoking Prevention and Tobacco Control Act (the "Act"). See 21 U.S.C. §§ 387-387u. The Act applies to "all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco and to any other tobacco products that the Secretary by regulation deems to be subject to" the Act. 21 U.S.C. § 387a(b); see also 21 U.S.C. § 387j(a)(1)(A) (defining "a new tobacco product," as relevant here, to be "any tobacco product . . . that was not commercially marketed in the United States as of February 15, 2007"). In 2016, the FDA "deem[ed]" e-cigarettes and related components (such as Liquid Labs' e-liquids) to be subject to the Act's requirements. See Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, 81 Fed. Reg. 28,974, 29,028 (May 10, 2016); see also Big Time Vapes, 963 F.3d at 440.

Because Liquid Labs' e-liquids qualify as new tobacco products, they may not be introduced into interstate commerce without the FDA's authorization. See 21 U.S.C. § 387j(a)(2). One way to obtain authorization is by submitting a premarket tobacco product application ("PMTA"). See, e.g., Big Time Vapes, 963 F.3d at 439; see also 21 U.S.C. § 387j(b)-(c).

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and some have "mod[ifiable] system[s]" that allow the user to adjust various aspects of the e-cigarette, see, e.g., JA 135. Liquid Labs' e-liquids are used in connection with open systems.

Under the Act, the FDA "shall deny" a PMTA if the applicant fails to "show[] that permitting such tobacco product to be marketed would be appropriate for the protection of public health." 21 U.S.C. § 387j(c)(2)(A). "[T]he finding as to whether the marketing of a tobacco product . . . is appropriate for the protection of the public health [is] determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." 21 U.S.C. § 387j(c)(4). On this subject, the Act directs the FDA to "tak[e] into account" both "the increased or decreased likelihood that existing users of tobacco products will stop using such products," and "the increased or decreased likelihood that those who do not use tobacco products will start using such products." 21 U.S.C. § 387j(c)(4)(A)-(B).

In addition to the Act and the deeming regulation, the FDA took several related regulatory steps. For example, the FDA issued guidance in June 2019 ("June 2019 Guidance") and April 2020 ("April 2020 Guidance") that "help[ed] manufacturers prepare [PMTA] applications ahead of the [discretionarily delayed submission] deadline," and "set[] out the agency's enforcement priorities," respectively. Prohibition Juice Co. v. U.S. Food & Drug Admin., 45 F.4th 8, 13-15 (D.C. Cir. 2022). Among other things, these documents highlighted that flavored e-liquids' had a "disproportionate appeal to children," id. at 13, and "noted the types of rigorous scientific evidence [the FDA] would accept in support of applications to market such products," id. at 15.

B

Liquid Labs submitted two PMTAs on September 4, 2020, covering twenty e-liquid products. The products spanned ten flavors, two of which are described as being tobacco flavored, and eighteen of which are described as having a "characterizing flavor" other than tobacco or menthol with names such as "OG Island Fusion," "Berry Au Lait, "OG Summer Blue," and "Shake."

In connection with the applications, Liquid Labs submitted evidence from a variety of sources, including an abuse liability study, a cross-sectional perception and intention study, a population modeling analysis, a clinical literature review, and "well-controlled non-clinical analyses of Liquid Labs' Products." Pet. Br. at 20. Liquid Labs also submitted a marketing plan setting forth, among other things, various measures Liquid Labs planned to take to discourage youths from using its products.

In September 2021, the FDA denied Liquid Labs' PMTAs.[2] In connection with its denials, the FDA sent Liquid Labs several documents, including a Marketing Denial Order, a document titled "Technical Project Lead (TPL) Review of PMTAs," JA 62, and two documents titled "Review for Flavored ENDS PMTAs," JA 52, 57.

[2] The denial order did not list Liquid Labs' tobacco-flavored e-liquids as products "lack[ing] sufficient evidence to demonstrate that the marketing of th[e] products is appropriate for the protection of public health." JA 10. Liquid Labs represents that approval for its tobacco-flavored e-liquids has been neither granted nor denied.

The Marketing Denial Order briefly explained why the applications "lack[ed] sufficient evidence to demonstrate that the marketing of the[] products [wa]s appropriate for the protection of public health." JA 1. It noted, for example, that "[i]n light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence" was "needed regarding the magnitude of the potential benefit to adult smokers," and such evidence could have been provided through "randomized controlled trial[s] and/or longitudinal cohort stud[ies]," as well as through "other evidence[,] but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time." JA 1. The FDA found that Liquid Labs' cross-sectional survey was "not sufficient" because "it d[id] not evaluate product switching or cigarette reduction resulting from use of these products over time or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors." JA 1-2.

The Technical Project Lead Review further discussed the FDA's rationale for denying Liquid Labs' applications. For example, it set forth the FDA's concern about youth use of flavored ENDS and regulatory actions the FDA has taken to address the issue. It also explained, among other things, (1) why the FDA focused "on the risk to youth nonusers as well as the potential benefit to adult smokers as current users," (2) why "only the strongest types of evidence" would be sufficient to show an adequate benefit to adult smokers, (3) why the FDA looked for "acceptably strong evidence that the flavored products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking," and (4)

how it concluded that although Liquid Labs' applications "contain other evidence regarding the potential benefit to adult users," the "other evidence [wa]s not adequate." JA 64.

The Technical Project Lead Review explained that Liquid Labs' "internet-based cross-sectional survey" evidence "[wa]s not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it d[id] not evaluate product switching or cigarette reduction resulting from use of these products over time or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors." JA 75. Accordingly, the FDA concluded that Liquid Labs had not shown that the benefits of the products sufficiently outweighed the risks they posed to youths.

In the Reviews for Flavored ENDS PMTAs, the FDA examined Liquid Labs' submissions to see if they "contain[ed] evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of [its] flavored ENDS over an appropriate comparator tobacco-flavored ENDS." JA 53, 58. The reviews noted that the PMTAs lacked both randomized controlled trials related to new product use and smoking behavior and longitudinal cohort studies on new product use and smoking behavior and one review specified that the "[o]ther evidence" submitted was "not sufficient to support the benefit to adult smokers of using these flavored ENDS . . . ." JA 54; see also JA 57 (noting "[e]vidence is absent in PMTAs").

Liquid Labs petitions for review.[3]

II[4]

A[5]

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[3] Liquid Labs also sought re-review from the FDA. After completing its re-review, the FDA again concluded that Liquid Labs' evidence did not "demonstrate a sufficient potential benefit to adult smokers to warrant rescission" of its prior denial. JA 317.

[4] This Court has jurisdiction pursuant to 21 U.S.C. § 387*l*(a)(1)(B).

[5] We review the FDA's order denying the PMTAs under the standards set forth in the APA, see 21 U.S.C. § 387*l*(b) (noting a "regulation or denial" "shall be reviewed in accordance with section 706(2)(A)" of the APA), and, thus, may hold it "unlawful and set [it] aside" if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," 5 U.S.C. § 706(2)(A). An agency acts arbitrarily or capriciously if, for example, it "entirely fail[s] to consider an important aspect of the problem," Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983), "offer[s] only a 'conclusory statement' which 'fail[s] to articulate a rational basis for its conclusion,'" or "cit[es] no data whatsoever in support of its decision," Sierra Club v. U.S. Env't Prot. Agency, 972 F.3d 290, 298 (3d Cir. 2020) (first quoting W.R. Grace & Co. v. E.P.A., 261 F.3d 330, 342 (3d Cir. 2001), then quoting Natural Res. Def. Council, Inc. v. E.P.A., 790 F.2d 289, 309 (3d Cir. 1986)).

When conducting this analysis, we "review the whole record or those parts of it cited by a party, and [give] due account . . . [to] the rule of prejudicial error." 5 U.S.C. § 706;

Liquid Labs contends that the FDA acted arbitrarily and capriciously in a number of respects. For the reasons below, we reject each of Liquid Labs' arguments.

1

Liquid Labs first argues that the FDA acted arbitrarily and capriciously by "pull[ing] a surprise switcheroo" by "requir[ing]" certain evidence it previously indicated would not be necessary and rejecting evidence it led Liquid Labs to believe would be sufficient.[6] Pet. Br. at 39. In doing so, the

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see also Nat'l Ass'n of Home Builders v. Defs. of Wildlife, 551 U.S. 644, 659 (2007); Shinseki v. Sanders, 556 U.S. 396, 409 (2009) (explaining that the "burden of showing that an error is harmful normally falls upon the party attacking the agency's determination"). Concomitantly, we "judge the agency's decision 'solely by the grounds [it] invoked.'" Rad v. Att'y Gen., 983 F.3d 651, 656 (3d Cir. 2020) (quoting SEC v. Chenery Corp., 332 U.S. 194, 196 (1947)) (alteration in original).

To the extent the issue pertains to an agency's interpretation of the statutes it administers, we follow the "familiar Chevron framework," first "giv[ing] effect to Congress' unambiguous intent" "if the statute is clear," and, second, "defer[ring] to an implementing agency's reasonable interpretation of that statute" "if the statute is silent or ambiguous with respect to a specific issue." Contreras Aybar v. Sec'y U.S. Dep't of Homeland Sec., 916 F.3d 270, 273 (3d Cir. 2019) (quoting De Leon-Ochoa v. Att'y Gen., 622 F.3d 341, 348 (3d Cir. 2010)).

[6] Specifically, Liquid Labs claims that the FDA unexpectedly required it to provide (1) randomized controlled

FDA, according to Liquid Labs, provided inadequate notice, upset its reliance expectations, and acted arbitrarily and capriciously.

Liquid Labs relies on several documents the FDA issued between June of 2019 and September 2021. The first is the FDA's June 2019 Guidance "intended to assist persons submitting . . . PMTAs." JA 205. The June 2019 Guidance explained, among other things, that although the Food, Drug, and Cosmetic Act "states that the finding of whether permitting the marketing of a product would be [appropriate for the protection of public health] will be determined, when appropriate, on the basis of well-controlled investigations," the FDA was also permitted to consider "other 'valid scientific evidence' if found sufficient to evaluate the tobacco product." JA 216; see also JA 250 ("FDA believes that in some cases, it may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies. . . . In cases where a product has not yet been sufficiently reviewed, new nonclinical and clinical studies may be necessary to support a marketing order."). It further stated that "[n]onclinical studies alone are generally not sufficient to

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trials and/or longitudinal cohort studies, (2) studies occurring "over time" and/or "long-term studies," and (3) studies comparing the "efficacy between different ENDS products." Reply Br. at 5, 7, 10.

Liquid Labs adds new arguments in its reply brief regarding a "net benefit" requirement and the FDA's "refusal to request additional evidence before issuing denial." See Reply at 12, 14. We decline to "reach arguments raised for the first time in a reply brief." Barna v. Bd. of Sch. Dirs. of Panther Valley Sch. Dist., 877 F.3d 136, 146 (3d Cir. 2017).

support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of public health." JA 216. "Nonetheless," the document continued, the FDA "in general," did not "expect that applicants w[ould] need to conduct long-term studies to support an application." JA 217. The Guidance also "recommend[ed that] an applicant compare the health risk of its product to both products within the same category and subcategory, as well as products in different categories as appropriate." JA 217.

According to Liquid Labs, the June 2019 guidance "encourag[ed] submission of the very evidence FDA [ultimately] reject[ed]," and "induced" the shortcomings highlighted in the FDA's denial of Liquid Labs' PMTA. Pet. Br. at 38. The second item that Liquid Labs relies on is a July 2021 internal FDA memorandum, which explained, among other things, that the "[t]he absence of" "a randomized controlled trial" and/or "a longitudinal cohort study" constituted "a fatal flaw, meaning any application lacking [such] evidence w[ould] likely receive a marketing denial order," JA 273-74, and an August 2021 internal memorandum that Liquid Labs asserts "justified" the July 2021 memorandum, Pet. Br. at 26.[7]

[7] Liquid Labs relies heavily on the FDA's July statements and its August justification that the absence of certain studies would constitute a "fatal flaw" in a PMTA application, but this ignores the fact that the memoranda that made this comment were rescinded either expressly or implicitly.

We join our sister circuit courts who have rejected these "surprise switcheroo" arguments. See Prohibition Juice, 45 F.4th at 20-21; Wages & White Lion Invs., LLC v. FDA, 41 F.4th 427, 438-39 (5th Cir. 2022)[8]; Breeze Smoke, LLC v. U.S. Food & Drug Admin., 18 F.4th 499, 506-07 (6th Cir. 2021), cert. denied, 142 S. Ct. 638 (2021).

With respect to the claim that the FDA surprisingly required randomized controlled trials and/or longitudinal cohort studies, "[t]he text of the FDA's [June] 2019 Guidance makes . . . clear" that "the FDA did not reverse course." Prohibition Juice, 45 F.4th at 21. Put simply, the FDA did not newly require those specific types of studies but instead found that Liquid Labs' other evidence was inadequate. The 2019 Guidance "said that [such studies] would not be necessary if applicants submitted similarly rigorous 'valid scientific evidence,'" but "nowhere guaranteed that unspecified other forms of evidence would necessarily be sufficient—only that they might be, so the FDA would consider them." Id.; accord Wages & White Lion, 41 F.4th at 438-39; Breeze Smoke, 18 F.4th at 506-07; Gripum, LLC v. United States Food & Drug Admin., 47 F.4th 553, 559-60 (7th Cir. 2022). Further, the July 2021 memorandum "did not necessarily foreclose reliance on other forms of rigorous evidence," and the August memorandum "expressly required the agency to consider other

[8] Liquid Labs relies heavily on an earlier opinion from the Court of Appeals for the Fifth Circuit granting a stay pending merits review. See Wages & White Lion Invs., LLC v. U.S. Food & Drug Admin., 16 F.4th 1130 (5th Cir. 2021). The merits panel, however, denied the petition for review. See Wages & White Lion Invs., 41 F.4th 427.

forms of evidence if sufficiently robust." Prohibition Juice, 45 F.4th at 22.

Further, in denying Liquid Labs' applications, the FDA acted in conformity with the June 2019 Guidance. Nothing in the Marketing Denial Order, the Technical Project Lead Review, and the two Reviews for Flavored ENDS PMTAs "required" Liquid Labs to include "product-specific [randomized controlled trials]/longitudinal cohort studies." Reply Br. at 5.[9] Each document states that the FDA would—and indicates that it in fact did—consider other evidence. Liquid Labs' studies, however, did not produce the kind of evidence the FDA consistently sought. For example, the June 2019 Guidance recommends that "PMTAs for flavored products [ ] examine [both] the impact of the flavoring on consumer perception . . . especially given the attractiveness of flavors to youth and young adults," and the "adult appeal of

[9] Liquid Labs also contends that an FDA press release "announced that it [would] require[] the very studies it originally expected it didn't need." Pet. Br. at 39. The press release does not reveal that the FDA changed its requirements. Indeed, it specifically states that "the agency [was] not foreclos[ing] the possibility that other types of evidence"—i.e., other than randomized controlled trials and longitudinal cohort studies—"could be adequate if sufficiently robust and reliable." See Press Release, FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health (Aug. 26, 2021), https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-applications-about-55000-flavored-e-cigarette-products-failing-provide-evidence .

such flavors in their decisions to initiate use, cease use of more harmful products, or dual use." JA 246; see JA 241-42 (recommending "considering" "[p]ublished literature or applicant-initiated studies evaluating the effects of the ENDS on users, including effects on initiation, switching behavior, cessation, and dual use; and on nonusers' initiation of the product."). Further, the Guidance recommends that "an applicant compare the health risks of its products to both products within the same category and subcategory, as well as products in different categories as appropriate." JA 217; see also JA 244. Liquid Labs' abuse liability study compares its "OG Blue" flavor e-liquid with cigarettes and nicotine gum but not with its "Bacco" flavor or other tobacco-flavored e-liquid. Similarly, the cross-sectional survey neither shows a benefit to flavoring nor provides meaningful information regarding actual switching or reduction, and both Liquid Labs' literature review and a third-party literature review indicate uncertainty regarding the role of flavors in smoking cessation. Thus, the FDA did not deny Liquid Labs' applications solely because they lacked randomized controlled trials or longitudinal cohort studies. Rather, the record indicates that the FDA properly denied them because the other evidence Liquid Labs submitted was insufficient.

Accordingly, the FDA did not "reverse course" and newly require randomized controlled trials and/or longitudinal cohort studies, and therefore did not upset Liquid Labs' reliance interests, provide inadequate notice, or act arbitrarily and capriciously.

Contrary to Liquid Labs' assertion, the FDA also did not arbitrarily and capriciously mandate "over time/long-term

studies." Reply at 7.[10] The Marketing Denial Order, Reviews for Flavored ENDS PMTAs, and Technical Project Lead Review all demonstrate that the FDA wanted reliable evidence that Liquid Labs' flavored e-liquids, among other things, helped adult smokers cut down on their cigarette use or switch to using ENDS products only. So did the FDA's June 2019 Guidance. See, e.g., JA 217. Reliable evidence of these behavioral changes is more likely to come from a study conducted over time because data collected over a short period may not show whether a particular change is temporary or long-lasting. To this end, the FDA stated that "it might accept evidence other than long-term studies, if that evidence had sufficient scientific underpinnings to meet the [Act]'s statutory mandate of demonstrating that flavored ENDS devices are appropriate for the protection of public health." Breeze Smoke, 18 F.4th at 506-07 (emphasis omitted). Thus, the FDA does not require PMTA applicants to conduct long-term studies.[11]

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[10] Liquid Labs conflates "long-term" studies with studies examining behavior "over time." First, the FDA materials show that the phrase "long-term study" measures the duration of a study. For example, the FDA describes "long-term studies" as lasting six months or more. Studies that measure behavior over time, however, can last shorter periods. In fact, the Technical Project Lead Review indicates that studies occurring "over time" could be shorter than six months. Second, although a study concerning behavioral changes over time could be the focus of a "long-term" study, such a study may not be necessary to secure the information sought.

[11] That said, to the extent Liquid Labs is claiming "the FDA's statement that it would consider evidence other than long-term studies" "announc[ed]" that "'long-term studies

Moreover, the FDA did not require "long-term studies" from Liquid Labs. Both the Marketing Denial Order and the Technical Project Lead Review refer to studies analyzing behavior "over time," JA 1-2, 73-74 & n.xxiii, but, as explained above, that does not mean that a long-term study is required. Rather, "the FDA has all along required 'valid scientific evidence,' and its denial orders explained how the . . . data petitioners submitted fell short of the mark." Prohibition Juice, 45 F.4th at 23. Accordingly, Liquid Labs' "over time/long-term studies" argument is also unavailing.

2

We also join our sister circuits in concluding that the FDA permissibly "required a comparison of a manufacturer's 'flavored products' with 'tobacco-flavored ENDS' products in their ability . . . to assist adult smokers to quit or switch." Reply Br. at 10 (emphasis omitted); see Wages & White Lion, 41 F.4th at 434; Prohibition Juice, 45 F.4th at 19-20, 23-24. "The governing statute expressly asks for evidence concerning whether an applicant's 'tobacco product presents less risk than other tobacco products,' . . . and the FDA's [June] 2019

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were likely unnecessary,'" they are "over-read[ing]" it. Prohibition Juice, 45 F.4th at 22-23 (quoting Wages & White Lion, 16 F.4th at 1140-41). In its June 2019 Guidance, the FDA "broadened the types of evidence it would consider," meaning "[i]nstead of limiting applicants to the two types of evidence it usually requires, the agency allowed manufacturers to submit evidence in other forms." Id. at 21. "But at the same time the agency made clear it would not relax the scientific rigor of the requisite public health demonstration." Id.

Guidance told manufacturers that the agency would look for comparisons between the proposed product and 'tobacco products in the same category or subcategory.'" Prohibition Juice, 45 F.4th at 23 (first quoting 21 U.S.C. § 387j(b)(1)(A), then quoting June 2019 Guidance at 13). The "FDA is then required to consider 'the information submitted to the Secretary as part of the application,' which necessarily includes the comparative efficacy reports that applicants must provide." Wages & White Lion Invs., 41 F.4th at 434 (quoting 21 U.S.C. § 387j(c)(2)) (emphasis omitted). The FDA is also required to "consider 'the increased or decreased likelihood that existing users of tobacco products will stop using such products,'" which "necessarily implies a comparative analysis." Id. (quoting 21 U.S.C. § 387j(c)(4)(A)).[12] Thus, the statute and June 2019 Guidance are clear about comparative analysis.[13] Accordingly, "[b]ecause the [June] 2019 Guidance gave fair notice of the analysis the agency would perform and

[12] Additionally, even if such express authority were lacking, the "FDA certainly has implied authority"—for the reasons the Court of Appeals for the Fifth Circuit explained—to consider comparative risk as it did here. Wages & White Lion, 41 F.4th at 435.

[13] Liquid Labs also contends that it was misled because the June 2019 Guidance "focuses exclusively on the physiological health risks associated with the compared products, not behavioral impacts." Reply Br. at 10-11; see also id. at 25. As the Wages & White Lion court explained, however, "[i]nitiation and cessation behaviors are physiological health risks." 41 F.4th at 434 (emphasis omitted); see also Prohibition Juice, 45 F.4th at 19-20 ("The degree to which a harmful product entices and addicts new users is inarguably a component of the 'health risk' it poses.").

the purpose of those comparisons, . . . the agency did not create unfair surprise by focusing on comparisons between otherwise similar flavored and nonflavored products."[14] Prohibition Juice, 45 F.4th at 24.[15]

[14] Liquid Labs' related argument that the FDA, in effect, engaged in the modified risk tobacco products inquiry or the required proof akin to that necessary for drugs is also unpersuasive. As discussed herein, the FDA did not impose "entirely different (and far more stringent) requirements," Pet. Br at 52, than those contemplated by the governing statute, see also 21 U.S.C. §§ 355(b)(1)(A), 387k. "Moreover, the fact that the FDA has other authorities through which it can approve other products . . . does not release the FDA from following its statutory mandate here to approve only tobacco products the sale of which it determines 'would be appropriate for the protection of the public health,'" and Liquid Labs has given us "no persuasive reason to think that those other authorities somehow limit the inquiry the FDA may make in reaching" its "determination." Prohibition Juice, 45 F.4th at 20 (quoting 21 U.S.C. § 387j(c)(2)); see also Gripum, LLC, 47 F.4th at 559.

[15] Liquid Labs claims that it provided evidence aligning with the FDA's June 2019 Guidance. Liquid Labs has not shown, however, that the FDA erred in concluding that the evidence was insufficient. Wages & White Lion, 41 F.4th at 439; see also Breeze Smoke, 18 F.4th at 507 ("declin[ing] to embrace" petitioner's claim "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").

For these reasons, the FDA did not apply unannounced or changed standards for PMTAs.

3

The FDA's decision to decline to review Liquid Labs' marketing plan does not change the result because there is no indication the plan would have made up for the deficiencies the FDA identified in Liquid Labs' applications. See Delaware Riverkeeper Network v. Sec'y Pa Dep't of Env't Prot., 833 F.3d 360, 377 (3d Cir. 2016) ("[M]istakes that have no bearing on the substantive decision of an agency do not prejudice a party."); see also, e.g., Prohibition Juice, 45 F.4th at 25 (concluding petitioner failed to show that the FDA's failure to consider its marketing plan "could have changed the agency's decision on their applications"); Wages & White Lion, 41 F.4th at 442 (concluding that even if the FDA inadequately reviewed petitioners' marketing plans, the error was harmless because petitioners failed to "show that they would have received authorization had [the] FDA considered the[] plans").[16] For

[16] In a divided opinion, the Court of Appeals for the Eleventh Circuit remanded after concluding the FDA's failure to review the petitioners' marketing plans was both arbitrary and capricious and harmful. See Bidi Vapor LLC v. U.S. Food & Drug Admin., 47 F.4th 1191 (11th Cir. 2022). Among other things, the Bidi Court distinguished Prohibition Juice on the grounds of "concessions . . . made . . . at oral argument" before the Court of Appeals for the District of Columbia Circuit. Id. at 1208. The purported concessions echoed the Prohibition Juice petitioners' briefing, which did not "identify how they were harmed from the FDA's failure to consider essentially the same [marketing] measures it had previously rejected."

example, to address youth use, Liquid Labs' marketing plan lists, among other things, "age verification measures," a "mystery shopper" program, Pet. Br. at 12, and a prohibition on marketing material "that could be perceived to be targeting individuals below the legal vaping age," JA 322-23, but these are similar, if not identical, to the kinds of approaches the FDA found did not address this serious problem, see, e.g., JA 89-91, 125-27 (April 2020 Guidance); see also Prohibition Juice, 45 F.4th at 25 (explaining that "self-verification of age at the point of sale and . . . less vibrant marketing unappealing to youth" "track measures the FDA in its 2020 guidance deemed inadequate"); Wages & White Lion, 41 F.4th at 442 (explaining the "FDA had already explained," for example, that "products . . . [being] only sold in age-gated vape and specialty tobacco shops and through age-gated online sales" "do not work") (emphasis omitted). Liquid Labs has not explained how the approaches in its plan differ from ones previously found insufficient or how its marketing plans would have cured other noted deficiencies in its applications, particularly given the FDA's earlier conclusion that "focusing on how the product was sold would not be sufficient to address youth use of [flavored cartridge-based] products."[17] JA 125.

Prohibition Juice, 45 F.4th at 25 ("In response to questioning . . . at oral argument, the manufactures again did not identify . . . ."). Liquid Labs also did not provide such an explanation, so it is like Prohibition Juice and thus different from Bidi.

[17] Liquid Labs tried to distinguish its marketing plan from "many" other companies', but it fails to explain how its purportedly distinctive features—e.g., selling via online third-party distributors rather than selling through its own website—make a meaningful difference or address the concerns about youth usage.

Because Liquid Labs has not shown that its marketing plans differ from those previously rejected or that its plans would have rectified the scientific deficiencies, the marketing plans would not change the result. Accordingly, even assuming the FDA erred in declining to review Liquid Labs' marketing plans, the error was harmless. See Shinseki v. Sanders, 556 U.S. 396, 411 (2009) (stating one of "the factors that inform[s] a reviewing court's 'harmless-error' determination" is "an estimation of the likelihood that the result would have been different").

4

Contrary to Liquid Labs' claim, the FDA did not ignore that Liquid Labs sought approval for "bottled e-liquids intended for use with open-systems devices." Pet Br. at 45-46. The FDA acknowledged that "there may be differential appeal of certain product styles," but pointed to evidence where "the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired flavor options" as "underscoring the . . . role of flavor in driving appeal," and explained, based on the evidence it reviewed, that "the role of flavor is consistent" "across . . . different device types." JA 68-69. Because these observations and conclusions are backed "with substantial evidence, . . . we have no basis to second-guess [them]." Prohibition Juice, 45 F.4th at 26; Wages & White Lion, 41 F.4th at 437-38. We therefore reject Liquid Labs' argument that the FDA ignored the specific characteristics of its products.

Finally, Liquid Labs argues that the FDA erred by failing to consider all segments of the population, including

adults currently using flavored ENDS who may lose their ability to access them and who may turn to the "illicit market" as a result. Pet. Br. at 51.[18]

Liquid Labs' argument lacks merit. As an initial matter, all non-tobacco and/or menthol flavored ENDS are not banned, and thus, there is no reason for the FDA to examine Liquid Labs' speculative "entire[] eliminat[ion]" claim. Pet Br. at 50. In any event, the FDA explained that: (1) the relevant statutory authorities required it to account for "the risks and benefits to the population as a whole," JA 64 n.ii; (2) its "review [wa]s focused on the risk to youth nonusers as well as the potential benefit to adult smokers as current users, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth," JA 64 n.ii; see JA 65 n.vii; and (3) it considered, among other things, (a) "the likelihood that an authorization will increase or decrease the number of tobacco users in the overall population," JA 65 n.vii, (b) "the degree of benefit to a flavored ENDS product over a tobacco-flavored variety in facilitating

[18] Liquid Labs also argues that the FDA did not consider "less disruptive alternatives" to issuing the denial order. Pet. Br. at 51 (quoting Wages & White Lion, 16 F.4th at 1139). The FDA, however, "was not required to consider alternative regulatory approaches before denying the manufacturers' applications for premarket approval." Prohibition Juice, 45 F.4th at 26. Further, the portion of the Wages & White Lion opinion that Liquid Labs cites discusses alternatives in the context of its conclusion that the FDA "chang[ed] from its no-long-term-studies-necessary policy to its apparent long-term-studies-required policy." 16 F.4th at 1139. We have already concluded, however, that no such change occurred.

smokers completely switching or significantly reducing their smoking," JA 72, and (c) the lack of conclusive evidence "regarding the role of flavors in prompting switching among adult smokers," JA 72; see also JA 64 n.vi ("[I]n the absence of strong evidence generated by directly observing the behavioral impacts of using a flavored product vs. a tobacco-flavored product over time, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth."). Thus, the record shows that the FDA considered whether Liquid Labs' products were appropriate for the protection of public health from several vantage points, provided evidence for its particular focus, and concluded that the evidence Liquid Labs submitted came up short.

B

In light of the foregoing, Liquid Labs' additional arguments lack merit. The FDA reviewed Liquid Labs' application in conformity with, among other things, its statutory authorities and publicly issued guidance, and thus did not act ultra vires. Likewise, because the FDA did not adopt a "new secret standard" or otherwise change course, it also did not violate the Act or APA and had no obligation to proceed through notice-and-comment rulemaking.

III

For the foregoing reasons, we will deny the Petition for Review.