No. 22-

IN THE

Supreme Court of the United States

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

Petitioners,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

In 2016, FDA extended its jurisdiction over "tobacco products" under the Federal Food, Drug, and Cosmetic Act to electronic nicotine delivery systems ("ENDS")—products that contain no tobacco themselves and are a less harmful alternative to combustible cigarettes. FDA's decision required Petitioners to obtain marketing authorization from FDA to continue selling their products. Petitioners submitted premarket applications that followed closely the instructions for supporting evidence FDA provided in public meetings, a guidance document, and a proposed rule. Approximately one year later, FDA denied Petitioners' applications for non-tobacco-flavored ENDS products based on a new, previously unannounced evidentiary standard requiring data from studies comparing the flavored products to tobacco-flavored ENDS products in terms of their efficacy at promoting adult smokers' switching or cigarette reduction over time. Because Petitioners' applications lacked this longitudinal comparative efficacy evidence, FDA failed to consider the marketing and sales-access restrictions the agency had previously described as "critical" to its determination and rejected other evidence in Petitioners' applications, including from certain studies FDA had previously recommended. The Fourth Circuit found FDA's decision not arbitrary or capricious under the Administrative Procedure Act.

The questions presented are:

(1) Whether FDA's marketing denial order was arbitrary and capricious because the agency failed to timely notify Petitioners of the new evidentiary standard before denying their applications.

(2) Whether FDA ignored relevant factors and important aspects of the problem to Petitioners' prejudice when the agency failed to consider or rejected evidence that FDA had previously instructed Petitioners to include.

CORPORATE DISCLOSURE STATEMENT

Pursuant to Supreme Court Rule 29.6, the undersigned counsel of record certifies that Petitioners Avail Vapor, LLC; Blackship Technologies Development, LLC; and Blackbriar Regulatory Services, LLC (collectively, "Avail") have no parent corporation and that no publicly held company owns 10 percent or more of the stock of any of the Petitioners. There is no other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of this case.

PARTIES TO THE PROCEEDINGS

Petitioners Avail Vapor, LLC; Blackship Technologies Development, LLC; and Blackbriar Regulatory Services, LLC were the petitioners in the court of appeals.

Respondent United States Food and Drug Administration was the respondent in the court of appeals.

RELATED PROCEEDINGS

United States Court of Appeals (4th Cir.), *Avail Vapor, LLC, et al. v. United States Food and Drug Administration*, No. 21-2077 (judgment entered Dec. 12, 2022).

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Before the deadline for applicants to submit premarket tobacco product applications to keep their ENDS products on the market, FDA outlined in public meetings and guidance documents its instructions and recommendations for preparing applications that could lead to marketing authorization and issued a proposed rule identifying required contents. Avail followed FDA's guidance and recommendations when it prepared its applications and performed the studies FDA endorsed. Avail even looked to FDA's enforcement guidance that targeted ENDS devices that differed significantly from the bottled e-liquids Avail manufactured to ensure its marketing plan included the types of advertising and sales-access restrictions FDA had specifically identified as adequate measures to combat youth initiation.

But ten months after the submission deadline, FDA decided to adopt and apply a new evidentiary standard for applications for non-tobacco-flavored ENDS products, including Avail's bottled e-liquids. FDA adopted this new evidentiary standard without notice or warning, and only disclosed it when the agency issued the first of hundreds of orders denying marketing authorization for some 99% of all timely filed applications for ENDS products. Despite Avail's submission of extensive scientific evidence tailored to FDA's prior representations, FDA denied Avail's application because it failed to include the studies that FDA now newly required and instead included extensive evidence that FDA had previously recommended and described as "critical" to its evaluation, but now chose to ignore or reject.

The notice that FDA, or any agency, must provide to regulated stakeholders when the agency changes policy

is central to Avail's case. Here, FDA provided no timely notice of its *sub silentio* changes to the evidentiary standard and studies it would accept. As a result, Avail received a marketing denial order ("MDO") premised on new, *post hoc* evidentiary requirements that Avail had no fair opportunity to meet.

The Fourth Circuit misunderstood this point, as exemplified by its erroneous belief that "Avail attempts to tie the hands of the FDA to certain forms of evidence and kinds of studies in what is a rapidly evolving field [and] in focusing upon procedural points, Avail encourages us to neglect the forest for the trees." App. 16a. This Court should grant the instant petition and find FDA's conduct arbitrary and capricious. In the process, the Court can resolve a circuit split, provide clarity on the notice agencies must provide before changing their policies, and combat the outcome-driven review of agency action conducted by the court below.

OPINION BELOW

The Fourth Circuit's opinion (App. 1a-37a) is reported at 55 F.4th 409. The opinion upheld a marketing denial order that FDA issued to Avail on September 15, 2021 (App. 38a-54a).

JURISDICTION

The judgment of the court of appeals was entered on December 12, 2022. The Chief Justice extended the deadline for petitioning for writ of certiorari to May 11, 2023. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

Pertinent statutory provisions are reproduced in the appendix as follows:

A. **5 U.S.C. § 706(2).** App. 131a.

B. **21 U.S.C. § 387*j*.** App. 131a-133a.

C. **21 U.S.C. § 387*l*(b).** App. 134a.

STATEMENT OF THE CASE

I. FDA's Regulatory Authority over ENDS Products

In 2009, Congress enacted the Family Smoking Prevention and Tobacco Control Act ("TCA") to grant FDA authority over tobacco products. Pub. L. No 111-31, 123 Stat. 1776 (2009). The TCA defined a "tobacco product," in relevant part, as "any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product." 21 U.S.C. § 321(rr) (2009). The TCA prohibited the marketing of any "new" tobacco product – in general, a product not marketed as of February 15, 2007 – unless FDA granted a marketing authorization order for that product. 21 U.S.C. § 387j.

Although the TCA originally applied only to certain traditional tobacco products, Congress authorized FDA to "deem" other tobacco products to be subject to the Act. 21 U.S.C. § 387a(b). In 2016, FDA implemented a rule that deemed electronic nicotine delivery systems ("ENDS") to be subject to the Act. 81 Fed. Reg. 28973 (May 10, 2016).

But by that point millions of ENDS products were already commercially marketed. So, FDA adopted a discretionary enforcement policy that allowed those products to remain on the market so long as the sponsor submitted a premarket tobacco product application ("PMTA") for that product by August 2018, and until FDA reached a decision on marketing authorization. *See* 81 Fed. Reg. at 29009-15. FDA subsequently extended the submission deadline to August 2022, but later accelerated the deadline to September 2020 to comply with a district court order. *See Vapor Technology Ass'n v. FDA*, 977 F.3d 496, 497-502 (6th Cir. 2020).

II. FDA's Instructions to Manufacturers and Evidentiary Standard

The TCA provides that FDA shall grant marketing authorization for a new tobacco product if the applicant shows, among other things, "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)(1)(A), (2)(A). The agency's APPH finding "shall be determined with respect to the risks and benefits of the population as a whole, including users and nonusers of the tobacco product, and taking into account" (1) "the increased or decreased likelihood that existing users of tobacco products will stop using such products," and (2) "the increased or decreased likelihood that those who do not use tobacco products will start using such products." 21 U.S.C. § 387j(c)(2)(A), (c)(4).

Before the September 2020 PMTA submission deadline, FDA communicated its instructions and recommendations for applicants to show that their

products satisfied the APPH standard through several means, including public meetings, an ENDS PMTA Guidance, and a proposed PMTA rule. But none of those recommendations mentioned the evidentiary standard for flavored ENDS products that FDA ultimately applied when it later denied Petitioners' PMTAs.

A. FDA's Public Meetings

At an October 2018 public meeting, an FDA representative stated: "No specific studies are required for a PMTA; it may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies given other data sources can support the PMTA." Iilun Murphy, *Premarket Tobacco Product Application Content Overview*, at 26 (October 23, 2018), https://perma.cc/2JF4-J3ZR.

FDA recommended that applicants "compare the new tobacco product to a representative sample of tobacco products on the market (i.e., either grandfathered or with authorization)" and "[i]nclude justification for why using evidence or data from other products is appropriate." *Id.* at 11. In the area of human subject studies, FDA recommended including evidence from single-point-in-time studies on consumer perceptions and appeal of the subject product and noted that such studies were "widely accepted" as predictors for initiation and cessation. *Id.* at 13, 16. The presentation specified that "[p]roduct perceptions/intentions, including how consumers (especially youth) perceive, use, or intend to use the products is useful information to FDA." *Id.* at 16. On the issue of youth initiation, FDA stated that "[i]nferences regarding youth may be . . . derived from marketing

data, scientific literature reviews, national surveys, and/or bridging information." *Id.* at 18.

Nowhere in the presentation did FDA suggest that manufacturers of flavored ENDS products should conduct a switching study comparing the rates of reduction in use of combustible cigarettes by users of flavored ENDS products against those of users of tobacco-flavored ENDS products over time. The only reference to switching studies stated: "Switching studies: Participants could be directed to substitute an e-cigarette with similar nicotine for usual brand cigarette." *Id.* at 20. Far from prescribing a required comparator product, FDA suggested instead that applicants provide a "[r]ationale for selection of comparator products (e.g., e-liquid nicotine concentrations, flavors, etc.)." *Id.*

In a slide titled "What is Appropriate for Protection of Public Health?", FDA described the evidence it required to find that a tobacco product meets the statutory standard for marketing authorization as follows:

> These are considerations that FDA has used in deciding whether a product is appropriate for the protection of public health:
>
> - Are the levels of HPHCs and other constituents of toxic concern in the new tobacco product similar or lower than levels of similar [tobacco products] or other appropriate comparator products currently on the US market?

> - Does the scientific evidence provided in the application support that the use of the [tobacco product] has a lower risk of disease for the individual than the use of other similar or appropriate comparator [tobacco products] on the market?
>
> - Will the marketing of the new [tobacco product] affect the likelihood of nonuser uptake, cessation rates, or other significant shifts in user demographics in a manner to decrease morbidity and mortality from tobacco product use?

Id. at 32.

At a similar public meeting in 2019, FDA repeated many of these points, including its statements on switching studies and the three "considerations" for determining whether a tobacco product satisfies the statutory standard. Emily R. Busta, *Premarket Tobacco Product Application (PMTA) Review Pathway*, at 13, 15, 16, 18, 22, 34 (Oct. 28, 2019), https://perma.cc/QR9E-XKR7.

B. FDA's Final ENDS PMTA Guidance

In June 2019, FDA published its final guidance on PMTAs for ENDS products. *See* CA.A220-74 ("PMTA Guidance").[1] The purpose of the PMTA Guidance was

1. "CA.A" refers to the appendix filed with the Fourth Circuit.

to "assist persons submitting [PMTAs] for [ENDS]" products and to "enable ENDS manufacturers to consider and strengthen their applications." CA.A223. In the Guidance, FDA stated: "Given the relatively new entrance of ENDS on the U.S. market . . . limited data may exist from scientific studies and analysis. Nonetheless, in general, FDA does not expect that applicants will need to conduct long-term studies to support an application." CA.A235. FDA stated that "[a]lthough randomized clinical trials could address cessation behavior of users of tobacco products, FDA believes this would also be true for observational studies (perception, actual use, or both) examining cessation behaviors." CA.A260.

The PMTA Guidance nowhere suggested that applicants should compare flavored ENDS products against tobacco-flavored ENDS products to determine whether more smokers reduced or eliminated their combustible cigarette usage with the flavored ENDS product over time. The section of the Guidance that speaks to comparison studies focused on physiological health risks associated with the compared products and again emphasized that applicants could choose what they believed to be appropriate comparators and should justify their selections. CA.A235. FDA also specifically recommended that applicants evaluate the risks of ENDS products in relation to the risks of combustible cigarettes. CA.A236. Similarly, the section that addressed cessation did not mention comparative cessation studies and specifically suggested that it would be appropriate to include information from peer-reviewed journals on the likelihood of product use by nonusers, including youth. CA.A260.

The PMTA Guidance suggested that applicants "may propose specific restrictions on sale and distribution that can help support a showing that permitting the marketing of the product would be [appropriate for the protection of public health]." CA.A234. The Guidance recommended including a detailed marketing plan "to enable FDA to better understand the potential consumer demographic" and "better estimate the potential impact on public health." CA.A261. FDA promised to "weigh[] all of the potential benefits and risks from the information contained in the PMTA to make an overall determination of whether the product should be authorized for marketing." *Id.*

C. FDA's Proposed PMTA Rule

In September 2019, FDA issued a proposed rule governing PMTAs that reiterated that FDA did "not expect that long-term clinical studies (i.e., those lasting approximately 6 months or longer) [would] need to be conducted for each PMTA." FDA, *Premarket Tobacco Product Applications and Recordkeeping Requirements, Proposed Rule*, 84 Fed. Reg. 50566, 50619 (Sept. 25, 2019). FDA confirmed that marketing plans would be "critical to FDA's determination of the likelihood of changes in tobacco product use behavior" and that the agency "will review the marketing plan to evaluate potential youth access to, and youth exposure to, the labeling, advertising, marketing, or promotion of, a new tobacco product." *Id.* at 50581.

Nowhere in the proposed PMTA rule did FDA require or even recommend that applicants seeking marketing authorization for flavored ENDS products conduct switching studies comparing the flavored ENDS products against tobacco-flavored ENDS products.

D. FDA's 2020 Enforcement Guidance

On January 2, 2020, FDA issued a new guidance document ("2020 Enforcement Guidance") in which it modified its enforcement priorities under its deferred enforcement policy.[2] CA.A89. In light of then-increasing youth usage of certain ENDS products, FDA stated that it would prioritize for enforcement: (i) flavored, *cartridge-based* ENDS products other than tobacco- or menthol-flavored ENDS products; (ii) all other ENDS products for which the manufacturer failed to take adequate measures to prevent minors' access; and (iii) any ENDS products targeted to minors or whose marketing is likely to promote use by minors. CA.A92. The 2020 Enforcement Guidance did not address the information applicants should include in their PMTAs.

In the 2020 Enforcement Guidance, FDA highlighted certain characteristics of flavored, cartridge-based products as making them attractive to youth, including small size, ease of concealment, high nicotine content, and ease of use due to a lack of settings to change and the convenience of pre-filled replacement cartridges. CA.A104, 108. FDA excluded from the "cartridge-based ENDS products" definition, and thus the top "priority" category for enforcement, "self-contained, disposable" ENDS products, even though these products share these same characteristics with cartridge-based ENDS products. CA.A98 n.21. With respect to bottled e-liquids like Avail's that are sold in specialty vape shops, FDA emphasized at least three times in the Guidance that

2. The enforcement guidance was revised and updated in April 2020 due to the extension of the PMTA submission deadline from May 2020 to September 9, 2020.

"[t]his policy should have minimal impact on small manufacturers (e.g., vape shops) that primarily sell non-cartridge-based ENDS products, unless they market to youth or fail to take adequate measures to prevent youth access." CA.A107; *see also* CA.A113, CA.A133.

FDA underscored that, in assessing whether a manufacturer is taking "adequate measures to prevent minors' access" to ENDS products, FDA intended to consider factors such as (i) whether the manufacturer had adequate programs to monitor retailer compliance with age-verification and sales restrictions, including an up-front retailer screening process; (ii) whether the manufacturer establishes and enforces penalties against non-compliant retailers; (iii) whether retailers check identification at the door; and (iv) for online sales, whether an independent, third-party age- and identity-verification service that compares customer information to public records is used. CA.A111.

III. Avail's PMTAs

On September 8, 2020, Avail submitted its bundled PMTAs for its bottled, nicotine-containing e-liquids. CA.A14. Based on FDA's representations on PMTA requirements, Avail commissioned an extensive research program designed to address specific components of the final PMTA Guidance through behavioral studies, and which contained significant evidence on cessation. These studies included a focus group study, a two-week online diary to examine participant behavior, validation/summative testing, and a cross-sectional perception and intent study specifically designed to address FDA's guidelines for perception and behavior research in the context of a PMTA. CA.A316-18.

Avail also submitted a marketing plan that tracked the restrictions FDA had identified as "adequate measures" to prevent youth access in its 2020 Enforcement Guidance. CA.A111. These restrictions included requiring age-gating in retail stores and identity verification before any purchases; using an independent age- and identity-verification service to ensure online sales were limited only to individuals who were 21; requiring distributors to submit written policies on their youth-access restriction procedures and restricting sales to responsible retailers; and requiring retailers to submit a record of compliance with their youth-access restriction policies. CA.A39-40. Any distributor or retailer found to be non-compliant would be considered in breach of contract and all sales to them would cease. CA.A40.

IV. FDA's *Sub Silentio* Changes to its Evidentiary Standard for Non-Tobacco-Flavored ENDS Products

Ten months after Avail submitted its PMTA, and without notice to anyone outside the agency, in July 2021, FDA issued an internal memorandum stating that, at the Acting Commissioner's urging, FDA would apply a new "standard for evidence" for some, but not all, PMTAs for flavored ENDS products. *See* CA.A61-72. This change deviated from FDA's original PMTA review plan and came just two weeks after the Acting Commissioner's testimony before Congress, during which she encountered substantial political pressure to deny all PMTAs for non-tobacco-flavored ENDS products.[3]

3. *See* Committee on Oversight and Accountability Democrats Press Release, *Subcommittee Hearing Offers Insight into Future of E-Cigarette Regulation* (June 23, 2021), https://perma.cc/74XV-8DR7.

Under the July 2021 memorandum, the Office of Science in FDA's Center for Tobacco Products ("CTP") was "tasked with developing a new plan to effectively manage the remaining non-tobacco flavored ENDS PMTAs" not already in substantive scientific review to enable FDA to take "final action on as many applications as possible by September 10, 2021." CA.A61. Under this new "standard for evidence," rather than review an entire PMTA and its contents in context, given the "large number of applications that remain[ed] to be reviewed by September 9, 2021,"[4] FDA would "conduct a Fatal Flaw review . . . a simple review in which the reviewer examines the submission to identify whether or not it contains the necessary type of studies." CA.A62. FDA decided the "fatal flaw" would be the absence of randomized controlled trials or longitudinal cohort studies demonstrating that an applicant's non-tobacco-flavored ENDS products provide a greater benefit to adult smokers in terms of promoting smoking cessation relative to tobacco-flavored ENDS products. CA.A61. Any application lacking this evidence would "likely" be denied. CA.A62.

Although FDA claims that this memorandum was later superseded, the "fatal flaw" analysis is substantially reflected in FDA's internal "scientific review" forms. In these forms, FDA described the scope of its review as follows:

> This review determines whether the subject PMTAs contain evidence from a randomized

4. FDA expected 6,800 product applications but received *6.5 million*, exceeding its anticipated volume "by orders of magnitude." FDA, *Deemed Product Review: A Conversation with the Office of Science* (June 11, 2021), https://perma.cc/Z65M-ZWMT.

> 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 their flavored ENDS over an appropriate comparator tobacco-flavored ENDS.

CA.A18.

On August 17, 2021, FDA issued another internal memorandum with a subject of "PMTA Review: Evidence to Demonstrate Benefit of Flavored ENDS to Adult Smokers." CA.A73. The August 17, 2021 memorandum purports to describe FDA's "findings with respect to the type of evidence that may support a finding that the marketing of a flavored ENDS is appropriate for the protection of public health." *Id.* Despite increases in youth use of *disposable* ENDS devices since the 2020 Enforcement Guidance banned flavored cartridge-based ENDS products, the memorandum does not differentiate flavored bottled e-liquids from cartridge-based or disposable ENDS devices in terms of their roles in promoting youth initiation. CA.A76-78. The memorandum instructs that, based on its "completion of numerous scientific reviews over the last 10 months," CA.A81, product-specific evidence enabling a comparison between the applicant's new flavored ENDS product and an "appropriate comparator" tobacco-flavored ENDS product as to their impact on tobacco use behavior among adult smokers would be required. CA.A81-82. This evidence could be generated through either a randomized controlled trial or a longitudinal cohort study. CA.A82.

On August 25, 2021, the day before FDA issued its first marketing denial orders for non-tobacco-flavored ENDS

products, two FDA officials signed a three-sentence internal memorandum purportedly rescinding the August 17, 2021 memorandum. CA.A88. However, as discussed below, FDA incorporated substantial sections of the memorandum into its subsequent Technical Project Lead report on Avail's application and nearly identical reports for other applicants that also received denial orders for their flavored ENDS products.

As with the July 9, 2021 internal memorandum before it, FDA failed to contemporaneously disclose the conclusions it reached in its August 17, 2021 memorandum to applicants.

V. Avail's Marketing Denial Orders and Technical Project Lead Report

On August 26, 2021, FDA revealed via a press release that marketing of flavored ENDS products would be authorized only if PMTAs included studies, such as a randomized controlled trial or longitudinal cohort study, showing that an applicant's non-tobacco-flavored ENDS products were more effective at promoting switching or cessation of combustible cigarette use than comparable tobacco-flavored ENDS products over time.[5] Only two weeks later, FDA announced that it had issued MDOs for more than 946,000 flavored ENDS products.[6]

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5. FDA, 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://perma.cc/8ZH8-SQ7F.

6. FDA, Press Release, *FDA Makes Significant Progress in Science-Based Public Health Application for Review, Taking Action on Over 90% of More than 6.5 Million 'Deemed' New*

On September 15, 2021, FDA issued a marketing denial order to Avail. App. 38a-54a. The MDO demanded:

> robust and reliable evidence . . . regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS over an appropriate comparator tobacco-flavored ENDS.
>
> Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time.

App. 40a.

The MDO further stated:

> [a]lthough your PMTA contained four protocols for RCTs . . . to address the new products' abuse liability, the study reports were not submitted. All four protocols were described as randomized, open-label, crossover studies to evaluate nicotine pharmacokinetics and subjective effects with use of different e-liquid products and usual brand of combustible cigarettes in healthy adult smokers. No data

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Tobacco Products Submitted (Sept. 9, 2021), https://perma.cc/L9ZM-GFBW.

> from these RCT protocols was submitted for review; therefore, this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s); 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.

App. 40a-41a. Before issuing the MDO, FDA had not notified Avail that its PMTA was in substantive scientific review or issued any deficiency letter to alert Avail that it needed to submit the data from the ongoing randomized controlled trials. The MDO nowhere mentioned the other behavioral studies or marketing plan submitted by Avail.

The MDO added that because "key evidence demonstrating [appropriateness for the protection of public health] is absent," "scientific review did not proceed to assess other aspects of your application." App. 41a. FDA's review ignored Avail's proposed marketing plan and its measures to safeguard against youth appeal and access. *Id.*

In its Technical Project Lead ("TPL") report supporting the MDO, FDA incorporated word-for-word much of its "rescinded" August 17, 2021 memorandum. *Compare* App. 55a-107a *with* CA.A73-87. The TPL report disclaimed any notion that a single-point-in-time survey would suffice to address smoking cessation. App. 82a-84a. In further contrast to its earlier representations, FDA also concluded that "the general scientific literature, though

informative for evaluation of some types of products, is not adequate to address this assessment because it does not provide product-specific information." App. 82a.

After Avail petitioned for review, FDA re-reviewed Avail's application. FDA's re-review again ignored Avail's marketing plan and reaffirmed the MDO, concluding that the PMTA did not "contain evidence from an RCT or longitudinal study or other evidence demonstrating the benefit to adult users of the applicant's flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes." App. 117a.

VI. FDA's Final PMTA Rule

FDA published its final PMTA rule ("Final Rule") on October 4, 2021, more than one year after Avail submitted its PMTAs, and just weeks after FDA issued boilerplate MDOs to Avail and hundreds of other applicants. FDA, *Premarket Tobacco Product Applications and Recordkeeping Requirements, Final Rule*, 86 Fed. Reg. 55300 (Oct. 4, 2021). The Final Rule confirms that the TCA "requires FDA [to] make an *individualized* determination of whether to deny an application based on the risks and benefits of a *specific* tobacco product." *Id.* at 55390 (emphasis added). The Final Rule also asserts that marketing authorization decisions will be "based on all of the contents of the application" and that FDA would not "make a determination on one static set of requirements." *Id.* at 55320, 55385. The Final Rule reaffirms that FDA does "not expect that applicants will need to conduct long-term clinical studies to support an application." *Id.* at 55387. The Final Rule states that marketing plans

"will directly inform [FDA's] assessment of who may be exposed to the [marketing processes] and, as a result, its consideration of the potential impact on youth initiation and use." *Id.* at 55324.

In striking contrast to the "fatal flaw" analysis adopted in July 2021 and the "check-the-box" forms that FDA used for "scientific review" to disqualify PMTAs for flavored ENDS products that lacked randomized controlled trials or longitudinal cohort studies, the Final Rule expressly declines "to create a series of criteria that either all products or a specific subset of products must meet be in order for marketing of such products to be considered [appropriate for the protection of public health]." 86 Fed. Reg. at 55386. The Final Rule states that determination of appropriateness for protection of the public health will be "based on all of the contents of the application." *Id.* at 55320.

Ironically, mere weeks after issuing Avail's MDO based on its new "standard for evidence," in the Final Rule, FDA agreed with a comment that it would be "fundamentally unfair" to apply retroactively new criteria for "acceptance" and "filing" of PMTAs to applications that had already been submitted. *Id.* at 55406.

VII. Proceeding Below

On September 30, 2021, Avail timely petitioned the Fourth Circuit for review of the MDO pursuant to 21 U.S.C. § 387*l*(a)(1)(B). Avail sought an order setting aside the MDO so that it could conduct the new longitudinal comparative efficacy studies FDA now requires and amend its applications with the resulting data. On December 12,

2022, the lower court denied Avail's petition. The circuit court fundamentally misunderstood Avail's arguments regarding FDA's internal memoranda relating to the changed evidentiary standard. App. 27a-28a. The circuit court also repeatedly conflated Avail's procedural challenges to FDA's *sub silentio* changes to its evidentiary requirements with the issue of FDA's substantive authority for requiring comparative efficacy evidence and issuing the MDO. App. 16a-20a, 25a-27a.

REASONS FOR GRANTING THE PETITION

"In a mockery of 'reasoned' administrative decision-making, FDA (1) changed the rules for private entities in the middle of their marketing application process, (2) failed to notify the public of the changes in time for compliance, and then (3) rubber-stamped the denial of their marketing applications *because of* the hitherto unknown requirements." *Wages & White Lion Invs., LLC v. FDA*, 41 F.4th 427, 442 (5th Cir. 2022) ("*Wages II*") (Jones, J., dissenting), *vacated* 58 F.4th 233, 234 (5th Cir. 2023) (granting petition for rehearing *en banc*).

The court below ignored FDA's failure to comply with the fundamental principle that agencies are required to provide regulated parties "fair warning" of what an agency requires or prohibits. And the court brushed over FDA's prejudicial failure to consider relevant factors and important aspects of the problem when the agency failed to consider or rejected evidence, including of benefits to adult smokers, that FDA had instructed applicants to include. By using the substantive outcome of FDA's actions to justify FDA's procedural failures, the lower court opened the door for any federal agency to change,

sub silentio, its policies, procedures, and requirements without concern that judicial review will find such actions arbitrary and capricious.

In response to similar petitions brought by applicants seeking marketing authorization for non-tobacco-flavored ENDS products, the Eleventh Circuit found FDA's actions to be arbitrary and capricious. *Bidi Vapor LLC v. FDA*, 47 F.4th 1191, 1203 (11th Cir. 2002). A three-judge motions panel from the Fifth Circuit also unanimously stayed MDOs for manufacturers of similar bottled e-liquid products as Petitioners'. *Wages and White Lion Invs., LLC v. FDA*, 16 F.4th 1130 (5th Cir. 2021) ("*Wages I*"). After a different merits panel denied those petitions on a 2-1 vote, the Fifth Circuit vacated the merits panel opinion and granted rehearing *en banc*. *Wages & White Lion Invs.*, 58 F.4th 233, 234 (vacating *Wages II* and granting petition for rehearing *en banc*). A separate Fifth Circuit motions panel considering another MDO also found that it was "not a close call" that FDA's new evidentiary standard constitutes a substantive rule that the agency improperly adopted without notice and comment. *R.J. Reynolds Vapor Co. v. FDA*, 65 F.4th 182, 2023 U.S. App. LEXIS 7022, **17-18 (5th Cir. Mar. 23, 2023). However, three other Circuits, like the Fourth Circuit here, have failed to hold FDA to account for its *sub silentio* adoption and application of its new evidentiary standard. *See Liquid Labs LLC v. FDA*, 52 F.4th 533 (3d Cir. 2022); *Gripum, LLC v. FDA*, 47 F.4th 553 (7th Cir. 2022); *Prohibition Juice Co. v. FDA*, 45 F.4th 8 (D.C. Cir. 2022).

The Court should grant Avail's petition to resolve the circuit split and hold FDA to the same administrative law standards as any other agency. This is particularly

important because, invoking its new evidentiary standard, FDA has rejected approximately 99% of all timely filed PMTAs and failed to authorize a single non-tobacco-flavored ENDS product. FDA's actions are not only devastating an industry; because many adult ENDS users are former or transitioning cigarette smokers who have quit or are attempting to quit smoking with flavored ENDS products, it is their health, as well as the health of cigarette smokers who may rely on flavored ENDS products to quit smoking in the future, that FDA's arbitrary and capricious actions are putting at risk.

I. The Circuit Court's Decision Conflicts with Administrative Law Principles Established by this Court Regarding Fair Warning, Reliance Interests, and Consideration of Important Aspects of the Problem

The circuit court's decision conflicts with this Court's precedents regarding the fair warning agencies must provide to regulated entities—particularly those with reliance interests in the agency's previous pronouncements—and an agency's obligation to consider all important aspects of the problem.

A. FDA secretly changed its evidentiary standard to impose a new longitudinal comparative efficacy study requirement after the fact.

An agency cannot pull the rug out from under a regulated party by imposing new requirements without notice after the party relied on the agency's prior representations and positions. *See FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009). A federal agency must give regulated entities "fair warning" of what the

agency expects of them. *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156 (2012). Anything less "would result in precisely the kind of 'unfair surprise' against which [this Court's] cases have long warned." *Id.* (collecting cases). "Those regulated by an administrative agency are entitled to know the rules by which the game will be played." *Alaska Prof'l Hunters Ass'n v. FAA*, 177 F.3d 1030, 1035 (D.C. Cir. 1999) (abrogated on other grounds by *Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92 (2015)).

"[F]air notice requires the agency to have 'state[d] with ascertainable certainty what is meant by the standards [it] has promulgated.'" *ExxonMobil Pipeline Co. v. United States DOT*, 867 F.3d 564, 578 (5th Cir. 2017) (quoting *Diamond Roofing Co. v. OSHRC*, 528 F.2d 645, 649 (5th Cir. 1976)). Only "[i]f, by reviewing the regulations and other public statements issued by the agency, a regulated party acting in good faith would be able to identify, with 'ascertainable certainty,' the standards with which the agency expects parties to conform, [will] the agency ha[ve] fairly notified a petitioner of the agency's interpretation." *Id.* at 578-79 (citing *Gen. Elec. Co. v. EPA*, 53 F.3d 1324, 1329 (D.C. Cir. 1995)). An agency acts arbitrarily and capriciously when it fails to adhere to this "[r]ule of law," and instead announces a new requirement at the same time it seeks to apply it. *Circus Circus Casinos, Inc. v. NLRB*, 961 F.3d 469, 476 (D.C. Cir. 2020).

FDA violated the fair notice requirement by basing Avail's MDO on Petitioners' failure to include longitudinal data from randomized controlled trials, longitudinal cohort studies, or other studies comparing the efficacy of their flavored ENDS products to tobacco-flavored ENDS products on adult smokers' switching or cigarette

reduction over time. App. 40a-41a. FDA did not publicize this new evidentiary standard until after the agency began its *en masse* denial of PMTAs for flavored products.

Before the submission deadline, FDA never recommended any particular studies for flavored ENDS products that differed from those for tobacco-flavored ENDS products at all. FDA can point to no publicly available document or communication before August 26, 2021, in which the agency stated or even suggested that it would require longitudinal comparative efficacy data as the *sine qua non* for a complete, individualized review of an application for a flavored ENDS product. FDA did not mention this evidentiary standard in its 2019 PMTA Guidance or in its proposed rule intended to "set forth requirements for premarket tobacco product applications." 84 Fed. Reg. at 50566. Nor did FDA reference this standard in its public meetings with stakeholders. Incredibly, FDA did not even mention the comparative efficacy evidentiary standard when it finalized the PMTA rule in October 2021 – the month *after* the agency disclosed the standard. 86 Fed. Reg. at 55300.

The court below found FDA's adoption of its new evidentiary standard was not arbitrary and capricious because the TCA requires the agency "to determine from the totality of the evidence before it whether marketing of a new tobacco product is 'appropriate for the protection of the public health.'" App. 17a (quoting 21 U.S.C. § 387j(c)(2)(A)). In other words, the court determined that FDA's new evidentiary standard was a reasonable interpretation of the TCA.

But even if FDA's new interpretation of the TCA were a reasonable one, the APA still required FDA to

give applicants "fair warning" of that interpretation. *SmithKline Beecham*, 567 U.S. at 156. The court below ignored this requirement and did not, because it could not, point to any document or communication in which FDA timely advised the public about the agency's new interpretation of the TCA.[7] For that reason alone, the decision below was incorrect. *Id.*

FDA will argue that its actions were not arbitrary and capricious because agencies may interpret statutes through "adjudication." FDA's argument lacks merit. FDA formulated its new interpretation of the TCA *before* it adjudicated any PMTAs for flavored ENDS and the agency did not apply that interpretation until it *later* adjudicated PMTAs *en masse* by issuing marketing denial orders for such products. Therefore, under the APA, FDA's interpretation of the TCA was a "rule making," not an "adjudication." *Compare* 5 U.S.C. § 551(4)-(5) (providing that a "rule" includes "the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy" and a "rule making" includes an

7. Notably, in December 2022, an expert panel convened at the invitation of the FDA Commissioner to evaluate the Center for Tobacco Products criticized CTP for a lack of "adequate guidance and transparency regarding CTP's expectations" and a "lack of clarity regarding review standards," concluding that applicants "will struggle to address the issues necessary to meet the APPH standard unless FDA clearly articulates its expectations." *See Operational Evaluation of Certain Components of FDA's Tobacco Program* (Dec. 2022), https://perma.cc/SVP9-DMJ4, at 11, 18, 20. The report found that "[a]s FDA's plans and approaches to tobacco regulation changed, such changes were not always announced and communicated clearly to external stakeholders *or even to staff*." *Id*. at 13 (emphasis added).

"agency process for formulating . . . a rule") *with* 5 U.S.C. § 551(6)-(7) (providing that an "order" is "the whole or part of a final disposition . . . of an agency matter other than rulemaking" and an "adjudication" is "the agency process for the formulation of an order").[8] And FDA must give the public advanced notice of new rules – either through notice and comment rule making (for substantive rules) or through guidance documents (for interpretive rules). *See* 5 U.S.C. § 553; 21 C.F.R. § 10.115(e); *see also R.J. Reynolds Vapor*, 65 F.4th 182, 2023 U.S. App. LEXIS 7022, *17 (concluding that FDA's "heightened evidentiary standard [for non-tobacco-flavored ENDS] bears all the hallmarks of a substantive rule") (cleaned up).

B. FDA did not notify Avail that the agency had changed its policy on the types of studies that would be required in a PMTA.

When an agency makes a "policy change," it must take into account "industry reliance on the [agency's] prior policy," *Encino Motorcars, LLC v. Navarro*, 579 U.S. 221, 222 (2016), and it "must consider the alternatives that are within the ambit of existing policy," *DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913 (2020) (cleaned up).

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8. FDA purported to rescind its August 17, 2021 internal memorandum, but applied its new interpretation of the TCA set forth therein when it adjudicated Avail's PMTAs, as the nearly identical content of the TPL report illustrates. *See* CA.A73; CA.A27. Because FDA applied the same interpretation to deny Avail's petition, the "rescission" of the memorandum does not change the fact that the agency's new interpretation set forth in that memorandum was a "rule." *See Safari Club Int'l v. Zinke*, 878 F.3d 316, 332 (D.C. Cir. 2017) ("An agency cannot escape the requirements of § 553 by labeling its rule an 'adjudication.'").

FDA's actions represented a *sub silentio* change not only to the "standard for evidence" required of applicants, but also to the types of studies FDA found acceptable for flavored ENDS products. In its 2018 public meeting, FDA suggested no new clinical studies were necessarily required, but in 2021, the agency denied Petitioners' applications specifically because they failed to conduct such clinical studies in the form of a randomized controlled trial, longitudinal cohort study, or some other comparative efficacy study that tracked user behavior over time.

In its public meetings, FDA suggested it would determine whether the APPH standard was met by focusing on constituents of toxic concern, risk of disease, and decreases in morbidity and mortality from tobacco product use, all measures against which flavored ENDS products compare favorably to combustible cigarettes and for which flavored and tobacco-flavored ENDS products have essentially identical profiles based on their constituents. The MDO, however, was not based on these announced considerations vis-à-vis combustible cigarettes, but on Avail's lack of longitudinal comparative switching evidence.

Before the submission deadline, FDA repeatedly represented that it did not expect long-term clinical studies would be needed; afterward, however, FDA created "at the very least a strong presumption that such evidence is required." *Wages I*, 16 F.4th at 1141. Before the submission deadline, FDA specifically recommended single-point-in-time consumer studies on topics like perception and intent and disclaimed a need for randomized controlled trials conducted over time. In the TPL reports, based on its experience gained from reviewing applications *after*

the deadline, *see* App. 58a n.vi, 82a-84a, FDA rejected such studies and instead required longitudinal studies that assess study subject behavior over time.

Finally, rather than basing its decisions on "all of the contents of the application," including the advertising and sales-access restrictions found in Avail's marketing plans that FDA had previously represented were "critical," FDA failed to review the applications for any evidence beyond whether they contained the longitudinal comparative efficacy evidence that FDA now demanded—that is, one "static set of requirements" that FDA specifically disclaimed in its Final Rule.

Here, Avail relied on FDA's representations and did not conduct any long-term clinical studies or randomized controlled trials comparing flavored to tobacco-flavored products, but instead submitted multiple other studies FDA had previously endorsed, including single-point-in-time consumer perception and intent studies. But when FDA announced its initial *en masse* denials of PMTAs, the agency also "announced that it required the very studies it originally expected it did not need." *Wages I*, 16 F.4th at 1138. Even though FDA should have been aware that applicants like Avail relied on FDA's previous representations regarding study requirements, FDA did not consider such reliance, let alone potential alternatives to simply denying PMTAs for lacking the newly required studies, such as announcing the new study requirements and allowing applicants a reasonable time to conduct new studies and amend their applications with the results. FDA's failures render its denial of Avail's application arbitrary and capricious. *Regents*, 140 S. Ct. at 1913.

The lower court found that Avail "overread" the 2019 PMTA Guidance as saying that "long-term studies were likely unnecessary." App. 26a. But that is precisely what FDA said. *See* CA.A235 ("[I]n general, FDA does not expect that applicants will need to conduct long-term studies to support an application"). Avail can hardly be blamed for not including long-term studies in its PMTAs and instead including the single-point-in-time perception and intent studies FDA expressly recommended. Indeed, as Judge Jones observed, "from FDA's denials of 55,000 PMTAs one might reasonably infer that other manufacturers . . . were fooled by FDA's previous instructions." *Wages II*, 41 F.4th at 449 (Jones, J., dissenting).

In falsely suggesting that Avail "failed to look at the 2019 guidance in any depth," App. 25a, the lower court only highlighted its failure to properly consider not only the 2019 PMTA Guidance beyond FDA's arguments before the court, but also FDA's numerous other representations before the submission deadline. In excusing FDA's *sub silentio* change in the type of studies required, the lower court turned a blind eye to FDA's repeated representations not only in the PMTA Guidance, but at public meetings, and even in its proposed and ultimately final PMTA rule. For an applicant that supposedly "failed to look at the 2019 guidance in any depth," Avail managed to include in its application numerous studies that FDA had previously recommended, and only after the fact determined were not sufficiently "robust and reliable." App. 79a-85a.

The lower court's misapprehension of the requirement that FDA provide notice of a change in policy is confirmed by its reasoning that FDA's July and August 2021 internal

memoranda were "unlikely to create reliance interests" and that "each was rescinded prior to or superseded by FDA's marketing denial order issued on September 15, 2021." App. 27a. First, FDA's internal memoranda were evidence of the undisclosed policy change, not of some public representation or statement to applicants that could have created reliance interests. Second, merely stamping "rescinded" or "superseded" on a memorandum or in an administrative record is not effective in undoing the policy change when (i) the forms FDA reviewers utilized for Avail's PMTAs required exactly what was identified as required in the July 2021 "Fatal Flaw" memorandum and (ii) the August 2021 memorandum was incorporated into the TPL reports issued to Avail and hundreds of other applicants.

C. FDA ignored key aspects of Petitioners' PMTAs, including Petitioners' plans for limiting youth access and use of the products.

Agency action is arbitrary and capricious if the agency fails to "examine the relevant data and articulate a satisfactory explanation for its action," including when the agency "entirely fails to consider an important aspect of the problem." *Motor Vehicle Mfrs. Assn. of United States, Inc. v. State Farm Mut. Auto. Ins. Co.*, 469 U.S. 29, 43 (1983). Here, FDA failed to examine the relevant information in Avail's applications, including (i) the potential impact of Avail's marketing and sales-access restriction plans; and (ii) evidence that youth do not use Avail's bottled e-liquids.[9]

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9. Due to the factually intensive nature of the discussion surrounding FDA's overlooking evidence that Avail's bottled

FDA concedes that it did not bother to evaluate Avail's marketing and sales-access restriction plans for the "sake of efficiency." App. 78a-79a. Avail's plans were designed to ensure that the company's products are attractive and available only to adults and not to youth. That FDA did not bother to evaluate those plans is striking because FDA *requires* applicants to include such plans in their PMTAs, *see* 21 C.F.R. § 1114.7(f), and the agency had repeatedly described the plans as "critical" and promised that it *will* review such plans when evaluating PMTAs, *see, e.g.*, 84 Fed. Reg. at 50581.

The court below found that FDA need not review Avail's marketing plans because under the TCA those plans are irrelevant unless the applicant first establishes that its flavored ENDS are more effective than tobacco-flavored ENDS in helping adults reduce their smoking. App. 29a-33a. But the court did not, and could not, point to any language in the TCA supporting that conclusion. And FDA was on record as stating that an "applicant's marketing plans will help [the agency] determine whether permitting the marketing of a new tobacco product would be [appropriate for the protection of the public health]." 84 Fed. Reg. at 50581.

Instead, the lower court accepted FDA's *post hoc* rejection of the same youth access and marketing restrictions the agency had previously endorsed as "adequate measures" for manufacturers and sellers of

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e-liquids are not used by youth, Avail primarily discusses FDA's failure to consider the marketing and sales-access restriction plans, but intends to fully brief the lack of youth usage issue if certiorari is granted.

bottled e-liquids in its 2020 ENDS Enforcement Guidance. App. 29a-33a; CA.A111. But the lower court did not stop there. The court also accepted FDA's new requirement that any marketing restriction must be "novel" to be effective at reducing youth usage while not requiring FDA to explain this shift in policy. *Id.* The lower court ignored that, even in the face of zero evidence of youth usage of Avail's products, FDA treated Avail's bottled e-liquids the same as cartridge-based or disposable ENDS *devices* in contradiction of the agency's prior recognition that youth predominantly used those two types of ENDS products. App.34a-35a.[10] And, as it did with every other *sub silentio* change in policy or position by FDA, the lower court required no explanation. In short, the court below neglected to apply the most basic of administrative law requirements to FDA's actions. To allow this abandonment of meaningful judicial review opens the door for FDA, or any other federal agency, to change the rules of the game without notice and avoid "turn[ing] square corners in dealing with the people." *Regents*, 140 S. Ct. at 1909-10 (quoting *St. Regis Paper Co. v. United States*, 368 U.S. 208, 229 (1961) (Black, J., dissenting)).

II. The Circuit Courts Are Split on Two Fundamental Issues Regarding FDA's Compliance With the APA

1. Although the court below and the Third, Seventh, and D.C. Circuits have held that FDA did not violate the

10. Without warning or consideration of reliance interests, FDA found traditional sales-access restrictions ineffective for bottled e-liquids, App. 78a n.xix, when FDA had previously only considered such restrictions ineffective for flavored, cartridge-based products, CA.A110-11, 133-34. See Bidi, 47 F.4th at 1205, 1207-08.

APA by changing the evidentiary standard for flavored ENDS without giving proper notice to applicants, at least six judges on the Fifth Circuit have reached the opposite conclusion. *See Wages I*, 16 F.4th at 1138 ("Almost a year after the PMTA deadline, FDA issued its first marketing denial orders for various flavored e-cigarettes and announced that it required the very studies it originally expected it didn't need."); *Wages II*, 41 F.4th at 442 (Jones, J., dissenting from merits panel denial of petition); *Wages & White Lion Invs., LLC v. FDA*, 58 F.4th 233, 234 (vacating *Wages II* and granting petition for rehearing *en banc*); *R.J. Reynolds Vapor*, 2023 U.S. App. LEXIS 7022, *7 (staying FDA's denial order and finding that FDA, *inter alia*, "failed to reasonably consider the [applicant's] legitimate reliance interests concerning the need for longitudinal studies and marketing plans," and "has created a *de facto* rule banning all non-tobacco-flavored e-cigarettes without following APA notice and comment requirements"). In *R.J. Reynolds Vapor*, the Fifth Circuit motions panel found the contrary decisions from the other circuits (including the underlying decision here) "unpersuasive." *Id.* at *19 n.11.

2. Although the court below found that FDA did not violate the APA by ignoring a PMTA applicant's plans for limiting youth access to and use of its products, both the Fifth Circuit motions panel in *Wages I* and the Eleventh Circuit reached the opposite conclusion. *See* 16 F.4th at 1136-38; *Bidi*, 47 F.4th at 1203 ("Because the marketing and sales-access-restriction plans were relevant factors and addressed 'an important aspect of the problem,' it was arbitrary and capricious for [FDA] not to consider them.") (quoting *State Farm*, 463 U.S. at 43). In so holding, the Eleventh Circuit rejected the reasoning of the Fifth

Circuit's (now vacated) *Wages II* opinion and the D.C. Circuit's *Prohibition Juice* opinion. *See, e.g.*, 47 F.4th at 1206 ("We also disagree with our sister circuits' contrary decisions in [*Wages II* and *Prohibition Juice*]," because, "[f]or starters, we are not persuaded by our sister circuits' reading of [FDA's] 2020 [Enforcement] Guidance.").

Moreover, no other circuit court has agreed with the position of the court below that the APA permits FDA to ignore an applicant's marketing plans. In *Prohibition Juice*, the D.C. Circuit found that any APA violation was harmless under the facts of that case, but the court strongly suggested that FDA had not complied with its APA obligations. *See* 45 F.4th at 25 ("The manufacturers raise serious arguments that the FDA erred in deciding not to review their marketing plans on the ground that they presented nothing new, and that its explanation for the non-review fell short insofar as the FDA assumed the contents of plans without reading them."); *see also id.* at 46 (Katsas, J., concurring) ("As the Fifth Circuit has explained [in *Wages I*], 'it's unreasonable for the FDA to stop looking at proposed marketing plans because past ones have been unpersuasive.'"). Two judges on a split Sixth Circuit motions panel similarly found harmless error based on the facts before that court when denying a stay motion, but also questioned whether FDA had met its obligations under the APA. *See Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 507 (6th Cir. 2021) ("FDA likely should have more thoroughly considered Breeze Smoke's marketing plan" because an agency "must consider the 'relevant factors' when reaching a decision and may not 'entirely fail to consider an important aspect' of the relevant regulatory task") (quoting *State Farm*, 463 U.S. at 43); *see also id.* at 508 (Kethledge, J., dissenting) ("I would grant the motion for a stay" because "FDA

essentially decided these applications *en masse* rather than individually").[11]

III. This Case Presents a Question of Great Importance to the ENDS Industry, Former and Transitioning Smokers Who Use Flavored ENDS Products, and Cigarette Smokers Who Want to Quit Smoking.

It is not every day that FDA seeks to remove an entire class of products from the market. But that is exactly what FDA is attempting to do with respect to flavored ENDS. As the Fifth Circuit recently noted, "FDA admits that it 'has yet to grant' a single application to market non-tobacco-flavored e-cigarettes'" and the agency "has denied over 355,000 such applications, which amount to 99% of all timely filed PMTAs." *R.J. Reynolds Vapor*, 2023 U.S. App. LEXIS 7022, at *15. Indeed, the Fifth Circuit determined that FDA's actions appear to be "a *de facto* ban on non-tobacco-flavored e-cigarettes." *Id.* at *19. FDA's application of its previously undisclosed evidentiary requirements to deny PMTAs *en masse* is not only devastating for the ENDS industry, but poses a real risk to former and transitioning cigarette smokers who use flavored ENDS products, as well as current cigarette smokers who want to quit smoking.

For at least four reasons, removing all non-tobacco-flavored ENDS products from the market harms

11. This Court denied a motion to stay in *Breeze Smoke*. *See Breeze Smoke, LLC v. FDA*, 142 S. Ct. 638 (2021). In *Liquid Labs*, the Third Circuit did not address whether FDA erred in ignoring the applicant's marketing plans. Instead, the court found any error was harmless under the facts of that case. *See* 52 F.4th at 544. In *Gripum*, the Seventh Circuit found that the petitioner had waived or forfeited this issue. *See* 47 F.4th at 558 n.1.

the interests of former cigarette smokers who have successfully used flavored ENDS products to quit, transitioning cigarette smokers who use those products now, and current cigarette smokers who want to quit smoking.

First, FDA has stated that, because they do not involve combustion, "ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than combustible cigarettes, and biomarker studies demonstrate significantly lower exposure to HPHCs among current exclusive ENDS users than current smokers." CA.A34; *see also Breeze Smoke*, 18 F.4th at 505 (noting FDA acknowledgment "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").

Second, the latest estimates from the Centers for Disease Control indicate that nearly six percent of adults in the United States currently use ENDS products, whereas over eleven percent of adults in the United States currently smoke cigarettes. *See Early Release of Selected Estimates Based on Data from the 2022 National Health Interview Survey* (Apr. 23, 2023).[12]

Third, an overwhelming majority of adult ENDS users non-tobacco flavored ENDS. *See* CA.A30 (FDA stating that approximately 77% of adult ENDS users use non-tobacco-flavored ENDS); CA.A113 (FDA stating that "the majority of adult [ENDS] users use [non-tobacco-flavored ENDS]").

12. https://perma.cc/D25X-2ASE.

Fourth, among adult ENDS users, approximately 69.7% are former or current cigarette smokers, including 92.8% of users over 45 years old—the age group most susceptible to near-term adverse health impacts from smoking combustible cigarettes.[13]

In short, even though millions of adults who use ENDS as a less harmful alternative to cigarettes strongly prefer non-tobacco-flavored ENDS, FDA is taking that option away from them. That fact alone warrants this Court's review.

CONCLUSION

For the forgoing reasons, this Court should grant the petition for certiorari.

Respectfully submitted,

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13. CDC, *QuickStats: Percentage Distribution of Cigarette Smoking Status Among Current Adult E-Cigarette Users, by Age Group—National Health Interview Survey* (Mar. 10, 2023), https://perma.cc/TYR8-9KUV.

APPENDIX

TABLE OF APPENDICES

APPENDIX A — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT, DATED DECEMBER 12, 2022

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 21-2077

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

Petitioners,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondent.

AMERICAN VAPING ASSOCIATION, INC.; AMERICAN VAPOR MANUFACTURERS ASSOCIATION, INC.; CONSUMER ADVOCATES FOR SMOKE-FREE ALTERNATIVES ASSOCIATION, INC.; SMOKE-FREE ALTERNATIVES TRADE ASSOCIATION, INC.; UNITED VAPERS ALLIANCE, INC.; ARIZONA SMOKE FREE BUSINESS ALLIANCE, INC.; BREATHE EASY ALLIANCE OF ALABAMA; CONNECTICUT CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION;

Appendix A

FLORIDA SMOKE FREE ASSOCIATION, INC.; GEORGIA SMOKE FREE ASSOCIATION, INC.; HAWAII CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION; KANSAS SMOKE FREE ASSOCIATION; KENTUCKY VAPING RETAILERS ASSOCIATION, INC., D/B/A KENTUCKY SMOKE FREE ASSOCIATION; INDIANA SMOKE FREE ALLIANCE, INC.; IOWANS FOR ALTERNATIVES TO SMOKE AND TOBACCO, INC.; IOWA VAPE ASSOCIATION, INC.; LOUISIANA VAPE ASSOCIATION, INC.; MARYLAND VAPOR ALLIANCE; MICHIGAN VAPE SHOP OWNERS, INC.; MIDWEST VAPE COALITION, INC.; MINNESOTA SMOKE FREE ALLIANCE; MISSOURI SMOKE FREE, INC.; MONTANA SMOKE FREE ASSOCIATION, INC.; NEBRASKA VAPE VENDORS ASSOCIATION, INC.; NEVADA VAPING ASSOCIATION, INC.; NEW MEXICO SMOKE FREE ALLIANCE, INC.; NEW YORK STATE VAPOR ASSOCIATION, INC.; NORTH CAROLINA VAPING COUNCIL, INC.; OHIO VAPOR TRADE ASSOCIATION, INC.; ROCKY MOUNTAIN SMOKE FREE ASSOCIATION, INC.; RHODE ISLAND CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION; SMOKE FREE ALTERNATIVES COALITION OF ILLINOIS, INC.; SOUTH CAROLINA VAPOR ASSOCIATION, INC.; TEXAS CHAPTER OF SMOKE FREE ALTERNATIVES TRADE ASSOCIATION; TENNESSEE SMOKE FREE ASSOCIATION, INC.; VIRGINIA SMOKE FREE ASSOCIATION, INC.; WASHINGTON SMOKE

Appendix A

FREE ASSOCIATION, INC.; WEST VIRGINIA SMOKE FREE ASSOCIATION, INC.; DR. DAVID B. ABRAMS; CLIVE D. BATES; PROFESSOR DAVID T. SWEANOR, J.D.,

Amici Supporting Petitioners,

MEDICAL AND PUBLIC HEALTH GROUPS,

Amici Supporting Respondent.

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

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

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

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

WILKINSON, Circuit Judge:

The Family Smoking Prevention and Tobacco Control Act requires manufacturers of new tobacco products to obtain authorization from the United States Food & Drug Administration (FDA) prior to marketing their products. *See* Pub. L. 111-31, § 910, 123 Stat. 1776, 1807-12 (2009) (codified at 21 U.S.C. § 387j(a)). In reviewing a

manufacturer's Premarket Tobacco Product Application, FDA must determine that the marketing of the product is "appropriate for the protection of the public health." § 910(c)(4), 123 Stat. at 1810. The agency denied Avail Vapor LLC's application for its flavored electronic cigarettes, chiefly on the grounds that its products posed a serious risk to youth without enough offsetting benefits to adults. We now uphold that decision and deny Avail's petition for review.

I.

A.

Congress enacted the Tobacco Control Act (TCA) in 2009. It found that "[t]he use of tobacco products by the Nation's children" was "a pediatric disease of considerable proportions that result[ed] in new generations of tobacco-dependent children and adults." § 2(1), 123 Stat. at 1777. Further, "[v]irtually all new users of tobacco products are under the minimum legal age to purchase such products," and "[t]obacco advertising and marketing contribute significantly to the use of nicotine-containing tobacco products by adolescents." §§ 2(4), 2(5), 123 Stat. at 1777. Congress's previous attempts to curb adolescent tobacco use had failed, and thus the TCA sought "to address comprehensively the public health and societal problems caused by the use of tobacco products." § 2(7), 123 Stat. at 1777. Congress entrusted the FDA with this important task, finding that it "possesses the scientific expertise needed to implement effectively all provisions of the [TCA]." § 2(45), 123 Stat. at 1781.

Appendix A

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

The FDA must deny a PMTA if it finds that "there is a lack of showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." § 910(c)(2)(A), 123 Stat. at 1809. Whether a product is "appropriate for the protection of the public health" is "determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." § 910(c)(4), 123 Stat. at 1810. As part of this inquiry, the TCA explicitly requires the FDA to consider "the increased or decreased likelihood that existing users of tobacco products will stop using such products" and "the increased or decreased likelihood that those who do not use tobacco products will start using such products." § 910(c)(4)(A)-(B), 123 Stat. at 1810. Thus, the FDA is required to weigh the benefits of "cessation" associated with a new tobacco product against the risks of "initiation."

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

B.

The petition before us involves the public health debate surrounding the novel use of an ancient product. Electronic nicotine delivery systems (ENDS), also known as e-cigarettes, were introduced widely in the United States since Congress passed the TCA. In contrast to traditional cigarettes, ENDS heat a liquid that includes nicotine, chemicals, and flavors until it generates an aerosol or vapor, which can then be inhaled by the user. *See Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 270, 444 U.S. App. D.C. 357 (D.C. Cir. 2019). These products have the potential to benefit adult smokers if used as a complete substitute for combustible tobacco smoking, *i.e.*, if adult smokers "switch" to ENDS products, as they are less likely to cause disease and death. *See* U.S. Dep't of Health and Hum. Servs., *E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General* 186 (2016). These products still contain nicotine, however, which is an addictive substance known to harm the developing brain. *Id.* at 100-07.

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

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

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

communities. *Id.* Unlike combustible cigarettes, however, ENDS products had limited regulatory oversight, as the TCA did not give the FDA immediate jurisdiction over these products. *Id.* at 15.

To close this gap, FDA asserted regulatory jurisdiction over ENDS products in May 2016 in accordance with its authority to "deem" new products subject to the strictures of the TCA. *See* 21 U.S.C. § 387a(b); 81 Fed. Reg. 28,974 (May 10, 2016) ("Deeming Rule"). It noted that the Deeming Rule was necessary in substantial part due to "the continued dramatic rise in youth and young adult use of tobacco products such as e-cigarettes." *Id.* at 29,984. However, the FDA also recognized that this new rule meant that most ENDS products were already on the market without manufacturers having submitted a PMTA, a violation of the TCA. Thus, the FDA decided not to act on a product's lack of premarket authorization for two to three years while manufacturers prepared, and FDA reviewed, marketing applications. *Id.* at 28,977-78. After the Deeming Rule, FDA made a series of public announcements relevant to the matter at hand, which we examine below.

In the summer of 2017, FDA announced that it did not intend to initiate enforcement regarding PMTAs for newly regulated ENDS products for five years, *i.e.*, until 2022. J.A. 94. The extension reflected nationally representative data that suggested youth use of e-cigarettes had declined beginning in 2016. *Id.* The decline, however, did not last long. Whereas the downward trend in youth e-cigarette use in 2016 moved FDA toward more lenient regulation

of the ENDS industry, new information caused the FDA to change course. By late 2017, FDA started to see an explosion in complaints about ENDS products, and new data indicated an alarming increase in the use of ENDS products by middle and high school students. J.A. 94-95. Between 2017 and 2018, studies showed that e-cigarette use had increased by 78% in high school students and 48% in middle school students. J.A. 97. Considering this new data, FDA's then-Commissioner characterized the situation as a "youth vaping epidemic" in 2018. J.A. 75. The FDA began to use its enforcement discretion, issuing over 6,000 warning letters to manufacturers and more than 1,000 civil monetary complaints to retailers for the marketing and sale of ENDS products to minors. J.A. 97.

C.

While FDA was reckoning with the new and evolving information on youth ENDS use, it also issued guidance on PMTAs for ENDS manufacturers. FDA, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, Guidance for Industry* (June 12, 2019) ("2019 Final PMTA Guidance"); *see* J.A. 220-74. The final compliance date was simultaneously moved up from 2022 to September 9, 2020, in response to a suit initiated by a group of pediatric physicians. *See Am. Acad. of Pediatrics v. Food & Drug Admin.*, 379 F. Supp. 3d 461(D. Md. 2019); J.A. 94-95. FDA stated that in reviewing PMTAs, it "weighs all of the potential benefits and risks from the information contained in [a] PMTA to make an overall determination of whether the product should be authorized for marketing." J.A. 234. Further, the FDA stated that

while "[n]onclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health," there are some cases where it "may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies," such as when there was "an established body of evidence regarding the health impact . . . of [a manufacturer's] product or a similar product that can be adequately bridged to [the manufacturer's] product." J.A. 234, 268.

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

prioritize enforcement against all other ENDS products either marketed to youth or for which the manufacturer had failed to take adequate steps to prevent youth access. J.A. 107.

Notwithstanding these specific priorities, FDA made clear that it would "make enforcement decisions on a case-by-case basis" and that it "is continuously evaluating new information and adjusting its enforcement priorities in light of the best available data[.]" J.A. 92, 100. Importantly, FDA found that "evidence continues to accumulate, further confirming that youth are particularly attracted to flavored ENDS products." J.A. 103. New studies showed that flavors drove both initiation and continued regular use by youth. *Id.* Further, FDA noted that its previous attempts at restricting youth access to ENDS products had fallen flat, finding that "youth have continued access to these products in the face of legal prohibitions and even after voluntary actions by some manufacturers." J.A. 110. As for marketing access restrictions, FDA told manufacturers that it "believes that age verification alone is not sufficient to address this issue, given the most recent data that youth use of ENDS products continues to increase." J.A. 133.

After FDA implemented its 2020 Enforcement Guidance, the percentage of youth using e-cigarettes decreased. J.A. 29. But despite this decline, ENDS remained the most popular tobacco product among youth, "with youth use at levels comparable to what originally led FDA to declare a youth vaping epidemic in 2018." *Id.* Moreover, there was a substantial rise in youth use

of yet another type of flavored e-cigarettes, this time a system designed to be discarded after a single use. *Id.* These products were largely excluded from the 2020 Enforcement Guidance, and thus they remained on the market as a flavored option. *Id.* This fast product switching underscored the important role that flavors have in driving youth use, in whatever form or device the flavored e-cigarette is available. Up to and through the PMTA deadline, FDA received applications for over 6 million vaping products. *See* FDA, *Deemed Product Review: A Conversation with the Center for Tobacco Products Office of Science* (June 11, 2021). While the regulatory path may be a winding one, its constants are the persistence of youth use of flavored ENDS products and the obligation of FDA to incorporate new public health data into an evolving regulatory framework.

D.

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

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

Avail also filed its marketing plan with its PMTAs, which outlined measures designed to prevent underage use. Such measures consisted of naming its flavored e-liquids with "non-descriptive and non-characterizing names" that do not identify the product flavor to prevent appealing to youth. *See* J.A. 293. Avail believed its age-gated brick-and-mortar stores and independent age-verification services in Avail's point-of-sale system would prevent youth access to its products. *See* J.A. 295-97. Avail also required its distributors to submit a written policy on their age-verification procedures and a record of compliance with these policies. J.A. 314. While some other ENDS manufacturers were exploring innovative "access restriction" technology, whereby, for example, an ENDS product is tied to the thumb print of the purchaser, Avail's marketing plan included only garden variety restrictions that the FDA had previously found wholly inadequate in preventing youth use. Oral Arg. at 34:09; *see* 2020 Enforcement Guidance, J.A. 131-36.

Appendix A

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

> All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth. In light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS.
>
> Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs contained four protocols for [randomized controlled trials]....to address the new products' abuse liability, the study reports were not submitted...; therefore, this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s) . . . .

> Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

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

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

E.

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

Avail raises a flurry of objections to the FDA's marketing denial order. Avail's chief complaint is that the FDA arbitrarily imposed a new "comparative efficacy" standard, which asked applicants to demonstrate through certain long-term studies that their fruit-and dessert-flavored products better promote smoking cessation than tobacco-flavored products. This standard, Avail complains, was adopted with no explanation to applicants and without consideration of their reliance interests. Avail also raises a substantive objection, arguing that FDA's imposition of this comparative efficacy standard exceeded its statutory authority under the TCA.

All of Avail's objections founder on common ground. First, Avail attempts to tie the hands of the FDA to certain forms of evidence and kinds of studies in what is a rapidly evolving field. Second, in focusing upon procedural points, Avail encourages us to neglect the forest for the trees. Avail essentially argues that "the FDA's willingness to consider some forms of evidence, explicitly phrased as such, required the FDA to accept that evidence as meeting a statutory requirement even where the FDA found the evidence unsatisfactory." *Breeze Smoke, LLC v. United*

States FDA, 18 F.4th 499, 507 (6th Cir. 2021) (denying a judicial stay from a substantially similar marketing denial order). Avail's proposed restrictions simply run counter to FDA's broad statutory mandate to determine from the totality of the evidence before it whether marketing of new tobacco products is "appropriate for the protection of the public health." Tobacco Control Act, § 910(c)(2)(A), 123 Stat. at 1809.

II.

We proceed in accord with well-settled principles of administrative law. The TCA incorporates by reference the customary Administrative Procedure Act standard of review. *See* 21 U.S.C. § 387*l*(b) (citing 5 U.S.C. § 706(2)(A)). Under this standard, we are instructed to "hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Agency action is arbitrary and capricious "if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43, 103 S. Ct. 2856, 77 L. Ed. 2d 443 (1983).

Arbitrary and capricious review, however, comes "with a presumption in favor of finding the agency action valid." *Ohio Valley Env't Coal. v. Aracoma Coal Co.*, 556 F.3d 177,

192 (4th Cir. 2009). Further, in reviewing agency action, "due account shall be taken of the rule of prejudicial error," 5 U.S.C. § 706, which is an administrative law "harmless error rule." *Shinseki v. Sanders*, 556 U.S. 396, 406, 129 S. Ct. 1696, 173 L. Ed. 2d 532 (2009) (internal quotations omitted). Avail carries the burden of showing that any procedural error by the FDA is harmful. *Id.* at 409.

A.

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

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

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

In reviewing Avail's PMTAs, FDA began with the same concern that motivated Congress's passage of the TCA: "use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction." J.A. 29-30. FDA then reviewed a litany of scientific evidence definitively showing the relationship between flavors and youth use of ENDS products. To start, ENDS products are the most used tobacco product among youth, and "[t]he majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time." J.A. 30. Further, youth ENDS users were more likely to use flavored products than adult ENDS users. *Id.*

FDA next examined studies which showed that flavors drove youth initiation of ENDS use, with most users reporting that their first experience with ENDS was with a flavored product. *Id.* And beyond initiation, flavors promoted regular ENDS use: nationally representative studies indicated that youth users consistently cited the availability of desirable flavors as the reason behind their use. J.A. 31. Further, "[r]esearch show[ed] that flavored ENDS are rated as more satisfying than tobacco-flavored ENDS, such that participants will work harder for and take more puffs of flavored ENDS compared to non-flavored ENDS." *Id.* Evidence also indicated that flavors can actually increase nicotine exposure by "potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use." *Id.* Thus "this evidence suggests flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth[.]" J.A. 31.

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

To FDA, the crux of the issue was that youth use of ENDS products was driving nicotine dependency, a matter of substantial public health concern. *Id.* "[N]icotine exposure during adolescence enhances the rewarding and reinforcing effects of nicotine in adulthood, and can induce short and long-term deficits in attention, learning, and memory." *Id.* The agency, having been tasked by Congress with preventing youth use of tobacco products that "are inherently dangerous and cause cancer, heart disease, and other serious adverse health effects," *see* Tobacco Control Act, § 2(2), 123 Stat. at 1777, noted that "there is a growing body of evidence showing a link between ENDS use and subsequent smoking among youth." J.A. 33. Other studies showed as well that there is an association between ENDS use and respiratory issues in young adults. *Id.*

Notwithstanding the substantial risks of youthful addiction and associated health issues, FDA considered

the possibility that flavored ENDS may help promote smoking cessation or switching to a less detrimental product as required by the statute. FDA noted scientific evidence that ENDS are healthier for tobacco users than combustible cigarettes. J.A. 34. But "whether this is true for any particular new ENDS product, and the implications for health risks from a particular product, are considered on a case-by-case basis." *Id.* For flavored ENDS, which pose a massive risk of addicting a new generation to nicotine, "the magnitude of the likely benefit would have to be substantial enough to overcome the significant risk . . . ." *Id.*

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

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

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

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

B.

Despite this thorough review, Avail argues that FDA pulled a "surprise switcheroo" on regulated parties by requiring certain types of evidence that FDA had previously represented were unnecessary for a successful PMTA, namely comparative efficacy evidence presented

through randomized controlled trials or longitudinal cohort studies. *Wages & White Lion Invs., L.L.C. v. United States FDA*, 16 F.4th 1130, 1138 (5th Cir. 2021) (granting stay of marketing denial order); *but see Wages & White Lions Invs., LLC v. Food & Drug Admin.*, 41 F. 4th 427, 430 (5th Cir. 2022) (merits panel denying the petition for review). Petitioners contend that, in rejecting its applications, "FDA focused solely on whether PMTAs for flavored ENDS products contained particular long-term studies on the products' effectiveness at promoting smoking cessation—studies that FDA had previously represented were not expected or necessary for PMTAs . . . ." Pet'rs' Opening Br. at 1.

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

It is a bedrock principle of administrative law that "agencies should provide regulated parties fair warning

of the conduct [a regulation] prohibits or requires." *Romero v. Barr*, 937 F.3d 282, 295 (4th Cir. 2019) (internal quotations omitted) (alteration in original). This means that an agency may not change its policy *sub silentio* or without fair notice to regulated entities. *See, e.g., FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515, 129 S. Ct. 1800, 173 L. Ed. 2d 738 (2009). And further, "[w]hen an agency changes course . . . it must be cognizant that longstanding policies may have engendered serious reliance interests that must be taken into account." *Dep't of Homeland Sec. v. Regents of the Univ. of Calif.*, U.S. , 140 S. Ct. 1891, 1913, 207 L. Ed. 2d 353 (2020) (internal quotations omitted). The agency, however, did not traduce these principles here. FDA told manufacturers about the type and quality of evidence required to be included with their PMTAs. Avail failed to include this evidence and this failure, rather than the absence of certain studies in its PMTAs, resulted in FDA issuing a marketing denial order.

1.

FDA never guaranteed that manufacturers could carry their evidentiary burden under the TCA without providing long-term data *See Prohibition Juice*, 45 F.4th at 21. Instead of looking to the overall context of the FDA's public statements, Avail highlights isolated statements which allegedly show that FDA "switched" the evidence it required in a PMTA. Avail makes a fuss about the 2019 Final PMTA Guidance, which stated, "in general, FDA does not expect that applicants will need to conduct long-term studies to support an application." Pet'rs' Opening Br. at 8; *see also* J.A. 235. Avail argues that it relied on

this sentence in drafting its PMTAs, and thus FDA failed to consider its reliance interests when it switched the evidentiary standard along the way. It is not, however, the fault of FDA that petitioners failed to look at the 2019 guidance in any depth. If it had, it would have found "a more complicated story." *Gripum*, 47 F.4th at 559.

The 2019 Final PMTA Guidance made clear that FDA required "valid scientific evidence" under which the FDA could evaluate the health risks of the new ENDS products. J.A. 234. In that same document, FDA noted that "[n]onclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health." *Id.* However, FDA recognized that due to the relative novelty of ENDS, "in some cases, it *may* be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies," such as if there was "an *established body of evidence* regarding the health impact . . . of your product or a similar product that can *be adequately bridged* to your product." J.A. 268. (emphases added). FDA further warned manufacturers that "[p]ublished literature reviews . . . or reports may be acceptable to support a PMTA, but are considered a less robust form of support for a PMTA." J.A. 269.

The FDA also "recommend[ed] an applicant *compare* the health risks of its product to both products within the same category and subcategory, as well as products in different categories as appropriate." J.A. 235 (emphasis added). This is because "FDA reviews the health risks

associated with changes in tobacco use behavior (e.g., initiation, switching, dual use, cessation) that are likely to occur with the marketing of the new tobacco product." *Id.* In other words, FDA said that "it *might* accept evidence other than long-term studies," but only "if that evidence had sufficient scientific underpinnings" to enable the FDA to weigh the risks of initiation against the benefits of switching and cessation. *Breeze Smoke*, 18 F.4th at 506-07 (emphasis in original). To the extent that Avail is suggesting that the willingness to accept other evidence meant that "long-term studies were likely unnecessary," it is "over-read[ing]" this guidance. *Prohibition Juice*, 45 F.4th at 22-23; *see also Liquid Labs*, 52 F.4th at 542 n.11.

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

clear it would not relax the scientific rigor of the requisite public health demonstration." *Prohibition Juice*, 45 F.4th at 21. FDA did not, in other words, abandon its statutory obligation to consider whatever evidence was necessary to make a sound determination of a new tobacco product's impact upon public health.

2.

Avail's argument with respect to two FDA internal memoranda is even weaker. Petitioners point to these documents as proof that FDA denied its applications solely because they lacked randomized controlled trials and longitudinal cohort studies. *See* Pet'rs' Opening Br. at 15-17; *see also* J.A. 61-87 (text of internal memoranda dated July 9, 2021 and August 17, 2021). What Avail fails to recognize, however, is that these internal documents were just that: internal. Not only are internal documents unlikely to create reliance interests, but the record also makes clear that each was rescinded prior to or superseded by FDA's marketing denial order issued on September 15, 2021. *See* J.A. 88. In fact, the Technical Project Lead Review accompanying FDA's marketing denial order made clear that long-term studies are not required by looking to "any acceptably strong evidence" in Avail's applications. J.A. 27.

Agencies are customarily given latitude in their internal discussions and debates when they do not become agency policy. *See City of Virginia Beach v. U.S. Dep't of Com.*, 995 F.2d 1247, 1252-53 (4th Cir. 1993) (noting that action by agencies should be judged "on the basis of their

final decisions" and not "for matters they considered before making up their minds"). That latitude needs to be broad in the case of a statutory charge as general as this one, where internal discussions involve "complex predictions within the [FDA's] area of special expertise." *Nat'l Audobon Soc'y v. U.S. Army Corps of Eng'rs*, 991 F.3d 577, 583 (4th Cir. 2021). Petitioners not only wish to restrict FDA's consideration of certain forms of evidence, but also to locate a point where agency deliberations become frozen in time. The result would be gridlock, an agency decisional process robbed of the value of ongoing dialogue.

3.

As part of their arbitrary and capricious review, courts must examine the care and thoroughness of agency action. A careful approach to a problem inspires more judicial confidence than some back-of-the-hand dismissal. An agency must thus address the issues such that a reviewing court "can understand enough about the problem confronting the agency to comprehend the meaning of the evidence relied upon and the evidence discarded; the questions addressed by the agency and those bypassed; the choices open to the agency and those made." *Aracoma*, 556 F.3d at 192-93 (internal quotations omitted), The carefulness of FDA's review is nowhere better illustrated than in its administrative re-review of Avail's PMTAs. As part of this process, FDA looked thoughtfully at each of Avail's four behavioral studies, the nature of which we discussed above. *See* Section I.D, *supra*. FDA's re-review is part of the administrative record before this court.

See J.A. 46-60. We find it particularly telling that Avail itself asked for this administrative re-review. *See* J.A. 47. FDA's decision on re-review forms part of "the grounds that the agency invoked when it took the action," which was ultimately the issuance and continuing validity of its marketing denial order. *Michigan v. EPA*, 576 U.S. 743, 758, 135 S. Ct. 2699, 192 L. Ed. 2d 674 (2015).

FDA discussed in-depth the deficiencies of Avail's four behavioral studies. The two-week online diary study did not collect data specific to the products in petitioners' applications, and therefore could not present the proper comparative efficacy data necessary to offset the known risks to youth associated with flavored ENDS products. J.A. 56-57. As for the evidence submitted from a series of focus groups, Avail did not provide information showing that the small focus groups were representative of current adult users of tobacco products *other* than e-cigarettes. J.A. 57. Without representative data on adult smokers of traditional cigarettes, the focus groups could not measure switching or cessation. The evidence from Avail's "perceptions and intent to use study" similarly did not stratify its results by participants' tobacco-use status, and therefore did not "support conclusions on current adult smokers' behavioral intentions to try, or switch to, Avail's products." *Id.* Finally, petitioners' data from a "human factors summative protocol," which surveyed 18 adults about the usability and safety of one Avail flavor in four nicotine strengths "did not examine behavior change or use of ENDS," in general or with Avail's products. *Id.* Such information was necessary to demonstrate a benefit to adult smokers under the TCA. *Id.* Since none of these

studies were scientifically rigorous, FDA could not rely on them in determining whether Avail's products were "appropriate for the protection of the public health."

III.

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

A.

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

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

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

B.

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

Id. (quoting *Sanders*, 556 U.S. at 407). This doctrine "prevents reviewing courts from becoming 'impregnable citadels of technicality' and preserves the relative roles of courts and agencies in implementing substantive policy." *Id.* (quoting *Sanders*, 556 U.S. at 407).

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

In the face of these warnings, Avail's marketing plan might have aided its application by presenting novel access restrictions beyond those that the FDA previously determined were not working. Instead, Avail's plan focused solely on age verification and avoiding marketing that would make its products attractive to youth. This was insufficient. *See Prohibition Juice*, 45 F.4th at 25 (explaining that "self-verification of age at the point of sale and . . . less vibrant marketing unappealing to youth" "track measures the FDA in its 2020 guidance deemed inadequate"); *Wages & White Lion*, 41 F.4th at 442 (noting the "FDA had already explained" that limiting products to

"age-gated vape and specialty tobacco shops and through age-gated online sales" "do *not* work"); *Liquid Labs*, 52 F.4th at 544 (finding that "age verification measures, a mystery shopper program . . . and a prohibition on marketing material that could be perceived to be targeting individuals below the legal vaping age . . . are similar, if not identical to the kinds of approaches the FDA found did not address this serious problem") (internal quotations omitted).

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

the plan would have made up for the deficiencies the FDA identified in [petitioner's] applications").

Finally, Avail errs in encouraging us to follow the Eleventh Circuit's decision in *Bidi Vapor LLC v. U.S. Food & Drug Administration*, which found arbitrary and capricious the FDA's decision not to review certain applicants' marketing plans. 47 F.4th 1191, 1195 (11th Cir. 2022). But petitioners in that case submitted novel marketing restrictions "not specifically mentioned in the 2020 Guidance" which merited a closer look by the agency. *Id.* at 1205 (identifying a unique "Trace/Verify technology" and an "authentication system designed to prevent counterfeit products from becoming accessible to youth"). Avail nowhere identified truly novel restrictions beyond age verification and "nondescriptive" marketing that would tip the scales in its favor. And in all events, the sequencing of review by the FDA can hardly be termed arbitrary. Considering marketing questions before verifying the underlying safety of the product to be marketed is to put the cart before the horse.

IV.

A.

We see no merit in Avail's remaining arguments that FDA acted arbitrarily and capriciously in reviewing petitioners' PMTAs. Avail argues that the FDA was required to consider the distinction between open and closed systems when adjudicating its PMTAs. According to Avail, FDA's 2020 Enforcement Guidance focused

on cartridge-based flavored ENDS products, and thus signaled to industry that open-system products, and the bottled e-liquids which accompany them, would be entitled to different treatment. As an initial matter, FDA *did* acknowledge the differences between products in its denial order, stating that "there may be differential appeal of certain product styles." J.A. 31; *see also Prohibition Juice*, 45 F.4th at 26. But even with these distinctions in mind, FDA determined that the scientific evidence shows that "the role of flavor is consistent" between open and closed systems. J.A. 31. It is not our job as a reviewing court to redo an agency's evaluation of relevant evidence. Indeed, we cannot "second guess an agency's reasonable choice of methodology." *American Whitewater v. Tidwell*, 770 F.3d 1108, 1116 (4th Cir. 2014). FDA's original focus on *enforcement* against cartridge-based ENDS products did not foreclose it from denying a marketing order for Avail's e-liquids, especially in light of the growing evidence that the role of flavors in driving youth initiation was consistent across products.

B.

We turn last to Avail's substantive challenge to the FDA's statutory authority. Petitioners argue that "FDA exceeded its statutory authority by imposing a new comparative efficacy standard that requires applicants seeking authorization to market flavored ENDS products to demonstrate that those products better promote smoking cessation than the appellant's otherwise identical tobacco flavored products." Pet'rs' Opening Br. at 2. We disagree and join the Third, Fifth, and D.C. Circuits in

determining that FDA acted within its statutory mandate when it required applicants to submit such "comparative efficacy" evidence. *See Liquid Labs*, 52 F.4th at 542-43; *Wages and White Lion*, 41 F.4th at 434-35 ; *Prohibition Juice*, 45 F.4th at 19-20.

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

And as part of the ultimate inquiry into whether an application is appropriate for the public health, the Secretary must also "tak[e] into account . . . the *increased or decreased likelihood* that existing users of tobacco products will stop using such products" on the one hand

and "the *increased or decreased likelihood* that those who do not use tobacco products will start using such products" on the other. *See* Tobacco Control Act, § 910(c)(4)(A)-(B), 123 Stat. at 1810 (emphasis added). It would seem apparent that "nothing can 'increase' or 'decrease' in a vacuum" and thus this phrase "necessarily implies a comparative analysis." *Wages and White Lion*, 41 F. 45h at 434.

V.

Under the TCA, the FDA has the daunting task of ensuring that another generation of Americans does not become addicted to nicotine and tobacco products. The TCA gives FDA the flexibility to determine whether marketing of a new tobacco product is appropriate for the protection of public health, taking into account evolving science and an ever-changing market. FDA made the determination that Avail's flavored ENDS products, seeking in all respects to mimic those sweet treats to which youth are particularly attracted, pose a substantial risk of youth addiction without enough offsetting benefits to adult smokers. FDA could not allow young adults to perceive e-cigarettes as another Baby Ruth or Milky Way, only to find themselves in the grip of a surreptitious nicotine addiction. This was hardly arbitrary. Substantial evidence supports the assertion that "[t]here is an epidemic of youth use of e-cigarette products, and flavored products like petitioners' are at the center of that problem." Gov't Response Br. 22. For the foregoing reasons, we deny Avail's petition.

DENIED

APPENDIX B — MARKETING DENIAL ORDER OF THE U.S. FOOD & DRUG ADMINISTRATION, DATED SEPTEMBER 15, 2021

U.S. FOOD & DRUG ADMINISTRATION
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

September 15, 2021

DENIAL

Avail Vapor LLC
Attention: Vincent J. Angelico, Ph.D., Director of Science and Regulatory Affairs
Blackbriar Regulatory Services LLC
820 Southlake Boulevard
North Chesterfield, VA 23236

FDA Submission Tracking Number (STN):
PM0001233, see Appendix A

Dear Dr. Angelico:

We are denying a marketing granted order for the products identified in Appendix A. Refer to Appendix B for a list of amendments received in support of your applications.

Appendix B

Based on our review of your PMTAs[1], we determined that the new products, as described in your applications and specified in Appendix A, lack sufficient evidence to demonstrate that the marketing of these products is appropriate for the protection of the public health (APPH). Therefore, you cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

If you choose to submit new applications for these products, you must fulfill all requirements set forth in section 910(b)(1). You may provide information to fulfill some of these requirements by including an authorization for FDA to cross-reference a Tobacco Product Master File.[2] You may not cross-reference information submitted in the PMTA subject to this Denial.

Based on review of your PMTAs, we identified the following key basis for our determination:

1. All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be

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1. Premarket Tobacco Product Applications (PMTAs) submitted under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

2. See guidelines at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/tobacco-product-master-files

adequate to outweigh the risks to youth. In light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS.

Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs contained four protocols for RCTs (BBRS 2020-02, BBRS 2020-03, BBRS 2020-04 and BBRS 2020-05) to address the new products' abuse liability, the study reports were not submitted. All four protocols were described as randomized, open-label, crossover studies to evaluate nicotine pharmacokinetics and subjective effects with use of different e-liquid products and usual brand of combustible cigarettes in healthy adult smokers. No data from these RCT protocols were submitted for review; therefore, this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these

> products over time or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors.
>
> Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

We cannot find that the marketing of your new tobacco products is APPH. The review concluded that key evidence demonstrating APPH is absent. Therefore, scientific review did not proceed to assess other aspects of the applications. FDA finds that it is not practicable to identify at this time an exhaustive list of all possible deficiencies.

Your PMTAs lack sufficient information to support a finding of APPH; therefore, we are issuing a marketing denial order. Upon issuance of this order, your products are misbranded under section 903(a)(6) of the FD&C Act and adulterated under section 902(6)(A) of the FD&C Act. Failure to comply with the FD&C Act may result in FDA regulatory action without further notice. These actions may include, but are not limited to, civil money penalties, seizure, and/or injunction.

Appendix B

We encourage you to submit all regulatory correspondence electronically via the CTP Portal[3],[4] using eSubmitter.[5] Alternatively, submissions may be mailed to:

Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The CTP Portal and FDA's Electronic Submission Gateway (ESG) are generally available 24 hours a day, seven days a week; submissions are considered received by DCC on the day of successful upload. Submissions delivered to DCC by courier or physical mail will be considered timely if received during delivery hours on or before the due date[6]; if the due date falls on a weekend or holiday, the delivery must be received on or before the preceding business day. We are unable to accept regulatory submissions by e-mail.

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3. For more information about CTP Portal, see https://www.fda.gov/tobacco-products/manufacturing/submit-documents-ctp-portal

4. FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.

5. For more information about eSubmitter, see https://www.fda.gov/industry/fda-esubmitter

6. https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/contact-ctp

If you have any questions, please contact Dyamond Govan, MS, Regulatory Health Project Manager, at (301) 837-7113 or Dyamond.Govan@fda.hhs.gov.

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2021.09.15 14:30:05 -04'00'
Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

Enclosures (**if provided electronically, the Appendices are not included in physical mail**):

Appendix A – New Tobacco Products Subject of This Letter Tobacco Products Subject of This Letter

Appendix B – Amendments Received for These Applications

Appendix B

Appendix A[7]
New Tobacco Products Subject of This Letter

Common Attributes of PMTAs	
Date of Submission:	September 8, 2020
Date of Receipt:	September 8, 2020
Applicant:	Avail Vapor, LLC
Product Manufacturer:	Blackbriar Regulatory Services, LLC ("BRS")
Product Category:	ENDS (VAPES)
Product Sub-Category:	ENDS Component

Appendix B
Amendment Received for These Applications

Submission Date	**Receipt Date**	**Applications being amended**	**Reviewed**	**Brief Description**
January 6, 2021	January 6, 2021	All	Yes	Submission of TPMF reference statement and updated HPHC report

7. Brand/sub-brand or other commercial name used in commercial distribution.

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STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD1	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD2	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD3	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD4	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD5	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD6	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD7	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD8	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle

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STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD9	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD10	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD11	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD12	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD13	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD14	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD15	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD16	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle

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STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD17	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD18	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD19	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD20	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD21	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD22	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD23	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD24	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle

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STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD29	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD30	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD31	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD32	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD33	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD34	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD35	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD36	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle

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STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD37	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD38	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD39	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD40	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD41	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD42	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD43	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD44	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle

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Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Menthol, Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Menthol, Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Menthol, Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Menthol, Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL

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Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Dessert	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Dessert	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Dessert	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Dessert	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL

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Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL

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Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Menthol, Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Menthol, Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Menthol, Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Menthol, Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL

Appendix B

Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	None	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	None	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	None	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	None	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	None	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	None	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	None	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
1 Bottle	None	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL

APPENDIX C — TECHNICAL PROJECT LEAD REVIEW OF PMTAS OF THE U.S. FOOD & DRUG ADMINISTRATION, DATED SEPTEMBER 15, 2022

FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Re-Review of PMTAs

New Products Subject of this Review[<?>]	
Submission tracking number (STN)	PM0001233, see Appendix A
Common Attributes	
Submission date	September 8, 2020
Receipt date	September 8, 2020
Applicant	Avail Vapor, LLC
Product manufacturer	Blackbriar Regulatory Services, LLC ("BRS")
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submissions	
All STNS	M F0000262, MF0000275, MF0000276, MF0000282, MF0000384, and MF0000401
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Appendix C

Technical Project Lead (TPL):

Digitally signed by
Cindy A. Tworek -S
Date: 2021.09.15 11:32:32 -04'00'
Cindy Tworek, Ph.D., M.P.H.
Chief, Social Science
Division of Population
Health Science

Signatory Decision:

Concur with TPL recommendation
and basis of recommendation
Digitally signed by
Matthew R. Holman -S
Date: 2021.09.15 14:29:22 -04'00'
Matthew R. Holman, Ph.D.
Director
Office of Science

[TABLES INTENTIONALLY OMITTED]

Appendix C

1. EXECUTIVE SUMMARY

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

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

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

Appendix C

Based on existing scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined for these applications that, to effectively demonstrate this benefit in terms of product use behavior, only the strongest types of evidence will be sufficiently reliable and robust most likely product specific evidence from a randomized controlled trial (RCT)[iv] or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis.[v,vi] Moreover, tobacco-flavored ENDS may offer

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

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

vi. For example, we would consider evidence from another study design if it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco-flavored products. In our review of PMTAs for flavored ENDS

the same type of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Therefore, to demonstrate the potential benefit to current users, FDA has reviewed these applications for any acceptably strong evidence that the flavored products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking.

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

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

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so far, we have learned that, in the absence of strong evidence generated by directly observing the behavioral impacts of using a flavored product vs. a tobacco-flavored product over time, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth.

Appendix C

2. BACKGROUND

2.1. NEW PRODUCTS

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

2.2. REGULATORY ACTIVITY

FDA issued an Acceptance letter to the applicant on November 12, 2020. FDA issued a Filing letter to the applicant on January 21, 2021.

Refer to Appendix B for a complete list of amendments received by FDA.

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

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

The Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) requires that "new tobacco products" receive marketing authorization from FDA under one of the pathways specified by the Act in order to be legally marketed in the United States. Under one pathway, the applicant submits a PMTA to FDA. Section 910 of the FD&C Act requires that, for a product to receive PMTA marketing authorization, FDA must conclude, among

other things, that the marketing of the product is APPH. The statute specifies that, in assessing APPH, FDA consider the risks and benefits to the population as a whole including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products.[vii]

It is well recognized that ENDS, and particularly flavored ENDS, pose a significant risk to nonusers, especially youth.[1,2] After observing a dramatic increase in the prevalence of ENDS use among U.S. youth in 2018, FDA's Commissioner characterized the problem as a youth vaping epidemic. FDA has initiated a series

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vii. This review focuses on risk to youth nonusers and the potential benefit to adult smokers as current tobacco product users, given that these are the subpopulations that raise the most significant public health concerns and therefore are the most relevant in evaluating the impact on the population as a whole. FDA has also considered the APPH standard with respect to the likelihood that an authorization will increase or decrease the number of tobacco users in the overall population. The availability of such products has generally led to greater tobacco use among youth overall, notwithstanding the decrease in cigarette smoking for youth, which reinforces the focus in this review on having sufficiently reliable and robust evidence to justify authorization of these PMTAs. Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students United States, 2011-76-1277, 2018. Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018.

of actions to address the risk and reduce youth use. Since August 2016, FDA has issued more than 10,000 warning letters and more than 1,400 civil money penalty complaints to retailers for the sale of ENDS products to minors. FDA has also issued a guidance that described a policy of prioritizing enforcement of non-tobacco/non-menthol flavored ENDS, "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the (2020 Enforcement Priorities Guidance). In this guidance, Market without Premarket Authorization" FDA described evidence that shows flavors (other than tobacco and menthol) were a key driver of the surge in ENDS use among youth and thus prioritized enforcement against certain flavored ENDS products, with the goal of protecting youth from these products.[viii]

After FDA implemented this enforcement policy prioritizing enforcement against a subset of ENDS products known to appeal to youth, there was a meaningful reduction in youth use prevalence. Youth ENDS use peaked in 2019 when these products were widely available. Although several other policy changes and interventions were occurring during this same time period,[ix] it is

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

ix. The change in ENDS product availability coincided with other events such as the enactment of legislation raising the federal

reasonable to infer that prioritizing enforcement against many flavored products resulting in their removal from the market contributed to the decline in use in 2020. Despite this decline, ENDS remained the most widely used tobacco product among youth, with youth use at levels comparable to what originally led FDA to declare a youth vaping epidemic. Moreover, despite the overall reduction in ENDS youth use observed in 2020, there was simultaneously a substantial rise in youth use of disposable ENDS, products that were largely excluded from the enforcement policy described in the 2020 Enforcement Priorities Guidance because, at that time that policy was developed, those products were the least commonly used device type among high school ENDS users and therefore remained on the market as a flavored option.[3,4]

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be [APPH] Through the PMTA review process, FDA conducts a science-based evaluation to determine whether marketing of a new tobacco product is APPH. Section 910(c)(4) requires FDA, in making the APPH determination, to consider the risks and benefits to the population as a whole, including users and nonusers of tobacco, and take into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to

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minimum age for sale of tobacco products from 18 to 21 years (Tobacco 21), the outbreak of e-cigarette, or vaping, product-use associated lung injury (EVALI), and public education campaigns which also may have contributed to the decline in ENDS use.

considering only information in a PMTA, but also extends to any other information before the Agency, including the relevant existing scientific literature (See Section 910(c)(2)). As described in greater detail below, in reviewing PMTAs for flavored ENDS, FDA evaluates, among other things, the potential benefit to adult smokers who may transition away from combustible cigarettes to the ENDS product, weighed against the known risks of flavored ENDS to youth.

The Risk to Youth of Flavored ENDS Products

As noted, the APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood[5] and thus youth are at particular risk of tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Indeed, almost 90 percent of adult daily smokers started smoking by the age of 18.[6] Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood.[7] On the other hand, youth and young adults who reach the age of 26 without ever starting to use cigarettes will most likely never become a daily smoker.[6] Because of the lifelong

implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

2.3.1.1. Youth use of flavored ENDS

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

The evidence shows that the availability of a broad range of flavors is one of the primary reasons for the popularity of ENDS among youth. The majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time. In the 2014 National Youth Tobacco Survey (NYTS), 65.1% of high school and 55.1% of middle school e-cigarette[x] users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xi] increased to 84.7% of high school users and 73.9% of middle school users.[3] Among high school

x. We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.

xi. Flavored product use in these studies means use of flavors other than tobacco.

e-cigarette users, the most common flavors used in 2020 were fruit (73.1%); mint (55.8%); menthol (37.0%); and candy, dessert, or other sweets (36.4%).[3] Among middle school e-cigarette users, the most common flavors used in 2020 were fruit (75.6%); candy, desserts, or other sweets (47.2%); mint (46.5%); and menthol (23.5%).[3]

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

Studies show that flavors influence youth initiation of ENDS use. In particular, data show that flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a flavored product. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first e-cigarette that they used

xii. The PATH Study Questionnaire from Wave 5.5 did not assess mint and menthol separately. However, subsequent data collections (ATS and Wave 6) have separated the two flavors.

was flavored.[12] In another PATH study, more youth, young adults and adults who initiated e-cigarette use between Wave 1 and Wave 2 reported use of a flavored product than a non-flavored product.[13] Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older.[14]

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

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

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

2.3.1.2. The appeal of flavors across ENDS devices

The role of flavors in increasing the appeal of tobacco products to youth — across tobacco product categories

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

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

It is also worth noting that the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace, that is, the options, especially flavors, that are available for consumers to choose from. Some evidence for this was observed in the trends both leading up to, and coinciding with, the shifting marketplace

following the 2020 Enforcement Priorities Guidance. In particular, the enormous rise in youth ENDS use from 2017-2019 coincided with the ascendance of JUUL (and copy-cat devices) in the marketplace, suggesting a relationship between the availability of JUUL as an option, and the sudden popularity of pod-based devices.[xiii] Then, as noted earlier, when FDA changed its enforcement policy to prioritize pod-based flavored ENDS, which were most appealing to youth at the time, we subsequently observed a substantial rise in use of disposable flavored ENDS[xiv]--a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users.[4] This trend illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired flavor options, underscoring the fundamental role of flavor in driving appeal.

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

In addition to the high prevalence of youth ENDS use, the data also suggest this use is leading to increases in nicotine dependence.[10] Indeed, responding to concerns related to youth ENDS dependence, at the end of 2018,

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

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

FDA held a public hearing to discuss the potential role of drug therapies to support e-cigarette cessation.[xv]

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

Youth and young adult brains are more vulnerable to nicotine's effects than the adult brain due to ongoing neural development.[31,32] Adolescence is a developmental period consisting of major neurobiological and psychosocial changes and is characterized by increased reward-seeking and risktaking behaviors (e.g., experimentation with drugs), coupled with heightened sensitivity to both natural and drug rewards and an immature self-regulatory system that is less able to modulate reward-seeking impulses (e.g., diminished harm avoidance, cognitive control, self-regulation).[33-37] Furthermore, evidence from

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

animal studies suggests that nicotine exposure during adolescence enhances the rewarding and reinforcing effects of nicotine in adulthood[38-41]; and can induce short and long-term deficits in attention, learning, and memory.[42-45]

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

Among youth who use ENDS, there is a risk of progression to other tobacco products of generally greater health risk. A 2017 systematic review and meta-analysis that summarized nine prospective cohort studies found significantly higher odds of smoking initiation (OR = 3.50, 95% CI: 2.38, 5.16) and past 30-day combusted cigarette use (OR = 4.28, 95% CI: 2.52, 7.27) among youth who had used ENDS at compared to youth who had not used ENDS.[46] Similar associations have been observed in longitudinal studies that have been published since the Soneji et al. review.[42,47-56] The 2018 NASEM report concluded that there is substantial evidence that ENDS use increases risk of ever using combusted tobacco cigarettes among youth and young adults.[57] The transition from non-cigarette product use to combusted cigarette use has been observed for other non-cigarette products, such as cigars, as well.[58] Although it is challenging to empirically separate causality from shared risk factors among youth combusted cigarette and ENDS users, some studies have found an association between ENDS and subsequent combusted cigarette use while controlling for similar risk profiles.[54]

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

2.3.1.5. Other health risks associated with ENDS use

In addition to the risk of tobacco initiation and progression among youth, there is epidemiologic evidence from the cross-sectional[xvi] Behavioral Risk Factor Survey system (BRFSS) suggesting positive associations between ENDS use among those who never smoked and some health outcomes. Two studies found associations between ENDS use and self-reported history of asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease with increased ENDS use (i.e., daily use) relating to increased odds of disease.[61,62] Another found an association between ENDS use and respiratory symptoms in younger adults (ages 18-34) but not in older

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

adults.[63] ENDS use has also resulted in acute harm to individuals through battery explosion-related burns and e-liquid nicotine poisoning.[64-66] Ultimately, as this is still a relatively novel product category, much remains unknown about other potential long-term health risks.

2.3.1.6. Conclusion

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

Appendix C

Balancing Known Risks to Youth with a Potential Benefit to Adults

Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be overcome by a sufficient benefit to adult users, and as the known risks increase, so too does the burden of demonstrating a substantial enough benefit. In the case of a new flavored ENDS product, the risk of youth initiation and use is substantial, given the clearly documented evidence described above. In order for marketing of a new flavored ENDS product to be found APPH, an applicant would have to show that the significant risk to youth could be overcome by likely benefits substantial enough such that the net impact to public health would be positive, taking into account all relevant evidence and circumstances, including whether there are effective limitations on youth access.

2.3.2.1. Potential benefit of new flavored ENDS

Current scientific literature demonstrates that ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than combustible cigarettes, and biomarker studies

demonstrate significantly lower exposure to HPHCs among current exclusive ENDS users than current smokers.[57] However, whether this is true for any particular new ENDS product, and the implications for health risks from a particular product, are considered on a case-by-case basis during the course of FDA's scientific review of a PMTA.

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

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

FDA's PMTA review includes an evaluation of any potential benefits of the product for the likely users, such as a possible reduction in health risks. In general, as FDA stated in its guidance for PMTAs for ENDS,[xvii] an

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

assessment of how a new product may be used by current smokers can be derived from a variety of sources. FDA may consider direct behavioral evidence on the specific products under review or indirect evidence derived from studies of behavioral intentions; pharmacological studies of nicotine delivery, abuse liability, and/or use topography; and bridging from studies based on comparable products. Further, in the case of a flavored ENDS product, to demonstrate that the marketing of the new product is APPH, the magnitude of the likely benefit would have to be substantial enough to overcome the significant risk of youth uptake and use posed by the flavored ENDS product.

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

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

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

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xix. Limiting youth access and exposure to marketing is a critical aspect of product regulation. It is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal such that the risk for youth initiation would be reduced. However, to date, none of the ENDS PMTAs that FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree

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We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS products. Our substantive review of PMTAs for ENDS and our completion of numerous scientific reviews over the last 10 months have deepened our understanding of the APPH evaluation with respect to behavior. In these reviews, the expectations for scientific evidence related to potential adult benefit can vary based on demonstrated risk to youth. Although indirect evidence or bridged data from the literature may still be appropriate for many new products, including tobacco-flavored ENDS, robust and direct evidence demonstrating potential benefit has been needed when the known risks are high as with all flavored ENDS products. At the same time, we have learned from experience that, in the absence of strong direct evidence, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth. For instance, applicants who do not conduct their own behavioral studies must rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. To date, that approach has not been sufficient in our evaluation of flavored ENDS PMTAs because, in contrast to the evidence related to youth initiation which shows clear and consistent patterns of real-world use

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significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use. Similarly, we are not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use ENDS. Accordingly, for the sake of efficiency, the evaluation of the marketing plans in applications will not occur at this stage of review, and we have not evaluated any marketing plans submitted with these applications.

that support strong conclusions--the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive.[xx] In fact, the findings are quite mixed and as a result the literature does not establish that flavors differentially promote switching amongst ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due, at least in part, to differences in the products studied. Therefore, given the state of the science on flavored ENDS, and the known risks to youth, FDA has reviewed these applications for any acceptably strong product-specific evidence.

More specifically, in order to adequately assess whether such an added benefit has been demonstrated, FDA has reviewed these applications for product-specific[xxi] evidence

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

xxi. By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their

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

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products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

xxii. Conversely, such longitudinal or product-specific data are not necessarily required to assess experimentation and appeal among youth. The available literature on youth initiation contains valid scientific evidence sufficient to evaluate the risk to youth of ENDS. The literature includes longitudinal cohort studies, such as the PATH study, which have been used to assess uptake of tobacco products, including flavored ENDS, among youth and young adults. These studies have evaluated the impact of flavors on the promotion of established regular use. Additionally, the literature includes large, nationally representative cross-sectional surveys, which are among the best available evidence to understand patterns of youth ENDS use and the key characteristics associated with such use These studies enable observation of youth behavior as it naturally occurs in representative samples of the U.S. population. These data available in the literature provide clear and overwhelming evidence that ENDS are the most widely used products by youth, the majority of youth users use a flavored ENDS, and that youth users are more likely to use flavored ENDS than adult ENDS users. We note that, in assessing the risks to youth from flavored

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

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to recall their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Consumer perception studies (surveys or experiments) typically assess outcomes believed to be precursors to behavior, such as preferences or intentions related to the new products, but are not designed to directly assess actual product use behavior. Moreover, the general scientific literature, though informative for evaluation of some types of products, is not adequate to address this assessment because it does not provide product-specific information. This is because the effectiveness of a product in promoting switching among

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ENDS, RCTs are not possible because it would be unethical to randomize youth never or naive users to try a particular ENDS to examine what impact it would have on initiation, experimentation, or progression to regular use.

smokers arises from a combination of its product features including labeled characteristics like flavor and nicotine concentration as well as the sensory and subjective experience of use (taste, throat hit, nicotine delivery), and can also be influenced by how the device itself looks and feels to the use.

While RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity; cohort studies enable stronger generalizability because conditions are closer to real-world. We are aware of these as trade-offs and generally do not favor one type over the other for addressing this question.

To be informative, a study using one of these two designs would measure the impact of use of the new or appropriate comparator product tobacco-flavored ENDS and flavored products on adult smokers' tobacco use behavior over time[xxiii]; include outcomes related to ENDS use and smoking behavior to assess switching and/

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

or cigarette reduction; and enable comparisons of these outcomes based on flavor type. In some cases, evidence on each individual flavor option may not be feasible; bridging data from one of the applicant's flavors to other flavors of the applicant's in the same flavor category (e.g., "fruit") may be appropriate. Furthermore, consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging.[xxiv] Likewise, if a flavor is tested with one nicotine concentration, it may be feasible for the applicant to bridge the study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging.

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

2.3.2.3. Conclusion

Given the known and substantial risk to youth posed by flavored ENDS, FDA has reviewed these applications for the presence of particularly reliable product-specific[xxv]

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

xxv. By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product

evidence to demonstrate a potential for benefit to adult smokers that could justify that risk. Based on our current understanding, a demonstration with sufficiently reliable and robust evidence that the flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS.

2.4. SCOPE OF REVIEW

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

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variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

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3. SCIENTIFIC REVIEW

Reviews were completed by Bria Graham-Glover and Hristina Dimova on September 15, 2021. The reviews determined that the PMTAs did not contain evidence from a randomized controlled trial and/or longitudinal cohort study examining the benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes. The PMTAs include four protocols for RCTs (BBRS 2020-02, BBRS 2020-03, BBRS 2020-04 and BBRS 2020-05) to address the new products' abuse liability, however the study reports have not been submitted. All four are randomized, open-label, crossover studies to evaluate nicotine pharmacokinetics and subjective effects with use of different e-liquid products and usual brand of combustible cigarettes in healthy adult smokers. Some of these RCT protocols (e.g. BBRS 2020-02 and BBRS 2020-05) include non-tobacco-flavored and tobacco-flavored e-liquids. No data from these RCT protocols were submitted for review; therefore, this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors. Accordingly, this evidence is not adequate and therefore, we did not assess other aspects of the application as part of this scientific review.

4. ENVIRONMENTAL DECISION

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

5. CONCLUSION AND RECOMMENDATION

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

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

1. All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth. In light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS.

   Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs contained four protocols for RCTs (BBRS 2020-02, BBRS 2020-03, BBRS 2020-04 and BBRS 2020-05) to address the new products' abuse liability, the study reports were not submitted. All four protocols were described as randomized, open-label, crossover studies to evaluate nicotine pharmacokinetics and subjective effects with use of different e-liquid products and usual brand of combustible cigarettes in healthy adult

smokers. No data from these RCT protocols were submitted for review; therefore, this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors.

Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

6. APPENDIX

Appendix A. New Products (attached)

Common Attributes<?><?>	
Submission date	September 8, 2020
Receipt date	September 8, 2020
Applicant	Avail Vapor, LLC
Product manufacturer	Blackbriar Regulatory Services, LLC ("BRS")
Product category	ENDs VAPES
Product subcategory	ENDS Component

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Appendix B. Amendments Received

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
January 6, 2021	January 6, 2021	PM0004499	All	Yes	Submission of TPMF reference statement and updated HPHC report

7. REFERENCES

1. U.S. Department of Health and Human Services. *E-cigarette Use Among Youth and Young Adults. A Report of the Surgeon General*. Atlanta, GA: U.S. Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2016.

2. U.S. Food and Drug Administration. *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised). Guidance for Industry*. Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products; April 2020.

3. Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. E-cigarette Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(37):1310-1312.

4. Wang TW, Gentzke AS, Neff LJ, et al. Disposable E-Cigarette Use among U.S. Youth — An Emerging Public Health Challenge. *New England Journal of Medicine*. 2021;384(16):1573-1576.

5. U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General.* Atlanta, GA: U.S. Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2012.

6. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National

Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2014.

7. Apelberg BJ, Corey CG, Hoffman AC, et al. Symptoms of tobacco dependence among middle and high school tobacco users: results from the 2012 National Youth Tobacco Survey. *Am J Prev Med*. 2014;47(2 Suppl 1):S4-14.

8. Gentzke AS, Wang TW, Jamal A, et al. Tobacco Product Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(50):1881-1888.

9. Wang TW, Gentzke AS, Creamer MR, et al. Tobacco Product Use and Associated Factors Among Middle and High School Students - United States, 2019. *MMWR Surveill Summ*. 2019;68(12):1-22.

10. Cullen KA, Liu ST, Bernat JK, et al. Flavored Tobacco Product Use Among Middle and High School Students - United States, 2014-2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(39):839-844.

11. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'Connor RJ. Use of Flavored E-Cigarettes and the Type of E-Cigarette Devices Used among Adults and Youth in the US-Results from Wave 3 of the Population Assessment of Tobacco and Health Study (2015-2016). *Int J Environ Res Public Health*. 2019;16(16).

12. Villanti AC, Johnson AL, Glasser AM, et al. Association of Flavored Tobacco Use With Tobacco Initiation and Subsequent Use Among US Youth and Adults, 2013-2015. *JAMA Netw Open*. 2019;2(10):e1913804.

13. Rose SW, Johnson AL, Glasser AM, et al. Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2014-2015. *Tob Control*. 2020;29(4):432-446.

14. Rostron BL, Cheng YC, Gardner LD, Ambrose BK. Prevalence and Reasons for Use of Flavored Cigars and ENDS among US Youth and Adults: Estimates from Wave 4 of the PATH Study, 2016-2017. *Am J Health Behav*. 2020;44(1):76-81.

15. Ambrose BK, Day HR, Rostron B, et al. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. *JAMA*. 2015;314(17):1871-1873.

16. Tsai J, Walton K, Coleman BN, et al. Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(6):196-200.

17. Audrain-McGovern J, Strasser AA, Wileyto EP. The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug Alcohol Depend*. 2016;166:263-267.

18. St Helen G, Dempsey DA, Havel CM, Jacob P, 3rd, Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug Alcohol Depend*. 2017;178:391-398.

19. Morean ME, Butler ER, Bold KW, et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PLoS One*. 2018;13(1):e0189015.

20. Leventhal AM, Goldenson NI, Cho J, Kirkpatrick MG, McConnell RS, Stone MD, Pang RD, Audrain-McGovern J, Barrington-Trimis JL. Flavored E-cigarette Use and Progression of Vaping in Adolescents. *Pediatrics*. 2019 Nov;144(5):e20190789.

21. Audrain-McGovern J, Rodriguez D, Pianin S, Alexander E. Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents. *Drug Alcohol Depend*. 2019;202:149-155.

22. Villanti AC, Johnson AL, Halenar M, et al. Menthol and mint cigarettes and cigars: Initiation and progression in youth, young adults and adults in Waves 1 - 4 of the PATH Study, 2013 - 2017. *Nicotine Tob Res*. 2020.

23. Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: tobacco marketing strategies. *Health Aff (Millwood).* 2005;24(6):1601-1610.

24. Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tobacco Control*. 2016;25(Suppl 2):ii62.

25. Camenga DR, Morean M, Kong G, Krishnan-Sarin S, Simon P, Bold K. Appeal and Use of Customizable E-cigarette Product Features in Adolescents. *Tob Regul Sci*. 2018;4(2):51-60.

26. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Prev Med Rep*. 2017;5:33-40.

27. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. *Jama*. 2019;322(21):2095-2103.

28. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine Tob Res*. 2015;17(2):186-192.

29. Yingst J, Foulds J, Veldheer S, et al. Measurement of Electronic Cigarette Frequency of Use Among Smokers Participating in a Randomized Controlled Trial. *Nicotine Tob Res*. 2020;22(5):699-704.

30. Vogel EA, Prochaska JJ, Ramo DE, Andres J, Rubinstein ML. Adolescents' E-Cigarette Use: Increases in Frequency, Dependence, and Nicotine Exposure Over 12 Months. *J Adolesc Health*. 2019;64(6):770-775.

31. Slotkin TA. Nicotine and the adolescent brain: insights from an animal model. *Neurotoxicol Teratol*. 2002;24(3):369-384.

32. Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *J Physiol*. 2015;593(16):3397-3412.

33. Bava S, Tapert SF. Adolescent brain development and the risk for alcohol and other drug problems. *Neuropsychol Rev*. 2010;20(4):398-413.

34. Bernheim A, Halfon O, Boutrel B. Controversies about the enhanced vulnerability of the adolescent brain to develop addiction. *Front Pharmacol*. 2013;4:118.

35. Casey BJ, Jones RM. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. *J Am Acad Child Adolesc Psychiatry*. 2010;49(12):1189-1201; quiz 1285.

36. Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain Cogn*. 2010;72(1):114-123.

37. Shulman EP, Smith AR, Silva K, et al. The dual systems model: Review, reappraisal, and reaffirmation. *Dev Cogn Neurosci*. 2016;17:103-117.

38. Kota D, Sanjakdar S, Marks MJ, Khabour O, Alzoubi K, Damaj MI. Exploring behavioral and molecular

mechanisms of nicotine reward in adolescent mice. Biochem *Pharmacol*. 2011;82(8):1008-1014.

39. Shram MJ, Lê AD. Adolescent male Wistar rats are more responsive than adult rats to the conditioned rewarding effects of intravenously administered nicotine in the place conditioning procedure. *Behav Brain Res*. 2010;206(2):240-244.

40. Natividad LA, Torres OV, Friedman TC, O'Dell LE. Adolescence is a period of development characterized by short- and long-term vulnerability to the rewarding effects of nicotine and reduced sensitivity to the anorectic effects of this drug. *Behav Brain Res*. 2013;257:275-285.

41. de la Peña JB, Ahsan HM, Tampus R, et al. Cigarette smoke exposure during adolescence enhances sensitivity to the rewarding effects of nicotine in adulthood, even after a long period of abstinence. *Neuropharmacology*. 2015;99:9-14.

42. Conner M, Grogan S, Simms-Ellis R, et al. Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study. *Tob Control*. 2017;27(4):365-372.

43. Holliday ED, Gould TJ. Chronic Nicotine Treatment During Adolescence Attenuates the Effects of Acute Nicotine in Adult Contextual Fear Learning. *Nicotine Tob Res*. 2017;19(1):87-93.

44. Counotte DS, Spijker S, Van de Burgwal LH, et al. Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. *Neuropsychopharmacology*. 2009;34(2):299-306.

45. Fountain SB, Rowan JD, Kelley BM, Willey AR, Nolley EP. Adolescent exposure to nicotine impairs adult serial pattern learning in rats. *Exp Brain Res*. 2008;187(4):651-656.

46. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2017;171(8):788-797.

47. Aleyan S, Cole A, Qian W, Leatherdale ST. Risky business: a longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users in Canada. *BMJ Open*. 2018;8(5):e021080.

48. Berry KM, Fetterman JL, Benjamin EJ, et al. Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths. *JAMA Netw Open*. 2019;2(2):e187794.

49. Hammond D, Reid JL, Cole AG, Leatherdale ST. Electronic cigarette use and smoking initiation among youth: a longitudinal cohort study. *Cmaj*. 2017;189(43):E1328-e1336.

50. Loukas A, Marti CN, Cooper M, Pasch KE, Perry CL. Exclusive e-cigarette use predicts cigarette initiation among college students. *Addict Behav.* 2018;76:343-347.

51. Treur JL, Rozema AD, Mathijssen JJP, van Oers H, Vink JM. E-cigarette and waterpipe use in two adolescent cohorts: cross-sectional and longitudinal associations with conventional cigarette smoking. *Eur J Epidemiol.* 2018;33(3):323-334.

52. Kintz N, Liu M, Chou CP, et al. Risk factors associated with subsequent initiation of cigarettes and e-cigarettes in adolescence: A structural equation modeling approach. *Drug Alcohol Depend.* 2020;207:107676.

53. Lozano P, Barrientos-Gutierrez I, Arillo-Santillan E, et al. A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents. *Drug Alcohol Depend.* 2017;180:427-430.

54. Stanton CA, Bansal-Travers M, Johnson AL, et al. Longitudinal e-Cigarette and Cigarette Use Among US Youth in the PATH Study (2013-2015*). J Natl Cancer Inst.* 2019;111(10):1088-1096.

55. Best C, Haseen F, Currie D, et al. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tob Control.* 2017;27(4):373-378.

56. Bold KW, Kong G, Camenga DR, et al. Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics*. 2018;141(1).

57. National Academies of Sciences Engineering Medicine. Public Health Consequences of E-Cigarettes. In. Washington, DC: National Academies Press; 2018.

58. Edwards KC, Sharma E, Halenar MJ, et al. Longitudinal pathways of exclusive and polytobacco cigar use among youth, young adults and adults in the USA: findings from the PATH Study Waves 1-3 (2013-2016). *Tob Control*. 2020;29(Suppl 3):s163-s169.

59. Gentzke AS, Creamer M, Cullen KA, et al. Vital Signs: Tobacco Product Use Among Middle and High School Students - United States, 2011-2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):157-164.

60. Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. Tobacco Product Use Among Middle and High School Students - United States, 2011-2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(22):629-633.

61. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association Between E-Cigarette Use and Chronic Obstructive Pulmonary Disease by Smoking Status: Behavioral Risk Factor Surveillance System 2016 and 2017. *Am J Prev Med*. 2020;58(3):336-342.

62. Osei AD, Mirbolouk M, Orimoloye OA, et al. The association between e-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS) 2016 & 2017. *BMC Pulm Med*. 2019;19(1):180.

63. Giovanni SP, Keller TL, Bryant AD, Weiss NS, Littman AJ. Electronic Cigarette Use and Chronic Respiratory Symptoms among U.S. Adults. *Am J Respir Crit Care Med*. 2020;201(9):1157-1160.

64. Chang JT, Anic GM, Rostron BL, Tanwar M, Chang CM. Cigarette Smoking Reduction and Health Risks: A Systematic Review and Meta-analysis. *Nicotine Tob Res*. 2021;23(4):635-642.

65. Vyncke T, De Wolf E, Hoeksema H, et al. Injuries associated with electronic nicotine delivery systems: A systematic review. *J Trauma Acute Care Surg*. 2020;89(4):783-791.

66. Rossheim ME, Livingston MD, Soule EK, Zeraye HA, Thombs DL. Electronic cigarette explosion and burn injuries, US Emergency Departments 2015 2017. *Tobacco Control*. 2019;28(4):472.

Appendix C

Appendix A
New Tobacco Products Subject of This Review

STN	PD Number	Product Name	Category	Subcategory
PM0001233	PD1	The Reef	ENDS(VAPES)	ENDS Component
PM0001233	PD2	The Reef	ENDS(VAPES)	ENDS Component
PM0001233	PD3	The Reef	ENDS(VAPES)	ENDS Component
PM0001233	PD4	The Reef	ENDS(VAPES)	ENDS Component
PM0001233	PD5	Lucky #7	ENDS(VAPES)	ENDS Component
PM0001233	PD6	Lucky #7	ENDS(VAPES)	ENDS Component
PM0001233	PD7	Lucky #7	ENDS(VAPES)	ENDS Component
PM0001233	PD8	Lucky #7	ENDS(VAPES)	ENDS Component
PM0001233	PD9	Golden Dawn	ENDS(VAPES)	ENDS Component
PM0001233	PD10	Golden Dawn	ENDS(VAPES)	ENDS Component
PM0001233	PD11	Golden Dawn	ENDS(VAPES)	ENDS Component
PM0001233	PD12	Golden Dawn	ENDS(VAPES)	ENDS Component
PM0001233	PD13	Rift X	ENDS(VAPES)	ENDS Component
PM0001233	PD14	Rift X	ENDS(VAPES)	ENDS Component
PM0001233	PD15	Rift X	ENDS(VAPES)	ENDS Component
PM0001233	PD16	Rift X	ENDS(VAPES)	ENDS Component
PM0001233	PD17	Amber Island	ENDS(VAPES)	ENDS Component
PM0001233	PD18	Amber Island	ENDS(VAPES)	ENDS Component

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PM0001233	PD19	Amber Island	ENDS(VAPES)	ENDS Component
PM0001233	PD20	Amber Island	ENDS(VAPES)	ENDS Component
PM0001233	PD21	Persian Winter	ENDS(VAPES)	ENDS Component
PM0001233	PD22	Persian Winter	ENDS(VAPES)	ENDS Component
PM0001233	PD23	Persian Winter	ENDS(VAPES)	ENDS Component
PM0001233	PD24	Persian Winter	ENDS(VAPES)	ENDS Component
PM0001233	PD29	Mountain Chill	ENDS(VAPES)	ENDS Component
PM0001233	PD30	Mountain Chill	ENDS(VAPES)	ENDS Component
PM0001233	PD31	Mountain Chill	ENDS(VAPES)	ENDS Component
PM0001233	PD32	Mountain Chill	ENDS(VAPES)	ENDS Component
PM0001233	PD33	Aphrodite X	ENDS(VAPES)	ENDS Component
PM0001233	PD34	Aphrodite X	ENDS(VAPES)	ENDS Component
PM0001233	PD35	Aphrodite X	ENDS(VAPES)	ENDS Component
PM0001233	PD36	Aphrodite X	ENDS(VAPES)	ENDS Component
PM0001233	PD38	Free Fall	ENDS(VAPES)	ENDS Component
PM0001233	PD39	Free Fall	ENDS(VAPES)	ENDS Component
PM0001233	PD40	Free Fall	ENDS(VAPES)	ENDS Component
PM0001233	PD41	Free Fall	ENDS(VAPES)	ENDS Component
PM0001233	PD42	Arctic Blast	ENDS(VAPES)	ENDS Component
PM0001233	PD43	Arctic Blast	ENDS(VAPES)	ENDS Component
PM0001233	PD44	Arctic Blast	ENDS(VAPES)	ENDS Component

Appendix C

Package Type	Package Quantity	Characterizing Flavor	Additional Property
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Dessert	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL

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Plastic Bottle	1 Bottle	Dessert	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Dessert	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Dessert	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL

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Plastic Bottle	1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Menthol, Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL

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Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	None	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	None	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	None	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	None	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	None	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	None	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 mL
Plastic Bottle	1 Bottle	None	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 mL

APPENDIX D — TECHNICAL PROJECT LEAD RE-REVIEW OF PMTAS OF THE U.S. FOOD & DRUG ADMINISTRATION, DATED FEBRUARY 24, 2022

FDA U.S. FOOD & DRUG ADMINISTRATION
Technical Project Lead (TPL) Re-Review of PMTAs

New Products Subject to this Re-Review	
Submission tracking numbers (STNs)	PM0001233, see Appendix A
Common Attributes	
Submission date	September 15, 2020
Receipt date	September 15, 2020
Applicant	Avail Vapor, LLC
Product manufacturer	Blackbriar Regulatory Services, LLC ("BRS")
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submissions	
All STNs	MF0000262, MF0000275, MF0000276, MF0000282, MF0000384, MF0000401
Recommendation	
Recommend new products subject to this re-review retain previously issued MDO	

Appendix D

Technical Project Lead (TPL): Digitally signed by
Cindy M. Chang -S
Date: 2022.02.24 07:28:43 -05'00'
Cindy Chang, Ph.D., M.P.H.
Chief, Epidemiology Branch 1
Division of Population Health Science,
Office of Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by
Matthew R. Holman -S
Date: 2022.02.24 08:22:24 -05'00'
Matthew R. Holman, Ph.D.
Director
Office of Science

[TABLES INTENTIONALLY OMITTED]

1. BACKGROUND

1.1 NEW PRODUCTS

The applicant submitted Premarket Tobacco Product Applications (PMTAs) on September 15, 2020, for the new products listed on the cover page and in Appendix A (collectively, the "applications").

Appendix D

1.2 REGULATORY ACTIVITY

FDA issued an Acceptance letter to the applicant on November 12, 2020. FDA issued a marketing denial order (MDO) for the products on September 15, 2021. The regulatory basis for that denial in the TPL review dated September 15, 2021 ("September 15, 2021 TPL review") is incorporated by reference. At the applicant's request, FDA conducted this re-review to further consider whether the applications contain evidence of a benefit to adult users sufficiently robust to outweigh the known risk to youth such that FDA should rescind the MDO and proceed to further scientific review to consider whether permitting marketing of the applicant's products is appropriate for the protection of the public health (APPH). Specifically, the applicant requested that FDA re-review several studies contained in its applications, including a cross-sectional survey (understood by FDA to be the "Avail Vapor E-liquids Focus Groups"), an online diary entry study (understood by FDA to be the "Diary Studies"), validation testing (understood by FDA to be the "Avail E-liquid Human Factors Summative Protocol"), and quantitative research (understood by FDA to be the "AVAIL Vapor 2020 Perceptions and Intent to Use Study"), and rescind the September 15, 2021 MDO. FDA's re-review confirms that the applicant's submission does not contain evidence of a benefit to adult users sufficiently robust to outweigh the known risk to youth.

The Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) requires that "new tobacco products" receive

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

As explained in the September 15, 2021 TPL review, it is well-recognized that flavored electronic nicotine delivery systems (ENDS) pose a significant risk to nonusers, especially youth. Given this known and substantial risk of flavored ENDS to youth, to demonstrate that permitting the marketing of flavored ENDS would be APPH, the applicant would need reliable and robust evidence of a potential benefit to the public health that outweighs the clear risks to youth. For the reasons explained in the September 15, 2021 TPL review, adult smokers are the group through which the potential benefit to public health is most substantial and could possibly overcome the known risk to youth. Accordingly, FDA's assessment of APPH for flavored ENDS focuses on the risk to

youth nonusers and the potential benefit to adult smokers as current users (i.e., increased switching and/or significant reduction in smoking).

As FDA has explained, applicants could demonstrate a potential benefit to adult smokers with sufficiently reliable and robust evidence that the flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or significantly reducing their smoking. As explained in the September 15, 2021-TPL review, tobacco-flavored ENDS may offer the same type of public health benefit as flavored ENDS, but do not pose the same degree of risk of youth uptake. Therefore, in order to adequately assess whether a potential benefit to adult smokers has been demonstrated, FDA has reviewed these applications for product-specific evidence that would enable a comparison between the applications' new flavored products and an appropriate comparator tobacco-flavored product (both ENDS) in terms of their impact on tobacco use behavior among adult smokers. Specifically, the Agency's reviews evaluated whether the applications contained product-specific evidence from a randomized controlled trial (RCT), longitudinal cohort study, 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 flavored ENDS over an appropriate comparator tobacco-flavored ENDS.

The September 15, 2021 TPL review concluded that the PMTAs did not contain sufficient evidence

demonstrating the benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or significantly reducing cigarette use. Accordingly, FDA issued an MDO for the products listed in Appendix A.

The applicant requested that FDA rescind its MDO, based on the applicant's belief that its PMTAs contained studies and/or data similar to that contained in the PMTAs associated with an MDO that the Agency rescinded. In an October 13, 2021 email, FDA informed the applicant that the Agency would consider its request that FDA re-review the September 15, 2021 MDO. In that email, FDA further explained that it did not intend to enforce the premarket review requirements for the applicant's products subject to the MDO while FDA considered its request. On November 1, 2021, FDA administratively stayed the MDO pending FDA's re-review of the applicant's PMTAs for evidence sufficient to support rescission of the MDO.

Upon re-evaluation of the submitted evidence in the applicant's PMTAs, as TPL, I conclude that the data submitted by the applicant, are insufficient to demonstrate a sufficient potential benefit to adult smokers to warrant rescission of the MDO. These conclusions are further described below.

2. SCIENTIFIC RE-REVIEW

In response to the applicant's request, Kathyrn Hartka completed a re-review of the applicant's

PMTAs on February 23, 2022 (the "February 23, 2022 review"), to determine whether the PMTAs contain evidence including from a RCT, longitudinal cohort study, or other evidence regarding the impact of the new products on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS[i] over an appropriate comparator tobacco-flavored ENDS.

The February 23, 2022 review, like the September 15, 2021-TPL review, found that the applicant's PMTAs do not contain evidence from an RCT or longitudinal cohort study or other evidence demonstrating the benefit to adult users of the applicant's flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes. The review noted that although the applicant submitted protocols for four abuse liability studies, no results from the studies were submitted by the applicant. As per the review, the applicant noted that these studies were still underway. The data had not been submitted when the MDO was issued on September 15, 2021.

The review further noted that in an online diary study submitted by the applicant, 16 adults that use Avail products (but not necessarily the products in the applicant's PMTAs) were followed for two weeks and were asked to report information either daily or every other day. Participants noted which flavors

i. Throughout this review, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* in this re-review refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

and brands from Avail and other manufacturers they used, using a grid listing flavors and manufacturers. Participants were not asked questions regarding the specific products from this application. Additionally, tobacco-flavored products were not included on the list or otherwise in the study. While these data allow limited examination of behavior change over time, these data were not specific to the products- in these PMTAs and they do not enable a comparison of flavored- and tobacco-flavored ENDS. Therefore, the applicant has failed to demonstrate that the findings from this study support conclusions regarding the potential benefit to current adult smokers of flavored Avail products over tobacco-flavored Avail products.

The February 23, 2022 review also noted that the applicant submitted evidence from three other studies: (1) "Avail Vapor E-liquids Focus Groups;" (2) "AVAIL Vapor 2020 Perceptions and Intent to Use Study;" and (3) "Avail E-Liquid Human Factors Summative Protocol."

In the first study, "Avail Vapor E-liquids Focus Groups," there were six focus groups with a total of 39 adult participants who were stratified by tobacco use status (i.e., ENDS users, non-ENDS tobacco users, and non-sers), including 10 adult participants in the current non-ENDS tobacco users group.[ii] Groups

ii. These are non-ENDS users who currently owned and/or regularly purchased and used cigarettes, cigars, chewing tobacco and/or nicotine products and had to have used at least one of the reported products more than 100 times in their life.

were asked a number of questions (see February 23, 2022 review for details). Among the questions, participants were asked about both flavored and non-flavored Avail products and their likelihood of using those products, and results were stratified by flavor and by tobacco user group. However, we would be unable to interpret the findings of the sample size of 10 because the applicant did not provide information for FDA to determine if the 10 participants are representative of all non-ENDS tobacco users. Additionally, the applicant did not provide a power analysis to determine if the sample size of participants recruited was adequate to detect a significant difference in the likelihood of tobacco use behavior of flavored ENDS users compared to tobacco-flavored ENDS users.

In the second study, "AVAIL Vapor 2020 Perceptions and Intent to Use Study," the applicant submitted a representative, cross-sectional survey with participants recruited from [REDACTED], stratified by tobacco-use status. The survey asked about participants' non-product-specific tobacco-use patterns, brand awareness, perceived harm, risk, addictiveness, perceptions of quitting (e.g., confidence in quitting cigarettes among current smokers) and dependence (e.g., craving to smoke cigarettes among past month smokers), or perceptions of Avail Vapor brand products relative to combusted cigarettes (though the items did not specify particular products), and intent to use by flavor, including flavored and tobacco-flavored ENDS. While data for intent to use by flavor were

presented, these were not stratified by tobacco use status, which prevents examination of the benefit to adult smokers. Therefore, as TPL, I find that the applicant has failed to demonstrate that the findings from these studies support conclusions on current adult smokers' behavioral intentions to try, or switch to, Avail products.

Finally, in the third study, "Avail E-Liquid Human Factors Summative Protocol," 18 adults were asked questions regarding the usability and safety of one Avail flavor in four nicotine strengths; the product was not specified but the image shown was a flavor not included in PM0001233. This study did not examine behavior change or use of ENDS, either in general or of Avail products specifically, which would be necessary to determine a benefit to adult smokers. Therefore, as TPL, I find that the applicant has failed to demonstrate that the findings from these studies support conclusions regarding the potential benefit to current adult smokers of flavored Avail products over tobacco flavored Avail products.

3. CONCLUSION AND RECOMMENDATION

The February 23, 2022 review confirmed that the PMTAs did not contain product-specific data from an RCT or longitudinal cohort study or other evidence demonstrating a benefit to adult users of the applicant's flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or reducing use of cigarettes. The PMTAs contained protocols for four incomplete

RCTs with abuse liability outcomes without resulting data. They also contained data from a longitudinal cohort study (i.e., the diary study) that was examined over time but lacked product specific data and a comparison between flavored and tobacco-flavored ENDS. Data from three other studies were also examined as other evidence. One study included data regarding intentions to use Avail products that compare flavored and tobacco-flavored ENDS among 10 adult users of non-ENDS tobacco products; however, the sample size of this study rendered the data uninterpretable because the applicant did not provide information to determine if these participants are representative of all non-ENDS tobacco users and they did not provide a power analysis to determine if the sample size of participants recruited was adequate to detect a significant difference in the likelihood of tobacco use behavior of flavored ENDS users compared to tobacco-flavored ENDS users. Other evidence from the other two studies either did not examine data stratified by tobacco-use status (i.e., probability-based cross-sectional survey) or did not examine behaviors associated with a benefit to adult smokers (i.e., human factors study), both of which prevent making conclusions about the benefit to adult smokers. Therefore, based on the re-review undertaken at the applicant's request, I find that the PMTAs for the applicant's new products lack sufficient evidence to demonstrate that permitting the marketing of the new products would be APPH. Thus, I recommend upholding the marketing denial order for these PMTAs.

Appendix D

4. APPENDIX

Appendix A. New Products

Common Attributes	
Submission date	September 15, 2020
Receipt date	September 15, 2020
Applicant	Avail Vapor LLC
Product manufacturer	Blackbriar Regulatory Services LLC ("BRS")
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

Appendix D

Appendix A New Tobacco Products Subject of This Review

STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD1	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD2	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD3	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD4	The Reef	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD5	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD6	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD7	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD8	Lucky #7	ENDS(VAPES)	ENDS Component	Plastic Bottle

Appendix D

STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD9	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD10	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD11	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD12	Golden Dawn	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD13	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD14	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD15	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD16	Rift X	ENDS(VAPES)	ENDS Component	Plastic Bottle

Appendix D

STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD17	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD18	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD19	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD20	Amber Island	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD21	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD22	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD23	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD24	Persian Winter	ENDS(VAPES)	ENDS Component	Plastic Bottle

Appendix D

STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD29	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD30	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD31	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD32	Mountain Chill	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD33	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD34	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD35	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD35	Aphrodite X	ENDS(VAPES)	ENDS Component	Plastic Bottle

Appendix D

STN	PD Number	Product Name	Category	Subcategory	Package Type
PM0001233	PD37	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD38	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD39	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD40	Free Fall	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD41	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD42	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD43	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle
PM0001233	PD44	Arctic Blast	ENDS(VAPES)	ENDS Component	Plastic Bottle

Appendix D

Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Menthol, Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Menthol, Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Menthol, Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Menthol, Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml

Appendix D

Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Dessert	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Dessert	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Dessert	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Dessert	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml

Appendix D

Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml

Appendix D

Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	Menthol, Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Menthol, Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Menthol, Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Menthol, Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	Fruit	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml

Appendix D

Package Quantity	Characterizing Flavor	Additional Property
1 Bottle	None	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	None	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	None	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	None	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	None	Nicotine: 0%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	None	Nicotine: 0.3%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	None	Nicotine: 0.6%, PG/VG: 30/70, E-liquid Volume: 60 ml
1 Bottle	None	Nicotine: 1.2%, PG/VG: 30/70, E-liquid Volume: 60 ml

Appendix D

Appendix B
Amendment Received for These Applications

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
January 6, 2021	January 6, 2021	PM001233	Yes	Submission of TPMF reference statement and updated HPHC report

APPENDIX E — RELEVANT STATUTORY PROVISIONS

STATUTORY PROVISIONS INVOLVED

A. 5 U.S.C. § 706(2) provides in pertinent part:

To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action. The reviewing court shall—

* * *

> (2) hold unlawful and set aside agency action, findings, and conclusions found to be— (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;

* * *

In making the foregoing determinations, the court shall review the whole record or those parts of it cited by a party, and due account shall be taken of the rule of prejudicial error.

B. 21 U.S.C. § 387j provides in pertinent part:

(a) In general. (1) New tobacco product defined. For purposes of this section the term "new tobacco product" means—

(A) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or

(B) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.

(2) Premarket review required.

(A) New products. An order under subsection (c)(1)(A)(i) for a new tobacco product is required unless—

(i) the manufacturer has submitted a report under section 905(j) [21 USCS § 387e(j)]; and the Secretary has issued an order that the tobacco product—

(I) is substantially equivalent to a tobacco product commercially marketed (other than for test marketing) in the United States as of February 15, 2007; and

(II) is in compliance with the requirements of this Act [21 USCS §§ 301 et seq.]; or

(ii) the tobacco product is exempt from the requirements of section 905(j) [21 USCS § 387e(j)] pursuant to a regulation issued under section 905(j)(3) [21 USCS § 387(j)(3)].

(B) Application to certain post-February 15, 2007, products. Subparagraph (A) shall not apply to a tobacco product—

(i) that was first introduced or delivered for introduction into interstate commerce for commercial distribution in the United States after February 15, 2007, and prior to the date that is 21 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act [enacted June 22, 2009]; and

(ii) for which a report was submitted under section 905(j) [21 USCS § 387e(j)] within such 21-month period, except that subparagraph (A) shall apply to the tobacco product if the Secretary issues an order that the tobacco product is not substantially equivalent.

Appendix E

C. 21 U.S.C. § 387*l*(b) provides:

Standard of review. Upon the filing of the petition under subsection (a) for judicial review of a regulation or order, the court shall have jurisdiction to review the regulation or order in accordance with chapter 7 of title 5, United States Code [5 USCS §§ 701 et seq.], and to grant appropriate relief, including interim relief, as provided for in such chapter. A regulation or denial described in subsection (a) shall be reviewed in accordance with section 706(2)(A) of title 5, United States Code.