No.

In the Supreme Court of the United States

FOOD AND DRUG ADMINISTRATION, PETITIONER

v.

WAGES AND WHITE LION INVESTMENTS, L.L.C., DBA TRITON DISTRIBUTION, ET AL.

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

APPENDIX TO THE PETITION FOR A WRIT OF CERTIORARI

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APPENDIX

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APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

No. 21-60766

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

CONSOLIDATED WITH

No. 21-60800

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION;
VAPETASIA, L.L.C., PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

[Filed: Jan. 3, 2024]

Appeal from the Food and Drug Administration
Agency Nos. 21 USC 3871, PM 0003531

Before RICHMAN, *Chief Judge*, and JONES, SMITH, STEWART, ELROD, SOUTHWICK, HAYNES, GRAVES, HIG-

GINSON, WILLETT, HO, DUNCAN, ENGELHARDT, OLDHAM, WILSON, and DOUGLAS, *Circuit Judges*.[*]

ANDREW S. OLDHAM, *Circuit Judge*, joined by RICHMAN, *Chief Judge*, and JONES, SMITH, ELROD, WILLETT, HO, DUNCAN, ENGELHARDT, and WILSON, *Circuit Judges*:

Over several years, the Food and Drug Administration ("FDA") sent manufacturers of flavored e-cigarette products on a wild goose chase.

First, the agency gave manufacturers detailed instructions for what information federal regulators needed to approve e-cigarette products. Just as importantly, FDA gave manufacturers specific instructions on what regulators did *not* need. The agency said manufacturers' marketing plans would be "critical" to the success of their applications. And the agency promulgated hundreds of pages of guidance documents, hosted public meetings, and posted formal presentations to its website —all with the (false) promise that a flavored-product manufacturer *could*, at least in theory, satisfy FDA's instructions. The regulated manufacturers dutifully spent untold millions conforming their behavior and their applications to FDA's say-so.

Then, months after receiving hundreds of thousands of applications predicated on its instructions, FDA turned around, pretended it never gave anyone any instructions about anything, imposed new testing requirements without any notice, and denied all one million flavored e-cigarette applications for failing to predict the agency's *volte face*. Worse, after telling manufacturers

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[*] JUDGE RAMIREZ joined the court after this case was submitted and did not participate in the decision.

that their marketing plans were "critical" to their applications, FDA candidly admitted that it did not read a single word of the one million plans. Then FDA denied that its voluminous guidance documents and years-long instructional processes meant anything. Why? Because, the agency said, it always reserved the implied power to ignore every instruction it ever gave and to require the very studies it said could be omitted, along with the secret power to not even read the marketing plans it previously said were "critical." It was the regulatory equivalent of Romeo sending Mercutio on a wild goose chase—and then admitting there never was a goose while denying he even suggested the chase. *Cf.* WILLIAM SHAKESPEARE, ROMEO AND JULIET act 2, sc. 4.

FDA justifies its behavior with two principal arguments. First, FDA argues that its years' worth of regulatory guidance was not worth the paper it was printed on because it was hedged with cautious qualifiers and never *guaranteed* that any particular submission would be granted. Second, and most disturbingly, FDA argues that its capriciousness should be forgiven as harmless because the agency promises to deny petitioners' applications even if we remand to make the agency follow the law.

Today we reject both propositions. As the Supreme Court recently reminded us: "If men must turn square corners when they deal with the government, it cannot be too much to expect the government to turn square corners when it deals with them." *Niz-Chavez v. Garland*, 593 U.S. 155, 172 (2021). No principle is more important when considering how the unelected administrators of the Fourth Branch of Government treat the

American people. And FDA's regulatory switcheroos in this case bear no resemblance to square corners. As for the agency's harmless-error argument, the Supreme Court recently, unanimously, and summarily rejected it. *Calcutt v. FDIC*, 598 U.S. 623 (2023) (per curiam). We do the same here with the expectation that FDA will give petitioners the benefit of a full and fair regulatory proceeding on remand, notwithstanding its prior promises to reject their applications no matter what.

I.

A.

In 2009, Congress enacted the Family Smoking Prevention and Tobacco Control Act ("TCA") to regulate tobacco products. *See* 21 U.S.C. §§ 387 *et seq*. The TCA prohibits manufacturers from selling any "new tobacco product" without authorization from FDA. *See id.* § 387j(a); *id.* § 387a(b) (delegating to FDA the authority to determine what constitutes new tobacco products). In 2016, FDA deemed e-cigarettes and their component parts[1] to be "new tobacco products." Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, 81 Fed. Reg. 28,973 (May 10, 2016) ("Deeming Rule"). The upshot: E-cigarette manufacturers had to submit premarket tobacco appli-

[1] The briefs and record materials in this case use a dizzying array of different terms to refer to e-cigarettes and their component parts: electronic cigarettes, e-cigarettes, electronic nicotine delivery devices ("ENDS"), nicotine cartridges, vaping products, vape pens, e-liquids, e-juice, and others. Unless context dictates otherwise, we refer to this list collectively as "e-cigarettes" throughout this opinion.

cations ("PMTAs") for FDA approval to sell their products. *See id.* at 28,977.

The TCA directs FDA to review the PMTAs to determine whether "permitting such tobacco product to be marketed would be appropriate for the protection of the public health." 21 U.S.C. § 387j(c)(2)(A). In making this determination, FDA must consider "the risks and benefits to the population as a whole." *Id.* § 387j(c)(4). This includes considering (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." *Id.* § 387j(c)(4)(A)-(B).

FDA then undertook to clarify these standards. The agency first announced that it would extend the PMTA compliance deadlines for several years so the agency could promulgate application instructions and the manufacturers could comply with them. *See* FDA, GUIDANCE FOR INDUSTRY, EXTENSION OF CERTAIN TOBACCO PRODUCT COMPLIANCE DEADLINES RELATED TO THE FINAL DEEMING RULE 5-11 (Aug. 10, 2017), https://perma.cc/WC42-ALYD ("Deadline Guidance").[2]

FDA provided its instructions on five relevant occasions. Warning: the detail that follows might be mind-numbing. But FDA's detailed instructions are important to explain what e-cigarette manufacturers

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[2] FDA originally set the PMTA deadline as August 8, 2022. *See* Deadline Guidance at 8. A district court in Maryland ordered FDA to shorten it. FDA complied with that order, later extended the deadline because of COVID, and eventually settled on a PMTA deadline of September 9, 2020. *See Vapor Tech. Ass'n v. FDA*, 977 F.3d 496, 497-502 (6th Cir. 2020) (summarizing shifting deadlines).

understood FDA would require of them. These details are important to understand why every single e-cigarette manufacturer in the entire Nation behaved just as petitioners did. And these details are important to explain why FDA cannot now pretend that it gave the regulated community fair notice of the PMTA requirements.

1. First, at a public meeting in October 2018, FDA stated in a formal presentation still available for download on the agency's website: "*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." FDA, PREMARKET TOBACCO PRODUCT APPLICATION CONTENT OVERVIEW 26 (Oct. 23, 2018), https://perma.cc/BV8D-HR7H ("October 2018 Guidance") (emphasis added). FDA recommended that applicants "[c]ompare the new tobacco product to a representative sample of tobacco products on the market (i.e., either grandfathered or with marketing authorization)" and "[i]nclude justification for why using evidence or data from other products is appropriate." *Id.* at 11. And regarding the question of youth use, FDA published this slide:

- Youth behavioral data **not** required at this time
- **However**, information allowing FDA to evaluate how the proposed new product may influence tobacco initiation and use among youth is useful to determine protection of public health

- Inferences regarding youth may be extrapolated from young adults, as well as derived from marketing data, scientific literature reviews, national surveys, and/or bridging information

- It is useful to clearly explain how such data can be extrapolated to youth for the specific products in the PMTA

Id. at 18.

2. Second, in June 2019, FDA promulgated a 52-page, single-spaced guidance document entitled "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry." A.284 ("June 2019 Guidance"). In it, FDA assured manufacturers that they need not perform long-term studies or submit long-term data in their PMTAs: "Given the relatively new entrance of [e-cigarettes] on the U.S. market . . . limited data may exist from scientific studies and analyses. . . . *Nonetheless, in general, FDA does not expect that applicants will need to conduct long-term studies to support an application*." A.298-99 (emphasis added) (footnote omitted); *see also* A.317 (same).

Rather, FDA specifically pointed to surveys as the kind of data that could support PMTAs: "Although 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." A.324. "Observational studies" include surveys. Petrs' EB Br. 9.

In the same guidance document, FDA also directed manufacturers to produce copious data about their mar-

keting plans. As one of many examples of FDA's marketing-plan directives, the agency said:

> FDA also recommends sharing your marketing plan to enable FDA to better understand the potential consumer demographic. In addition, and if the product is currently marketed, FDA recommends sharing sales data broken down by population demographics and tobacco use status. Sales data, if available, should be analyzed in regular (preferably 4-week or monthly) intervals and should include:
>
> - The Universal Product Code that corresponds to the product(s) identified in the PMTA;
>
> - Total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops) [*sic*] promotional discounts (e.g., buy-one-get-one free or percentage discount);
>
> - Demographic characteristics of product(s) purchasers, such as age, gender, and tobacco use status; and
>
> - Information on top selling brands as a comparison for all recommended information, if available, so FDA can assess the market for the PMTA product to better estimate the potential impact on public health.

A.325 (quotation omitted) (footnote omitted).

3. Third, at a public meeting in October 2019, FDA again published a formal presentation. Again, the pre-

sentation remains available on FDA's website. FDA, PREMARKET TOBACCO PRODUCT APPLICATION (PMTA) REVIEW PATHWAY 20 (Oct. 28-29, 2019), https://perma.cc/9S7Z-JQX8 ("October 2019 Guidance"). In that presentation, FDA told e-cigarette manufacturers how the agency intended to review and act upon PMTAs. Among other things, FDA stated:

- If FDA has questions or identifies additional information needed to render a decision, FDA may choose to issue a Deficiency Letter. The applicant can submit an amendment in response to the Deficiency Letter
- If the applicant submits a **major amendment** to their application, either at FDA's request or on its own initiative, a **new 180 day review period** would begin on the date which FDA receives the major amendment
  - FDA considers major amendments to be those that will require substantial review time. Examples of major amendments include: new data from a previously unreported study, detailed new analyses of previously submitted data, or required necessary information that was previously omitted
- FDA is *not* obligated to review unsolicited amendments

Id. at 20. And FDA assured manufacturers that "[a] decision w[ould] be made on each specific product, not the submission" as a whole. *Id.* at 21. At the same

meeting, FDA again told manufacturers what it expected to see regarding youth vaping: Manufacturers should "address how they are going to restrict youth access and youth use. . . . [W]hat are their marketing plans[?] What are the age verification plans[?] I mean these are some of the kinds of things that you might want to take time to describe in your application to ensure to FDA that your product will not . . . exacerbate the current situation in methods to curb and improve limiting youth access." A.347.

4. Fourth, 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." Premarket Tobacco Product Applications and Recordkeeping Requirements, 84 Fed. Reg. 50,566, 50,619 (Sept. 25, 2019) ("PMTA Proposed Rule").

Instead, FDA said that manufacturers' "marketing plans" were "*critical*" to the success of their PMTAs. *Id.* at 50,581 (emphasis added). And FDA focused manufacturers' attention on those plans in painstaking detail:

> The applicant's marketing plans will help FDA determine whether permitting the marketing of the new tobacco product would be APPH ["appropriate for the protection of public health," 21 U.S.C. § 387j(c)(2)(A)] because they will provide input that is critical to FDA's determination of the likelihood of changes in tobacco product use behavior, especially when considered in conjunction with other information contained in the application. FDA 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. For example, heavy use of online social media to promote a tobacco product without access restrictions, as opposed to actions such as paper mailings directed only to current smokers of legal age, indicates the potential for youth to be exposed to the promotion of the product. This information would help FDA make its APPH determination by showing whether a PMTA fully or accurately accounts for the likelihood of changes in tobacco product use behavior that may occur as a result of marketing the new tobacco product. For example, if the PMTA does not address youth access to the product, youth exposure to the product's labeling, advertising, marketing, and promotion, and youth initiation, such as describing how it proposes to restrict the sale or distribution of its product to limit potential youth access to the product (e.g., selling the tobacco product in adult-only establishments) or exposure to advertising (e.g., using age verification controls for digital advertising), FDA may be unable to determine that the applicant has made a showing that permitting the marketing of the new tobacco product would be APPH.

Id. at 50,581.

5. Fifth, in January 2020, FDA issued a 30-page, single-spaced enforcement guidance document entitled "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization." A.185

("2020 Enforcement Guidance").[3] In this guidance document, FDA stated that after the PMTA deadline in September 2020, it would prioritize enforcement resources against "flavored, cartridge-based ENDS products (other than a tobacco- or menthol-flavored ENDS product)." A.186.

What is a "flavored" e-cigarette product? As used in FDA's guidance documents and the parties' briefs, "flavored" e-cigarettes have flavors like blueberry, strawberry, and cherry, as well as various branded flavors like "Kauai Kolada," "Margarita Mixer," and "Mandarin Mint." *E.g.*, A.247. The term "flavored" does *not* include e-cigarettes that taste like tobacco or menthol. A.186.

What is a "cartridge-based" product? As used in FDA's guidance, a "cartridge-based" product "consists of, includes, or involves a cartridge or pod that holds liquid that is to be aerosolized through product use. For purposes of this definition, a cartridge or pod is any small, enclosed unit (sealed or unsealed) designed to fit within or operate as part of an electronic nicotine delivery system." A.192. These include e-cigarettes commonly known as "vape pens." The pen holds a small cartridge or pod, which is often but not always disposable, with a nicotine solution that a user vaporizes and inhales. Designs and styles vary, but cartridge-based products are generally smaller and lighter than open tank products that must be refilled with nicotine liquid by the user. *See, e.g.*, CDC, E-CIGARETTE, OR VAPING, PRODUCTS

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[3] FDA issued this guidance in January 2020 and revised it in April 2020 due to the extension of the PMTA submission deadline. *See* Petrs' EB Br. 12 n.3; *supra* n.2.

VISUAL DICTIONARY 9-12, https://perma.cc/5QD9-52NQ (last visited Dec. 21, 2023) ("CDC Visual Dictionary").

In its 2020 Enforcement Guidance, FDA explained in detail why it was focused on cartridge-based e-cigarettes. FDA stated:

> Of particular concern are the design features that appear to make the cartridge-based products so popular with young people. Attributes typically present in cartridge-based products include a relatively small size that allows for easy concealability, and intuitive and convenient features that facilitate ease of use, including draw activation, prefilled cartridges or pods, and USB rechargeability.

A.199. FDA explained that cartridge-based products are small, and hence can be more easily concealed at school or in social circumstances where youth need to hide them. *See ibid.* And many popular cartridge-based vaping pens have batteries that are recharged via USB ports and hence "blend in with other equipment" that youth might innocently possess. *Ibid.* Moreover, cartridge-based products are ready for immediate use, have no settings to adjust, have no tanks that need to be refilled, and require little or no assembly—all design features that make them more attractive to youth vapers. *See* A.199-200. Open tank systems, by contrast, are bigger, harder to conceal, less innocuous in appearance if found by a parent or teacher, not ready for immediate use, more complicated to adjust or assemble, require constant refilling with nicotine liquids, and generally cannot be recharged by plugging into a USB port. *See* A.200.

CDC Visual Dictionary at 10, 12 (cartridge-based vaping pen with USB-rechargeable battery on the left; open tank systems on the right).

FDA said it was important to issue the 2020 Enforcement Guidance because the agency had not previously distinguished between cartridge-based and tank-based e-cigarettes—a distinction it thought important because the former are comparatively more attractive to youth. *See* A.202. FDA's previous enforcement guidance also did not include mint-flavored e-cigarettes as "flavored" products—an omission it thought necessary to correct, again, based on comparative attractiveness to youth. *Ibid.* So FDA provided notice to the regulated industry about its then-current thinking, based on the then-existing data, so everyone was on fair notice that flavored (including mint-flavored) cartridge-based e-cigarettes were particularly attractive to youth users. FDA thus announced that it had "recalibrated its balancing of public health considerations in light of the public health threats and the significant new evidence described above." A.204.

* * *

The dizzying detail in the foregoing introduction has an important point: Never in this long, winding, and byzantine regulatory process of meetings, PowerPoint decks, proposed rules, comment periods, guidance documents, and enforcement priorities did FDA *ever* say that it was contemplating an across-the-board ban on flavored products. It emphasized all sorts of relatively minor distinctions—including whether mint is a flavor, the size difference between vape pens and tanks, and age-access restrictions for online ads. And FDA conspicuously announced when and how—supported by data and reasoned analysis—it "recalibrated" its understanding of public health to focus on nicotine cartridges as opposed to nicotine e-liquids. But at no point did the agency *ever* say that it was contemplating a categorical ban on flavored e-cigarettes.

Nor did FDA ever give fair notice that *flavored* product manufacturers had to submit robust scientific studies on *flavored* e-cigarette products. To the contrary, the entirety of FDA's pre-decisional guidance was premised on these facts:

- Limited scientific data exists for ENDS products generally (flavored or unflavored). *See* A.298-99, A.317 (June 2019 Guidance).
- Flavored PMTAs could and should include existing data regarding *unflavored* products generally to make inferences about the public health benefits of *flavored* products generally. *See* A.300 (June 2019 Guidance); October 2018 Guidance at 11-17.

- FDA did not expect flavored product manufacturers to conduct new, long-term, scientific studies that directly measured the behaviors of people who use Triton's and Vapetasia's flavored products specifically. A.299, A.317 (June 2019 Guidance).
- And FDA expected that flavored product manufacturers would submit observational studies, which include surveys. A.324 (June 2019 Guidance); *see also* October 2018 Guidance at 16-17 (discussing acceptable consumer perception data without any reference to conducting such surveys over time).

B.

1. Wages and White Lion Investments, LLC, doing business as Triton Distribution and Vapetasia, LLC (collectively "petitioners") manufacture bottles of flavored nicotine *liquids*. Vapers use such nicotine liquids to refill their tank systems and other e-cigarette products. Petitioners do *not* make e-cigarettes, vape pens, vape pods, vape cartridges or any other vaping device covered by the 2020 Enforcement Guidance. Petitioners bottle only the liquid, and hence it is common ground that FDA's 2020 Enforcement Guidance did not apply to petitioners or their liquids.

On September 9, 2020, approximately eight months after FDA issued its 2020 Enforcement Guidance, petitioners timely filed PMTAs for their flavored nicotine liquids. "Triton's bundled PMTA was nine gigabytes in size, consisting of hundreds of individual files, including the marketing and sales-access restriction plans containing the measures described above to limit youth

access and use of its products." Petrs' EB Br. 15. Petitioners submitted long-term, controlled, and peer-reviewed studies to show that e-cigarettes generally cause smokers to switch to vaping and thus save lives. *See, e.g.*, A.369-70, A.431. Petitioners also included observational studies in the form of cross-sectional surveys. *See, e.g.*, A.384, A.403, A.407, A.438. But in accordance with FDA's pre-decisional guidance, petitioners did not conduct new scientific studies on their specific flavored PMTA products. And petitioners did point to robust, reliable, and peer-reviewed scientific studies involving *unflavored* products to draw inferences about *flavored* products (including at least one study that reviewed randomized controlled trials and longitudinal cohorts to show the net public health benefits of e-cigarettes). *See, e.g.*, A.369-71 (collecting studies), A.431 (citing, *inter alia*, Riccardo Polosa et al., *The Effect of E-cigarette Aerosol Emissions on Respiratory Health: A Narrative Review*, 13 EXPERT REV. OF RESPIRATORY MED. 899 (2019)).

In accordance with FDA's instructions that manufacturers should focus on measures to restrict youth access, petitioners offered lengthy explanations for their marketing plans:

> Triton's bottled e-liquids are only sold in age-restricted vape and tobacco-specialty shops and through age-restricted online sales to customers who can show they are at least 21 years old. None of Triton or Vapetasia's ENDS products have been sold in convenience stores or other general retail outlets. Retailers selling the e-liquids must verify photo IDs of anyone who is 27 or younger before entering the establishment, immediately respond to and remedy

> any violations, actively display signs indicating that the products are not for sale to minors and that minors are not allowed on the premises, and are subject to contractual penalties if they fail to do so. Triton and its customers screen retailers before establishing or renewing distribution agreements and require retailers to develop internal compliance check programs, such as mystery shopper programs.

Petrs' EB Br. 16 (quotation omitted). Petitioners also implemented third-party verification services to ensure only adults could purchase the products online; voluntarily increased the minimum age for customers to 21 before it was legally required; imposed volume limits on purchases; limited labeling to exclude cartoons or childish images or vivid colors; limited online marketing to exclude human models; and limited other marketing to age-restricted channels. *See id.* at 16-18. Petitioners also included a survey to show that more than two-thirds of their customers are over the age of 35. *See id.* at 18.

2. On August 26, 2021, FDA issued a press release to announce the *en masse* denial of 55,000 flavored e-cigarette applications. *See* FDA, *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/LCD8-VWGQ ("August 2021 press release"). In that press release, FDA announced for the first time that, for flavored e-cigarette applications, the agency *would* require "a randomized controlled trial," a "longitudinal cohort study," or some other scientific study that was comparably "robust and reliable." *Ibid.* FDA said nothing to acknowledge that its new requirement for scientific studies conflicted with its previous guid-

ance. Rather, using its new scientific-studies-or-bust standard announced in the press release, FDA denied 946,000 flavored-product applications in just over two weeks. *See* FDA, *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 Tobacco Products Submitted* (Sept. 9, 2021), https://perma.cc/4F69-MRUB. As of today, FDA has not approved a single PMTA for a single one of the more than 1,000,000 flavored e-cigarette products submitted to the agency.

Immediately after receiving the new scientific-studies-or-bust requirement in the August 2021 press release, petitioners asked FDA for time to perform the newly required studies. Without acknowledging that request, on September 14 and 16, 2021, FDA issued marketing denial orders ("MDOs") to Triton and Vapetasia, finding that their PMTAs failed to include the once-optional-but-now-required scientific studies. Specifically, FDA stated:

> 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. . . . 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.

A.57. FDA also stated that it refused even to read petitioners' marketing plans. *See* A.93 n.xix; A.145 n.xix.

3. Petitioners timely moved to stay their marketing denial orders pending review in our court. A unanimous motions panel granted that motion, concluding that Triton was likely to succeed on the merits. *See Wages & White Lion Invs., LLC v. FDA*, 16 F.4th 1130 (5th Cir. 2021) ("*Stay Op.*"). Subsequently, a divided merits panel nonetheless rejected the petitions for review. *Wages & White Lion Invs., LLC v. FDA*, 41 F.4th 427 (5th Cir. 2022) ("*Panel Op.*"). In dissenting from the panel opinion, JUDGE JONES described FDA's actions as "a mockery of 'reasoned' administrative decisionmaking." *Id.* at 442 (Jones, J., dissenting). Specifically, JUDGE JONES explained:

> The majority's analysis of these MDOs looks almost exclusively at the bottom-line result of FDA's decisions and finds nothing to criticize. But the facts recited above speak for themselves. FDA refused to review petitioners' marketing restrictions, which it had repeatedly stated were key to discouraging youthful use of the products and were thus critical components of the PMTAs. FDA repeatedly counselled applicants that long term studies were likely unnecessary and it said nothing about comparative efficacy studies—until the PMTA deadline was long gone; and then it refused petitioners the opportunity to conduct such studies. Finally, FDA's defense against petitioners on the merits of their applications is loaded with post hoc rationalizations. Any of these errors is a "fatal flaw." Taken together, they are mortal wounds.

Id. at 446. We granted rehearing and vacated the panel opinion. 58 F.4th 233 (5th Cir. 2023) (mem.).

II.

The first question is whether FDA acted arbitrarily and capriciously in rejecting petitioners' PMTAs. It did. Four well-established and longstanding principles of administrative law independently require that result: (A) An agency cannot invent *post hoc* justifications for its decision in court and outside the administrative record. (B) An agency must provide fair notice before it deprives a citizen of property. (C) When an agency changes its position, it must display awareness of the change and explain it. And (D) even when an agency acknowledges and explains a change in its position, it cannot fault a regulated entity for relying in good faith on the previous one.

A.

First, the prohibition on *post hoc* rationalizations. This rule is even older than the Administrative Procedure Act of 1946, 5 U.S.C. §§ 551-559 ("APA"). It dates back at least to the first decision in *Chenery*, where the Court said: "The grounds upon which an administrative order must be judged are those upon which the record discloses that its action was based." *SEC v. Chenery Corp.* (*Chenery I*), 318 U.S. 80, 87 (1943). The agency is not free to defend its decision by supplying new, *post hoc* rationalizations for it when sued. *See, e.g.*, *Burlington Truck Lines v. United States*, 371 U.S. 156, 168-69 (1962); *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 419 (1971); *Am. Textile Mfg. Inst., Inc. v. Donovan*, 452 U.S. 490, 539 (1981); *DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1908-09 (2020).

Consider for example the most significant case ever to elucidate the arbitrary-and-capricious standard: *Motor Vehicle Manufacturers Association of the United States v. State Farm Mutual Auto Insurance Co.*, 463 U.S. 29 (1983). In that case, the National Highway Traffic Safety Administration ("NHTSA") rescinded its safety regulation for passive restraints (automatic seatbelts and airbags) in cars. *Id.* at 38. The agency reasoned that automatic seatbelts were ineffective because owners could easily detach them, thus reducing or eliminating the safety benefit. *Id.* at 39. At no point in the administrative record, however, did the agency even consider the possibility of mandating airbags—much less did the agency explain why an airbag mandate was inadvisable. *Id.* at 48. When the case entered the courts, the agency tried to provide the missing rationale. Specifically, its appellate counsel pointed to "questions concerning the installation of airbags in small cars" and "adverse public reaction" as reasons for the agency's failure to consider an airbag mandate. *Id.* at 50. The Supreme Court emphatically rejected that lawyerly effort: "The short—and sufficient—answer to petitioners' submission is that the courts may not accept appellate counsel's *post hoc* rationalizations for agency action. It is well-established that an agency's action must be upheld, if at all, on the basis articulated by the agency itself." *Ibid.* (quotation omitted); *accord, e.g.*, *Int'l Union, United Mine Workers of Am. v. Mine Safety & Health Admin.*, 626 F.3d 84, 94 (D.C. Cir. 2010) (rejecting statements at oral argument as prohibited *post hoc* rationalizations); *Conn. Dep't of Pub. Util. Control v. FERC*, 484 F.3d 558, 560 (D.C. Cir. 2007) (same).

So too here. In its pre-MDO guidance to manufacturers, FDA said that marketing plans were "critical" to

the success of e-cigarette applications. PMTA Proposed Rule, 84 Fed. Reg. at 50,581. It told manufacturers to submit their marketing plans in mind-numbing detail—including "sales data broken down by population demographics and tobacco use status"; sales data broken down by Universal Product Code and four-week intervals; sales data broken down "by U.S. census region, major retail markets, and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops) [*sic*] promotional discounts (e.g., buy-one-get-one free or percentage discount"; and comparable information for "top selling brands as a comparison" to the manufacturer's product. A.325. FDA also requested information on advertising, marketing strategies, point of sale restrictions, social media restrictions, and many other details. Why? Because all of this information was essential to "enable FDA to better understand the potential consumer demographic." *Ibid.*

In the MDOs, however, FDA explicitly stated that its instructions were all for naught. First, FDA determined that the *mere existence of flavor* was sufficient to justify denial of a PMTA because flavor standing alone was enough to prove that youth would use the proposed product and that youth use would outweigh any countervailing benefit to adults. Gone was any suggestion that a manufacturer could do anything to limit youth access to its products. And second, FDA stated that it did not even read the marketing plans it previously said were critical: "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*." A.145 n.xix (emphasis added).

At some point in this litigation, FDA's very able counsel presumably recognized that sentence spelled trouble for the agency. And as the Eleventh Circuit correctly held, FDA's refusal even to read the once-"critical" marketing plans constituted an arbitrary and capricious failure to consider "an important aspect of the problem." *Bidi Vapor LLC v. FDA*, 47 F.4th 1191, 1203 (11th Cir. 2022) (quoting *State Farm*, 463 U.S. at 43).

So at oral argument before the merits panel in our court, FDA's counsel flatly contradicted the administrative record and stated that FDA did in fact look at "summar[ies]" of petitioners' marketing plans. *Panel Op.*, 41 F.4th at 441. This position cannot conceivably be characterized as "[c]larifying what happened factually." *Id.* at 441 n.17. The administrative record says FDA did "not evaluate[] any marketing plans submitted with these applications." A.145 n.xix. At oral argument, FDA's counsel said the opposite. That is barred by the venerable prohibition on *post hoc* justifications that federal courts have consistently applied since at least *Chenery I*.

Moreover, even if we could look past the *post hoc* prohibition, FDA's *post hoc* statements underscore the agency's arbitrariness. For example, in its pre-MDO guidance documents, FDA excluded menthol-flavored e-cigarettes from its definition of "flavored" products. *See, e.g.*, A.186. And presumably because of that exclusion, FDA has approved menthol-flavored e-cigarette products notwithstanding its ban on "flavored" products. The rationale? According to the 2020 Enforcement Guidance, menthol products are less popular with youth than are flavored products. *See, e.g.*, A.198 (collecting survey data and finding "youth use of menthol-

flavored products is not as high as that for mint- and fruit- flavored products."). Yet in its en banc brief before the court, FDA makes a *post hoc* invocation of "recent data [that purportedly] demonstrate 'prominent menthol e-cigarette use' among middle- and high-school e-cigarette users." FDA EB Br. 23. And FDA makes no attempt to explain why, if that's true, it approved menthol products. Or more to the point, how it could rationally approve menthol products while denying petitioners' flavored products.

The dissent by JUDGE HAYNES disagrees. JUDGE HAYNES believes "the FDA clarified at oral argument that it *did* review summaries of Petitioners' marketing plans contained within their PMTAs" and that this is the "type of factual clarification we seek at oral argument." *Post*, at 79 (Haynes, J., dissenting). For this proposition, the dissent first cites *Cooper Cameron Corp. v. U.S. Dep't of Lab., OSHA*, 280 F.3d 539, 542 (5th Cir. 2002). Although that case has an agency as a party in the caption, it is not an administrative law case. Nor does it implicate *Chenery I*. The dissenting opinion cannot point to a single case where we allowed an administrative agency to defend its action by countermanding an express statement in the administrative record. *Cf. Schofield v. Saul*, 950 F.3d 315, 322 (5th Cir. 2020) (holding an agency can waive an argument in its favor but saying nothing about an agency's ability to countermand its record statements). Or any authority that allows agencies to rehabilitate deficiencies in the administrative record solely by answering friendly questions at oral argument.

We instead underscore our agreement with JUDGE GRAVES on this point:

> [T]his court may, and often does, seek clarification at oral argument. But the FDA's statement does not clarify. Among other things, the statement raises the question of why, if the FDA did review the summaries, it told Petitioners that it had "not evaluated any marketing plans." As it stands, the FDA's statement at oral argument is at odds with the record. For that reason alone, the court should disregard it.

Post, at 83 (Graves, J., dissenting).

B.

Second, the fair notice doctrine. It is common ground between the parties that the fair notice doctrine applies. Petitioners repeatedly invoked it at the stay stage, before the panel, and in their en banc brief. And FDA has never disputed its applicability. FDA's only contention is that it satisfied the doctrine when it "gave fair notice of the analysis the agency would perform" in adjudicating e-cigarette applications. FDA EB Br. 37 (quotation omitted). We therefore (1) begin with the fair notice doctrine and then (2) explain FDA's violation of it. Finally, we (3) reject FDA's attempts to find fair notice in the pre-decisional guidance documents that omitted it.

1.

The fair notice doctrine is a well-established principle of administrative law. *See Rollins Env't Servs. (NJ) Inc. v. EPA*, 937 F.2d 649, 654 n.1, 655 (D.C. Cir. 1991) (Edwards, J., concurring in part and dissenting in part) (fair notice doctrine is "basic hornbook law in the administrative context" and a "simple principle of administrative law"). At its core, the doctrine requires adminis-

trative agencies to give the public fair notice of their rules before finding a violation of them. As we explained the doctrine in one of the canonical fair notice cases:

> The respondents contend that the regulations should be liberally construed to give broad coverage because of the intent of Congress to provide safe and healthful working conditions for employees. An employer, however, is entitled to fair notice in dealing with his government. Like other statutes and regulations which allow monetary penalties against those who violate them, an occupational safety and health standard must give an employer fair warning of the conduct it prohibits or requires. . . .
>
> If a violation of a regulation subjects private parties to criminal or civil sanctions, a regulation cannot be construed to mean what an agency intended but did not adequately express. . . . [T]he Secretary as enforcer of the Act has the responsibility to state with ascertainable certainty what is meant by the standards he has promulgated.

Diamond Roofing Co. v. Occupational Safety & Health Rev. Comm'n, 528 F.2d 645, 649 (5th Cir. 1976); *see also Gates & Fox Co. v. Occupational Safety & Health Rev. Comm'n*, 790 F.2d 154, 156 (D.C. Cir. 1986) (relying on *Diamond Roofing* to formulate the D.C. Circuit's fair notice doctrine).

The fair notice doctrine is rooted in the Fifth Amendment's Due Process Clause. *Gen. Elec. Co. v. EPA*, 53 F.3d 1324, 1328-29 (D.C. Cir. 1995); *see also United States v. Chrysler Corp.*, 158 F.3d 1350, 1354-55 (D.C. Cir. 1998); Albert C. Lin, *Refining Fair Notice Doc-*

trine: What Notice is Required of Civil Regulations, 55 BAYLOR L. REV. 991, 992-98 (2003). Obviously, the Fifth Amendment is traditionally relevant to criminal proceedings. *See Gates & Fox*, 790 F.2d at 156. And in the criminal context, fair notice requirements are well understood. As Justice Holmes explained in overturning a criminal conviction, "a fair warning should be given to the world in language that the common world will understand, of what the law intends to do if a certain line is passed." *McBoyle v. United States*, 283 U.S. 25, 27 (1931).

But the fair notice doctrine also applies more broadly to civil administrative proceedings:

> [A]s long ago as 1968, we recognized this "fair notice" requirement in the civil administrative context. In *Radio Athens, Inc. v. FCC*, we held that when sanctions are drastic—in that case, the FCC dismissed the petitioner's application for a radio station license —"elementary fairness compels clarity" in the statements and regulations setting forth the actions with which the agency expects the public to comply.

Gen. Elec. Co., 53 F.3d at 1329 (quoting *Radio Athens, Inc. v. FCC*, 401 F.2d 398, 404 (D.C. Cir. 1968)); *see also ibid.* (emphasizing fair notice doctrine "has now been thoroughly 'incorporated into administrative law,'" far outside criminal proceedings (quoting *Satellite Broad. Co. v. FCC*, 824 F.2d 1, 3 (D.C. Cir. 1987))). For example, the D.C. Circuit applied the doctrine to a product recall in *Chrysler*. 158 F.3d at 1351, 1354-55. The D.C. Circuit applied the doctrine to a $25,000 fine in *General Electric*. 53 F.3d at 1327, 1329-30. And, most relevant to the present controversy, the D.C. Circuit has repeatedly applied the doctrine to the "drastic" sanction

of denying applications for radio and cellular licenses in cases like *Radio Athens*, 401 F.2d at 400, 404, *Satellite Broadcasting*, 824 F.2d at 2-4, and *McElroy Elecs. Corp. v. FCC*, 990 F.2d 1351, 1353, 1363 (D.C. Cir. 1993). If there is a "drasticness" distinction between the denial of a cellular license application and the denial of a tobacco marketing application, FDA does not point to it. And it is hard to imagine one, given the MDOs in this case will unquestionably put petitioners out of business. *See* EB Oral Arg. at 13:07-49. So we take it as undisputed that the fair notice doctrine applies.

Chrysler provides a helpful illustration of the doctrinal contours of the fair notice requirement. In that case, NHTSA promulgated a seatbelt safety standard called "Standard 210." *See Chrysler*, 158 F.3d at 1351. Standard 210 required carmakers to install seatbelt anchorages that could withstand certain pressure forces for certain durations of time. *Ibid.* The standard further required carmakers to conduct their pressure tests using a "pelvic body block," an L-shaped metal block resembling a human pelvis. *Ibid.* Standard 210 did not specify, however, *where* carmakers should install the pelvic body blocks in their tests. *Ibid.* (citation omitted). So Chrysler put the pelvic block against the seat back—a reasonable decision given how people sit in cars and given that "NHTSA's own test schematic for Standard 210, entitled 'Typical FMVSS 210 Anchorage Pull Test Setup,' shows the pelvic body block against the seat back." *Id.* at 1356. On those parameters, Chrysler's cars met Standard 210. *Ibid.*

NHTSA nonetheless required Chrysler to recall 91,000 cars. *Id.* at 1351. NHTSA pointed out that nothing in Standard 210 *guaranteed* that a car would

pass the testing pressures when the pelvic block was pressed against the seat back. *Id.* at 1355-56. To the contrary, the Standard itself did not specify a location for the block. *Id.* at 1356. And the agency put the world on notice that when a Standard is silent about testing locations, the carmaker must be able to meet the testing pressures at any and all testing locations. Specifically, the agency published this notice in the Federal Register:

> As a general matter, when a standard does not specify a particular test condition, there is a presumption that the requirements of the standard must be met at all such test conditions. This presumption that the standard must be met at all positions of unspecified test conditions may be rebutted if the language of the standard as a whole or its purposes indicate an intention to limit unspecified test conditions to a particular condition or conditions.
>
> In the case of the strength requirements in Standard No. 210, nothing in the language of the standard suggests that the strength requirements were only to be measured with the safety belt or other vehicle features at certain adjustment positions. Indeed, the purpose of the standard is to reduce the likelihood that an anchorage will fail in a crash. To serve this purpose, the anchorage must be capable of meeting the strength requirements with the safety belt and other vehicle features at any adjustment, since those features could be at any adjustment position during a crash.

Federal Motor Vehicle Safety Standards; Seat Belt Assembly Anchorages, 56 Fed. Reg. 63,676, 63,677 (1991). And when the pelvic block was moved *away* from the

seat back, the seatbelt anchors failed the pressure test. *Chrysler*, 158 F.3d at 1352. NHTSA argued that the plain language of the Federal Register put Chrysler on fair notice of its testing obligations and required recall of the unsafe cars. *Id.* at 1356. After Chrysler refused to institute a recall, NHTSA sued the carmaker. *Id.* at 1352.

Chrysler won. Even though the Federal Register told Chrysler that it needed to satisfy Standard 210 "at *all positions* of unspecified test conditions," 56 Fed. Reg. at 63,677 (emphasis added), the D.C. Circuit held this language was "far too general" to give Chrysler fair notice of its obligations to move the pelvic block. *Chrysler*, 158 F.3d at 1356. It also did not matter that NHTSA previously told regulated entities not to rely on the testing schematic attached to Standard 210 because "an agency is hard pressed to show fair notice when the agency itself has taken action in the past that conflicts with its current interpretation of a regulation." *Ibid.* (citing *Gen. Elec. Co.*, 53 F.2d at 1332). In sum, "Chrysler might have satisfied NHTSA with the exercise of extraordinary intuition or with the aid of a psychic, but these possibilities are more than the law requires." *Id.* at 1357.

2.

So too here. The differences between the October 2018 Guidance and the June 2019 Guidance on the one hand and FDA's across-the-board denials of every flavored PMTA on the other are far starker than in *Chrysler*.

Guidance: In the October 2018 Guidance, FDA told petitioners: "*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." October 2018 Guidance at 26 (emphasis added). It also told petitioners: "Youth behavioral data **not** required at this time." *Id.* at 18 (emphasis in original). And it never told petitioners they could not rely on existing data from *unflavored* products to support their *flavored* PMTAs. To the contrary, in the June 2019 Guidance, FDA *twice* told petitioners: "[I]n general, *FDA does not expect that applicants will need to conduct long-term studies to support an application*." A.299 (emphasis added); *see also* A.317 (same). FDA instead invited flavored manufacturers to rely on existing data (including studies of smokers and users of unflavored ENDS products) to make inferences about flavored ENDS products. October 2018 Guidance at 11-12. And both the June 2019 Guidance and the October 2018 Guidance invited petitioners to use "observational studies," which could include surveys. A.324 (June 2019 Guidance); *see also* October 2018 Guidance at 16-17.

MDOs: Then FDA flip-flopped. FDA turned around and denied petitioners' applications because they did not perform "a randomized controlled trial and/or longitudinal cohort study" or other comparably robust evidence that directly measured the behaviors of those who use their flavored products. *See* A.57, A.85 & n.vi. And when petitioners submitted voluminous, robust scientific studies to show e-cigarettes induce adults to switch from smoking (and thus save lives), FDA categorically rejected that data as irrelevant because it did not show *flavored* e-cigarettes promote more switching than *unflavored* ones. *See* A.57. And

FDA ignored as irrelevant petitioners' observational cross-section studies without any acknowledgement that the agency previously invited them.

3.

FDA's principal justification for its about-face is that it provided manufacturers fair notice of the PMTA requirements in the June 2019 Guidance. *See* FDA EB Br. 29-37. Specifically, FDA points to one sentence in that 52-page, single-spaced guidance document: "We recommend 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." A.299; *see also* FDA EB Br. 36 (relying on this sentence alone to provide fair notice). But it is undisputed that petitioners compared the health risks of their products to other products in the same or different categories. As FDA itself concedes in its en banc brief:

> Petitioners asserted in their application that "flavors are crucial to getting adult smokers to make the switch and stay away from combustible cigarettes," A379; that adult smokers prefer flavored e-cigarettes to tobacco-flavored e-cigarettes, A380; and that this preference "has powerful implications for not only the role of flavors in helping smokers' transition from smoking to vaping, but also in connection with helping vapers maintain smoking abstinence and preventing relapse to smoking," *id.*

FDA EB Br. 35. Thus, there is no question that petitioners compared the health risks of their products to other products as the June 2019 Guidance recommended.

The question is whether FDA gave petitioners fair notice of their need to provide *long-term scientific studies as proof* of those relative risks. And on that question, the very best sentence FDA can find is this one from its June 2019 Guidance: "Nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health." A.298. From that, FDA argues that it gave petitioners fair notice that they might be obligated to conduct new long-term scientific studies on their flavored products. FDA EB Br. 31. Of course, saying *X* might not be sufficient is a far cry from saying *Y* is necessary. But more fundamentally, the agency's position beggars belief because it ignores *the very next sentence* in the guidance document: "[I]n general, FDA does not expect that applicants will need to conduct long-term studies to support an application." A.299. FDA also ignores that the very same paragraph says "FDA understands that limited data may exist from scientific studies and analyses" to support e-cigarette applications. A.298. And FDA ignores that the very same guidance document comes back to this point a few pages later:

> Due to the emerging nature of ENDS products within the general tobacco market, FDA acknowledges that there may be limited nonclinical or clinical research conducted on specific ENDS products. Thus, it is likely that applicants will conduct certain investigations themselves and submit their own research findings as a part of their PMTA. *However, in general, FDA does not expect that applicants will have to conduct long-term studies to support an application.*

A.317 (emphasis added). The agency simply cannot contend that when it twice said "FDA does not expect that applicants will have to conduct long-term studies to support an application" for a specific flavored product, A.299, A.317, it put petitioners on fair notice that "FDA will deny your application if you do not conduct long-term studies on your specific flavored product."

Nor can FDA deny that it in fact required long-term studies. In its explanation for denying petitioners' applications, FDA imposed two requirements—randomized controlled trials and longitudinal cohort studies. Then it found both of those long-term scientific studies lacking in petitioners' applications, for the obvious reason that FDA previously said these studies were unnecessary:

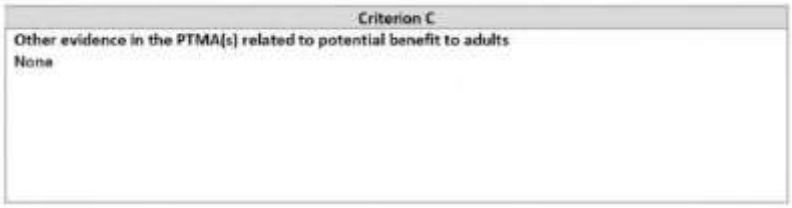
Presence of Evidence for Flavored ENDS Products

Criterion A	Present		Absent
Randomized Controlled Trial (RCT) on new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	Yes	No	N/A[2]
Was the RCT conducted using new products?	☐	☐	☒
Does the RCT include a tobacco-flavored arm and a flavored product arm[3]?	☐	☐	☒
Do the outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): N/A			

Criterion B	Present		Absent
Longitudinal Cohort Study (LCS) on new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	Yes	No	N/A[2]
Was the LCS conducted and does it include users of new products who are followed over time?	☐	☐	☒
Was use of tobacco-flavored products and other flavored products assessed[3]?	☐	☐	☒
Do outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): N/A			

A.70. That sure looks like a requirement that petitioners perform long-term scientific studies on their e-cigarette products; otherwise, it is hard to understand why FDA would devote the overwhelming majority of its decision document to rejecting the PMTAs for failing to include such studies.

True, FDA then included a single sentence regarding "other" scientific evidence:



Criterion C
Other evidence in the PTMA(s) related to potential benefit to adults
None

A.71 (Triton); *see also* A.134 (similar one-sentence rejection for Vapetasia). But FDA made clear it could be persuaded by "other evidence" "*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*." A.57 (emphasis added).

To the extent that "reliably and robustly" evaluating impact "over time" means a randomized controlled trial or a longitudinal cohort study, that is obviously a violation of the fair notice doctrine for the reasons explained above. FDA cannot require petitioners to perform such long-term/over-time studies after telling petitioners that, "[d]ue to the emerging nature of ENDS products within the general tobacco market, FDA acknowledges that there may be limited nonclinical or clinical research conducted on specific ENDS products." A.317; *see also* A.298 (same). Yet in its "technical project lead" supporting the MDOs, FDA said this about

the "other evidence" it would consider "on a case-by-case basis":

> 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 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.

A.85 n.vi (emphases added). Again, that looks like a requirement for direct observations and controlled scientific studies, supported by strong and robust statistical evidence, which FDA previously said it did not require.

If "reliably and robustly" evaluating impact "over time" instead means something else, petitioners (and the courts) are left simply to imagine what the agency might have had in mind. FDA and the dissenting opinions do not say what "other evidence" petitioners might have supplied to win approval. Instead, one of the dissenting opinions disputes the premise that an agency must specify the grounds for its decisions because, as the dissenting opinion puts it, "the FDA must use its science to evaluate the applications." *Post*, at 60 (Haynes, J., dissenting). It is obviously true that science matters —and it is also true that agencies must give regulated entities fair notice of *what* science matters. If an agency could instead move the scientific goalposts and then refuse to specify the new scientific goal line, the

administrative process would be governed not by science but by diktat.

And it is flatly untrue that petitioners' "other evidence" was "None." A.71 (Triton); *see also* A.134 (Vapetasia's MDO, stamping its "other evidence" as "N/A"). Rather, it is undisputed that petitioners *did* present *some* "other evidence." For example, Triton submitted:

> published studies and articles, as well as subject matter databases, related to the topic areas identified in FDA's PMTA Guidance: in vivo and in vitro toxicology (e.g., carcinogenesis, genotoxicity, mutagenicity, reactive oxygen species, inflammation, cytotoxicity, respiratory health, cardiovascular disease, and reproductive and developmental toxicity), clinical health, abuse liability and pharmacokinetics, trends in usage and factors that influence ENDS usage (e.g., susceptibility, consumer perception, initiation, cessation, transition), topography, human factors, biomarkers of harm and exposure, and population health (e.g., FDA's Population Assessment of Tobacco and Health (PATH)).

A.369-70. Triton also pointed to peer-reviewed studies, long-term randomized controlled studies, longitudinal cohort studies, short-term studies, and a meta-analysis by the National Academies of Science, Engineering, and Medicine to show the public health benefits of e-cigarette use by cigarette smokers. *See, e.g.*, A.431. The dissenting opinions do not explain why or how this science could be rejected out of hand with FDA's one-word rubber stamp labeled "None" or "N/A."

FDA, by contrast, *did* explain why the PMTAs could be summarily rejected for submitting "None" of the studies FDA belatedly demanded: It created a new, after-the-fact, categorical ban on using scientific data from *unflavored* products to support *flavored* PMTAs. In its MDOs, the agency said petitioners should have submitted scientific studies on the public health benefits of *their specific, flavored* e-cigarette liquids: As FDA put it, petitioners should have submitted "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]." A.57 (emphasis added). Or petitioners should have submitted some unspecified "other evidence" that "reliably and robustly evaluated" the public health benefits of *petitioners' specific* "new flavored" products. *Ibid.* This new approach—adopted for the first time in the MDOs and after years of contrary guidance—prohibited *flavored* product manufacturers from relying on existing data involving *unflavored* products.

The problem of course is that FDA never gave petitioners fair notice that they needed to conduct long-term studies on their specific flavored products. And crucially, FDA never told petitioners that their "other evidence" categorically could not include existing studies involving *unflavored* e-cigarettes. To the contrary, the entirety of FDA's voluminous pre-decisional guidance said the precise opposite: "Due to the emerging nature of ENDS products within the general tobacco market, FDA acknowledges that there may be limited nonclinical or clinical research conducted on specific ENDS products." A.317; *see also* A.298 (same). And FDA told petitioners they did *not* need to conduct long-term

studies on their specific products. *See* A.299, A.317. To the contrary, FDA promulgated detailed instructions on how petitioners could build a "bridge" from existing studies[4] to support their PMTAs. *See, e.g.*, A.332-36. Then FDA turned around and categorically banned flavored-product manufacturers from relying on any study that did not focus on the specific flavored product mentioned in the PMTA. Petitioners "might have satisfied [FDA] with the exercise of extraordinary intuition or with the aid of a psychic, but these possibilities are more than the law requires." *Cf. Chrysler*, 158 F.3d at 1357. That warrants vacatur of the MDOs and remand

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[4] The caveats FDA placed on "bridging" further underscore the capriciousness of its flip-flop in the MDOs. For example, in its predecisional guidance, FDA told e-cigarette manufacturers how they could "bridge" from existing literature reviews:

> [W]hen you submit a literature review to support an ENDS PMTA, FDA recommends that you consider the relevancy of the literature and adequacy of the study design in order to determine the likelihood that a particular body of literature will support a marketing order for the new tobacco product. For example, the following questions may be considered:
>
> • Is the tobacco product in the literature comparable in terms of technology to the new tobacco product?
>
> • Are there data (e.g., range of possible use, emissions under conditions of use, biomarkers of exposure) that can be used to adequately demonstrate comparability?
>
> • Was the product in the literature used in a population that adequately represents the target population for the new tobacco product?
>
> • Is the information in the literature sufficient to determine how the tobacco product was used?

A.334. At no point in that list of caveats did FDA even hint at what it later announced in the MDOs—that literature reviews involving *non-flavored* products are somehow categorically irrelevant to the public health benefits of *flavored* e-cigarettes.

to the agency for a lawful consideration of petitioners' applications.

C.

The third hoary principle of administrative law at issue in this case is the change-in-position doctrine. The APA "demand[s] that [the agency] display awareness that it *is* changing position. An agency may not, for example, depart from a prior policy *sub silentio* or simply disregard rules that are still on the books." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) (emphasis in original). Rather, an agency *must* provide a "detailed justification" for its change when "its new policy rests upon factual findings that contradict those which underlay its prior policy; or when its prior policy has engendered serious reliance interests that must be taken into account. It would be arbitrary or capricious to ignore such matters." *Ibid.* (citation omitted).

We (1) explain the change-in-position doctrine and then (2) analyze FDA's violation of it.

1.

The change-in-position doctrine requires careful comparison of the agency's statements at *T0* and *T1*. An agency cannot shift its understanding of the law between those two times, deny or downplay the shift, and escape vacatur under the APA. As the D.C. Circuit put it in the canonical case: "[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute." *Greater Bos. Television Corp. v.*

FCC, 444 F.2d 841, 852 (D.C. Cir. 1970) (footnote omitted); *accord Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 222 (2016) ("When an agency changes its existing position, it . . . must at least display awareness that it is changing position and show that there are good reasons for the new policy." (quotation and citation omitted)).

Take for example *Physicians for Social Responsibility v. Wheeler*, 956 F.3d 634 (D.C. Cir. 2020) ("*PSR*"). In that case, the Environmental Protection Agency had a "general[]" policy of allowing EPA grant recipients to serve on EPA advisory committees. *Id.* at 641. The source of that "general" policy was unclear; the D.C. Circuit established it by pointing only to a 2013 Office of the Inspector General report for the proposition that receiving an EPA grant "generally" did not create a financial conflict sufficient to disqualify the recipient from serving on an advisory committee. *See ibid.* (citing OFFICE OF THE INSPECTOR GENERAL, EPA, EPA CAN BETTER DOCUMENT RESOLUTION OF ETHICS AND PARTIALITY CONCERNS IN MANAGING CLEAN AIR FEDERAL ADVISORY COMMITTEES 9-10 (2013) https://perma.cc/8EES-WTNV ("2013 OIG Report")). The underlying OIG report was couched in all of the cautious language so often used for guidance documents drafted inside the Beltway. It purported to provide only "guidance." 2013 OIG Report at 10. It hedged that "[t]his report presents the opinion of the OIG and does not necessarily represent the final EPA position." *Id.* at cover page. And at no point did the 2013 OIG Report *ever promise* that grant recipients could serve on EPA advisory committees. To the contrary, the report *twice* cautioned that grants "could . . . potentially present an independence concern," so EPA required committee mem-

bers to fill out reports and subjected them to thorough independence reviews to identify potential conflicts. *Id.* at 10; *see also ibid.* (separately emphasizing a committee member's "research or grant is a potential area of concern" in certain circumstances).

However flexible, qualified, and hazy the preexisting "guidance" was, EPA changed it in October 2017. In that month, the then-new EPA administrator issued a "directive." *PSR*, 956 F.3d at 641. In that 2017 directive, the EPA administrator found it would "strengthen and improve the independence, diversity, and breadth of participation on EPA federal advisory committees" to disqualify EPA grant recipients from participation. *Ibid.* Several grant recipients who wanted to keep their committee assignments claimed EPA violated the APA in changing its pre-2017 guidance.

The D.C. Circuit agreed with the petitioners. The 2017 directive used words like "strengthen" and "improve"—which obviously connote change from the previous standards that needed strengthening and improving. And EPA conceded that the whole purpose of the directive was to change the agency's previous conflicts policy. *See* Brief for EPA at 42-43, *PSR*, 956 F.3d 634 (No. 19-5104), 2019 WL 6895452. ("Anyone reading the Directive and accompanying memorandum would understand that it was being issued precisely because EPA was marking a policy change."). Still, the D.C. Circuit held the agency was not *explicit enough* in announcing to the world that it was changing positions and that its directive was therefore tantamount to a sub silentio policy change. *PSR*, 956 F.3d at 645 (holding EPA said "not a peep" about its pre-2017 conflicts policy). The court of appeals held the change-in-position

doctrine required EPA both to explicitly acknowledge the old policy and explain why its new one was better. *Id.* at 647-48. And it mattered not one bit that the previous policy was couched in cautious qualifiers as nonbinding "guidance" from the Inspector General. It also did not matter that EPA's directive comported with every applicable substantive law on ethics, conflicts, and advisory committees. Nor did it matter that EPA thought a more robust conflicts policy would serve the public interest. What mattered, the D.C. Circuit held, is that EPA did not acknowledge the 2013 OIG Report and explain its reasons for changing positions. *Ibid.*

Or consider *Southwest Airlines Co. v. FERC*, 926 F.3d 851 (D.C. Cir. 2019). That case involved even more flexible agency policies and standards. FERC had a "general[]" policy of relying on two prior-year inflation data to determine whether an oil pipeline's rate increase was "substantially" too high. *HollyFrontier Refin. & Mktg. LLC v. SFPP, LP*, 162 FERC ¶ 61,232, para. 16 (Mar. 15, 2018). When FERC deviated from that policy to reject Southwest's challenge to a pipeline's rate increase, FERC noted that it never promised to apply the same two-year-data approach to every rate challenge. To the contrary, the Commission emphasized, its heavily qualified standards—replete with cautionary language like "generally" and "substantially"—gave it "considerable discretion" to take a different approach where the facts and the agency's expertise warranted it. Brief for FERC at 17, *Southwest Airlines*, 926 F.3d 851 (No. 18-1134), 2019 WL 1043117. FERC further emphasized that its approach in Southwest's case—to consider more recent data that more accurately reflected the economic reality of the challenged pipeline rate—

was unquestionably more accurate than petitioners' contrary approach. *Id.* at 22.

The D.C. Circuit granted the petition for review anyway. True, FERC never *promised* to use any particular cost index. *Southwest Airlines*, 926 F.3d at 858. And true, FERC's approach had the virtue of using the "best available information," which unquestionably served the public interest and best fulfilled the commission's statutory obligations. *Id.* at 856. But none of that mattered because the fundamental fact remained: FERC previously used one cost index, and then it turned around and used a different one without acknowledging the change. *Id.* at 858-59.

2.

Again, so too here. The differences in FDA's positions between the October 2018 Guidance and the June 2019 Guidance on the one hand and the MDOs on the other are radically starker than the difference between EPA's positions in *PSR*. The pre-MDO guidance documents said: "No specific studies are required for a PMTA." October 2018 Guidance at 26. The pre-MDO guidance also said: "[I]n general, FDA does not expect that applicants will need to conduct long-term studies to support an application." A.299; *see also* A.317 (same). If an agency is arbitrary and capricious when it (1) acknowledges changing its position from (2) a policy reflected in a solitary OIG report, *see PSR*, 956 F.3d at 645-48, how much more arbitrary and capricious is the agency when it (1) refuses to acknowledge the change in its position from (2) its own voluminous guidance documents, PowerPoint decks, and enforcement memoranda promulgated over years and reiterated in numerous different ways? Indeed, the *PSR* court even required

EPA to explain its change from the position of a *different government agency* (the Office of Government Ethics). *Id.* at 646-47. This is an *a fortiori* case.

Nor can FDA deny that it changed its position based on the qualified language in its pre-MDO guidance documents. It is unquestionably true that the pre-MDO guidance documents had all manner of disclaimers, qualifiers, and cautionary language. Those documents had headings like "***Contains Nonbinding Recommendations***." A.299; A.317. And FDA never promised or committed itself to doing any particular thing on any particular application. But precisely the same thing was true in *PSR* and *Southwest Airlines*. In *PSR*, the "guidance" was even more cautionary—it wasn't even issued by EPA but instead was issued by the Inspector General, and it contained similar "guidance" disclaimers. And in *Southwest Airlines*, all agreed that FERC never promised to use any particular cost index in adjudicating Southwest's claims. But that does not matter for purposes of the change-in-position doctrine. In all three cases—*PSR*, *Southwest Airlines*, and this one—the agency violated that doctrine by changing its position without acknowledging the change, and it cannot avoid judicial review by pointing to cautionary headers and words like "generally." *See, e.g.*, *Southwest Airlines*, 926 F.3d at 858.

Nor can FDA deny that it changed its position on cartridge-versus-open systems. In its 2020 Enforcement Guidance, FDA found a material distinction between cartridge-based flavored products and other products, like the e-liquids made by petitioners, that generally refill open-tank systems. *See* A.201-04. Then in its August 2021 press release and its MDOs,

FDA imposed an across-the-board ban on *all* flavored products, regardless of device type. As in *PSR* and *Southwest Airlines*, it might very well be true that the agency has the power to impose the policy it wants to impose. And it might very well be true that FDA's ban better serves the public health. But again, that does not matter under the change-in-position doctrine. All that matters here is that the agency unquestionably changed its position and then pretended otherwise.[5]

Were there any doubt on this score, although we think there is none, it would be resolved by the 2020 Enforcement Guidance. In that document, FDA acknowledged all manner of relatively minor changes in its understanding of the public health standard. For example, it went to great lengths to differentiate e-cigarette cartridges from tanks, and to discuss whether "mint" is a flavor. And FDA did so, it acknowledged, because those distinctions reflected changes in the agency's position. *See* A.204. Not only does that prove that FDA understood its obligations to acknowledge such changes, but it also put the public on notice of what it should expect from FDA when and if the agency changed its po-

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[5] FDA's categorical ban has other statutory problems. For example, the TCA states that FDA must follow notice-and-comment procedures before adopting a "tobacco product standard." *See* 21 U.S.C. § 387g(c)-(d). And Congress specifically called a ban on tobacco flavors a "tobacco product standard." *See id.* § 387g(a)(1)(A) (referring to tobacco flavors, "including strawberry, grape, orange, clove, cinnamon, pineapple, vanilla, coconut, licorice, cocoa, chocolate, cherry, or coffee, that is a characterizing flavor of the tobacco product or tobacco smoke"); *see also id.* § 387g(a)(2) (cross-referencing notice-and-comment obligation to revise flavor standards). FDA unquestionably failed to follow § 387g's notice-and-comment obligations before imposing its de facto ban on flavored e-cigarettes.

sition. Reasonable manufacturers in petitioners' shoes could expect FDA to continue updating its approach to flavored e-cigarette products. But no reasonable manufacturer could read the 2020 Enforcement Guidance and think the agency would publicly disclose picayune distinctions like whether mint is a flavor while silently requiring the long-term studies it previously said were unnecessary.

FDA failed to acknowledge its multiple changes in position between the pre-MDO guidance documents and the MDOs. That too warrants vacatur of the agency actions and remand for further proceedings. *See, e.g.*, *Southwest Airlines*, 926 F.3d at 859.

D.

The fourth and final deeply rooted administrative law principle at issue in this case is the good faith reliance doctrine. Under it, even when an agency lawfully changes its position, it cannot fault a party for relying in good faith on the prior one. *See, e.g.*, *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156-57 (2012) (prohibiting agency from penalizing party for "good-faith reliance" on the agency's prior positions (citation omitted)); *Fox*, 556 U.S. at 515 (requiring agency to consider "serious reliance interests").

Consider for example *Satellite Broadcasting*. The dispute in that case centered on whether petitioner timely filed an application for a microwave radio license by tendering it to FCC's office in Washington, D.C. *Satellite Broad.*, 824 F.2d at 2. FCC's regulations were ambiguous about where such applications should be filed. One could reasonably read them to require timely filing in Washington. *Ibid.* Or one could rea-

sonably read them to require timely filing only in Gettysburg, Pennsylvania. FCC chose the former reading, rejected petitioner's latter reading, and rejected the applications as untimely. *Ibid.*

The D.C. Circuit agreed with Satellite Broadcasting, reversed the commission's ruling, and remanded. The court of appeals reasoned the FCC's documents could be reasonably interpreted to require either result. *See id.* at 3 & n.4. But it was precisely because the petitioner could reasonably understand that its actions were permissible that the agency could not ignore that reasonable reliance, reach a contrary result, and reject the applications:

> The Commission through its regulatory power cannot, in effect, punish a member of the regulated class for reasonably interpreting Commission rules. Otherwise the practice of administrative law would come to resemble "Russian Roulette." The agency's interpretation is entitled to deference, but if it wishes to use that interpretation to cut off a party's right, it must give full notice of its interpretation. We accordingly vacate as arbitrary and capricious the FCC's order dismissing these applications and remand this case for their reinstatement *nunc pro tunc*.

Id. at 3-4 (footnote omitted).

Yet again, so too here. Even if we agreed with our sister circuits' decisions that FDA's pre-MDO guidance documents could be reasonably read to put manufacturers on notice of their obligations to perform long-term

scientific studies,[6] those documents certainly could be read in good faith the way petitioners read them. There is ample language spread out across multiple documents, multiple PowerPoint decks, and multiple public meetings to say "[n]o specific studies are required for a PMTA"; "[y]outh behavioral data [is] not required at this time"; and manufacturers need not "conduct long-term studies to support an application." *See* October 2018 Guidance at 18, 26; A.299; A.317. There is not a single sentence anywhere in the voluminous record before us that says: "manufacturers should submit long-term scientific studies on the differences between their new flavored e-cigarette products and other non-flavored e-cigarette products." And even if (counterfactually) the agency gave conflicting instructions—"you need not submit long-term studies" and "you should submit long-term studies"—the regulated entity cannot have its application denied because it chose one or the other. *See Satellite Broad.*, 924 F.2d at 4. It follows *a fortiori* that when the agency says: "you need not submit long-term studies" and "this is general guidance," the regulated entity cannot have its application denied because it did not submit long-term studies. To hold otherwise is to turn "the practice of administrative law [into] 'Russian Roulette,'" *ibid.*—where the regulated entity chooses to trust the agency's affirmative statement ("you need not submit long-term studies")

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[6] *See, e.g., Prohibition Juice Co. v. FDA*, 45 F.4th 8, 22-23 (D.C. Cir. 2022); *Avail Vapor, LLC v. FDA*, 55 F.4th 409, 423 (4th Cir. 2022); *Liquid Labs LLC v. FDA*, 52 F.4th 533, 542 n.11 (3d Cir. 2022); *Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 506-07 (6th Cir. 2021).

and simply hopes the administrative gun ("this is general guidance") has no bullet in the chamber.

Any doubt on this score is resolved by the FDA's approach to flavored e-cigarettes more generally. Recall that for FDA to prevail, not only must its understanding of the pre-MDO rules be reasonable, but the manufacturers' understanding of those rules also must be *unreasonable*. *See id.* at 3-4. FDA received over one million PMTAs for flavored e-cigarette products—and not a single one of them contained the scientific studies that FDA now requires and that (it says) any reasonable manufacturer would have known *ex ante* were required. It is perhaps possible that FDA did its part to give the regulated community clear guidance and that one million out of one million not only got it wrong but got it *unreasonably* wrong. But administrative law does not turn on such infinitesimal possibilities. *See Chrysler*, 158 F.3d at 1357. It instead prohibits administrative agencies from saying one thing, pulling a surprise switcheroo, and ignoring the reasonable reliance interests engendered by its previous statements.

E.

Against all of this, FDA's counterargument boils down to this: Some other circuits agree with the agency. It is true that five circuits have sided with FDA, while the Eleventh Circuit and ours have found the agency acted arbitrarily and capriciously. But law is not a nose-counting exercise. *Compare, e.g.*, *Cochran v. SEC*, 20 F.4th 194, 237 (5th Cir. 2021) (en banc) (Costa, J., dissenting) ("Five circuits have considered the question. By a count of 15-0, every judge deciding those cases has [found no jurisdiction.]"), *with Axon Enter., Inc. v. FTC*, 598 U.S. 175, 195-96 (2023) (unanimously finding juris-

diction in *Cochran*). Rather, the relevant question is whether our sister circuits have spotted a defect in petitioners' arguments that we have missed. With deepest respect for our colleagues who have seen this case the other way, we think not.

Take for example FDA's principal authority, *Prohibition Juice Co. v. FDA*, 45 F.4th 8 (D.C. Cir. 2022). There the D.C. Circuit rejected the e-cigarette manufacturer's arbitrary-and-capricious claim for two reasons. First, the court of appeals pointed to the June 2019 Guidance, which it read to say "randomized controlled trials or longitudinal studies would not be necessary if applicants submitted similarly rigorous 'valid scientific evidence.'" *Id.* at 21 (quoting June 2019 Guidance at 12, which appears at our A.298). Again, with deepest respect to our colleagues on the D.C. Circuit, that is not what the June 2019 Guidance said. Here is the quoted passage in full:

> The FD&C [Food, Drug, and Cosmetic] Act states that the finding of whether permitting the marketing of a product would be APPH will be determined, when appropriate, on the basis of well-controlled investigations (section 910(c)(5)(A)). However, section 910(c)(5)(B) of the FD&C Act also allows the Agency to consider other "valid scientific evidence" if found sufficient to evaluate the tobacco product. Given the relatively new entrance of ENDS on the U.S. market, FDA understands that limited data may exist from scientific studies and analyses. If an application includes, for example, information on other products (e.g., published literature, marketing information) with appropriate bridging studies, FDA intends to review that information to determine wheth-

> er it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be APPH. Nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health.
>
> *Nonetheless, in general, FDA does not expect that applicants will need to conduct long-term studies to support an application*. As an example for nonclinical assessments, long-term studies such as carcinogenicity bioassays are not expected to be included in an application. For clinical assessments, instead of conducting clinical studies that span months or years to evaluate potential clinical impact, applicants could demonstrate possible long-term health impact by including existing longer duration studies in the public literature with the appropriate bridging information (i.e., why the data used are applicable to the new tobacco product) and extrapolating from short-term studies. In addition, nonclinical in vitro assays that assess the toxicities that are seen following long-term use of tobacco products may be supportive of these clinical assessments. These studies, used as a basis to support a PMTA, should be relevant to the new tobacco product and address, with robust rationale, acute toxicological endpoints or other clinical endpoints that may relate to long-term health impacts. In this context, FDA considers long-term studies to be those studies that are conducted over six months or longer.

A.298-99 (emphasis added and footnotes omitted). This passage explicitly states that, instead of performing long-term studies, manufacturers could submit "ex-

isting longer duration studies in the public literature with the appropriate bridging information" and "nonclinical in vitro assays that assess the toxicities that are seen following long-term use of tobacco products." A.299.

And it is undisputed that petitioners submitted the specified information. They submitted information from existing studies, along with "bridging" information to connect it to their PMTA products. *See supra*, at 33-35. Neither the D.C. Circuit nor any other court of appeals that has sided with FDA can point to a single word in the June 2019 Guidance (or any other guidance) that says existing data on *unflavored* e-cigarette use is categorically irrelevant to the public health benefits of *flavored* e-cigarettes.

The D.C. Circuit's second explanation is that "FDA nowhere guaranteed that unspecified other forms of evidence would necessarily be sufficient—only that they might be, so the FDA would consider them." *Prohibition Juice*, 45 F.4th at 21. That is true; FDA never guaranteed that any particular study would be sufficient to garner approval of a PMTA. But FDA did tell manufacturers to submit "existing longer duration studies in the public literature with the appropriate bridging information" and "nonclinical in vitro assays that assess the toxicities that are seen following long-term use of tobacco products." A.299. Petitioners undisputedly submitted those studies. And then FDA turned around and said those studies were *categorically* insufficient because manufacturers should have performed long-term scientific studies of the kind the June 2019 Guidance said were unnecessary.

One of today's dissenting opinions points to a different court of appeals decision—the Fourth Circuit's in *Avail Vapor*. *See post*, at 84 (Graves, J., dissenting). In that case, the Fourth Circuit described a PMTA as:

> 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.

Avail Vapor, 55 F.4th at 425.

With greatest respect to our dissenting colleague and our sister circuit, that analogy is misplaced. Unlike a driving test, the statutory text in § 387j(c)(4)(A)-(B) is not disjunctive. The two statutory requirements: "likelihood that existing users of tobacco products will stop using such products" (scientific evidence) and the "likelihood that those who do not use tobacco products will start using such products" (marketing plans) are linked with a conjunctive "and." *Ibid.* The statute

does not proceed sequentially; rather, it commands the agency to take *both* criteria into account.

Section 387j(c)(4)(A)-(B) is perhaps better understood as a standardized test with two sections, scored as a composite. Because a low score on part one of a two-part test can be counterbalanced by a high score on the other, the administrator must grade both sections. To put a finer point on it, imagine a hypothetical ENDS product that gets only one existing smoker to quit, but has a marketing plan so restrictive that no non-smokers could access it and use it to start vaping. That product has an obvious net public health benefit. And FDA could not reject a PMTA for it after scoring only half of its test.

In any event, even if the "and" in § 387j(c)(4)(A) could or should be read as "or," that is *still* not enough to save the FDA. As noted, the Eleventh Circuit held the agency repeatedly represented that the marketing plans were "critical" and "necessary" to a successful application. *Bidi Vapor*, 47 F.4th at 1203-04. The agency cannot now claim they were in fact always meaningless.

* * *

In sum, FDA's denials of petitioners' PMTAs were arbitrary and capricious. The agency did not give manufacturers fair notice of the rules; the agency did not acknowledge or explain its change in position; the agency ignored reasonable and serious reliance interests that manufacturers had in the pre-MDO guidance; and the agency tried to cover up its mistakes with *post hoc* justifications at oral argument. The contrary views expressed by some of our sister circuits do not ad-

dress our principal concerns with FDA's decisionmaking. We therefore hold the agency acted unlawfully.

III.

Finally, FDA argues that even if it arbitrarily and capriciously denied petitioners' applications, that error was harmless. FDA reasons that there is nothing special about petitioners' applications, so the agency will deny them on remand even if we send the case back and order FDA to conform its decisionmaking to the APA. FDA EB Br. 27-28.

FDA misunderstands how harmless error review works under the APA. We (A) explain the harmless error rule and then (B) hold it provides no help to the agency.

A.

In administrative law, the harmless error rule is quite narrow. "It is a well-established maxim of administrative law that if the record before the agency does not support the agency action, or if the agency has not considered all relevant factors, the proper course, except in rare circumstances, is to remand to the agency for additional investigation or explanation." *Calcutt*, 598 U.S. at 628-29 (quotation and citation omitted). "The reviewing court is not generally empowered to conduct a *de novo* inquiry into the matter being reviewed and to reach its own conclusions based on such an inquiry." *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 744 (1985). Once we identify an error in the agency's decision, our work is almost always done: If the agency rests its decision on "grounds [that] are inadequate or improper, *the court is powerless* to affirm the administrative action by substituting what it considers to be a

more adequate or proper basis." *SEC v. Chenery Corp.* (*Chenery II*), 332 U.S. 194, 196 (1947) (emphasis added).

Consider for example *Calcutt*. In that case, FDIC sanctioned the CEO of a bank. The CEO petitioned for review in the Sixth Circuit, and the court of appeals identified two legal errors in the agency's decision. The Sixth Circuit nonetheless held those errors were harmless and denied the CEO's petition. The Supreme Court of the United States unanimously and summarily reversed. *Calcutt*, 598 U.S. at 628.

Two parts of the *Calcutt* summary reversal bear emphasis. First, the Court emphasized that the "ordinary" rule is that a federal court must remand to the agency as soon as it identifies a legal error in the agency's decision. *Id.* at 629 ("[T]he Sixth Circuit should have followed the ordinary remand rule here."); *see also Gonzales v. Thomas*, 547 U.S. 183, 187 (2006) (per curiam) (applying "the ordinary remand rule"); *INS v. Orlando Ventura*, 537 U.S. 12, 18 (2002) (same). That ordinary remand rule has deep roots in administrative law. Part of it is rooted in the admonition, dating back at least to *Chenery I*, that agency decisions must stand or fall on the explanation the agency gave at the time. Courts are simply not free to look past the error on the supposition that the error would not affect the agency's decisionmaking. And part of it is rooted in the Court's recognition that the Administrative *Procedure* Act requires agencies to follow *procedures*, and those *procedures* are what give agency decisions legitimacy. A court cannot forgive procedural violations simply because the court thinks they did not matter. "[T]he guiding principle, violated here, is that the function of the reviewing court ends when an error of law is

laid bare." *FPC v. Idaho Power Co.*, 344 U.S. 17, 20 (1952).

Second, *Calcutt* recognized "[i]t is true that remand may be unwarranted in cases where there is not the slightest uncertainty as to the outcome of the agency's proceedings on remand." 598 U.S. at 629-30 (quotation omitted). That is a different way of saying remand may be unnecessary where the petitioner could not have been prejudiced. *Shinseki v. Sanders*, 556 U.S. 396, 409 (2009) (requiring courts to consider whether an error was prejudicial); 5 U.S.C. § 706 (same). But, the *Calcutt* Court emphasized, this rule applies "*only in narrow circumstances*." 598 U.S. at 630 (emphasis added). Specifically, "[w]here the agency was *required* to take a particular action, . . . that it provided a different rationale for the necessary result is no cause for upsetting its ruling." *Ibid.* (emphasis in original) (quotation and citation omitted). But in any case where the agency's decision was *discretionary*, the ordinary remand rule must apply. *Ibid.* As the *Calcutt* Court put it: The harmless-error "exception does not apply in this case. FDIC was not required to reach the result it did; the question whether to sanction petitioner—as well as the severity and type of any sanction that could be imposed—is a discretionary judgment." *Ibid.* (emphasis omitted).

The upshot: APA errors are only harmless where the agency would be *required* to take the same action no matter what. In all other cases, an agency cannot avoid remand.[7]

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[7] Of course, an agency cannot ***demand*** remand where the law is clear and where an agency has failed to heed a prior remand order.

B.

This case is controlled by *Calcutt*. All agree that FDA's standards for adjudicating PMTAs are discretionary. Those applications are highly fact-specific. And the ultimate decision to approve or deny an application turns on FDA's ever-evolving understanding of what "public health" requires. The harmless-error rule simply does not apply to such discretionary administrative decisions.

Similarly, we have held an "APA deficiency is not prejudicial only when it is one that clearly had no bearing on the procedure used or the substance of decision reached." *United States v. Johnson*, 632 F.3d 912, 930 (5th Cir. 2011) (quotation and citation omitted). Thus, *Johnson* prohibits us from holding an APA error is harmless simply because the petitioner did not or could not show that but for the error the agency would have decided the matter differently ("the substance of decision reached"). Rather, the rule is stated in the disjunctive, and it provides an error is harmful unless it had "*no* bearing on the procedure used *or* the substance of decision reached." It is hard to imagine an APA error that could have "*no* bearing on the procedure used." And in any event, each of FDA's errors in this case plainly affected "the procedure used" and hence were not harmless. On that score, we agree with the entirety of the Eleventh Circuit's analysis and its applica-

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See, e.g., *Lewis v. United States*, --- F.4th ---, ---, No. 21-30163, 2023 WL 8711318, at *4 (5th Cir. Dec. 18, 2023); *El Paso Elec. Co. v. FERC*, 76 F.4th 352, 366 (5th Cir. 2023). The principle that unites both lines of precedent is that an administrative agency cannot avoid judicial review by gaming the APA's remand rules.

tion of a harmless error rule identical to *Johnson*'s. *See Bidi Vapor*, 47 F.4th at 1205-08.

* * *

The petitions for review are GRANTED, FDA's marketing denial orders are SET ASIDE, and the matters are REMANDED to FDA.

HAYNES, *Circuit Judge*, joined by STEWART, SOUTHWICK, HIGGINSON, and DOUGLAS, *Circuit Judges*, dissenting:

In 2009, Congress enacted the Family Smoking Prevention and Tobacco Control Act ("TCA"), Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified at 21 U.S.C. §§ 387-387(u)), to empower the FDA in the fight against tobacco products, which Congress considered "the foremost preventable cause of premature death in America." TCA § 2(13), 123 Stat. at 1777. Concerned that "past efforts to restrict advertising and marketing of tobacco products ha[d] failed adequately to curb tobacco use by adolescents," TCA § 2(6), 123 Stat. at 1776, Congress submitted authority to the FDA to regulate tobacco products in the interest of public health and, specifically, the protection of our country's youth. *See Big Time Vapes, Inc. v. FDA*, 963 F.3d 436, 444 (5th Cir. 2020) ("Obviously, the TCA's purpose sounds in (1) protecting public health and (2) preventing young people from accessing (and becoming addicted to) tobacco products.").

Over time, e-cigarettes, including "vaping" models, came into play. The notion was that these were safer than regular cigarettes and might get those who are smokers to become vapers and, ultimately, neither. As I discuss more fully below, the e-cigarettes are *not* safe. Just as being shot in the stomach might be less likely to cause death than being shot in the head, but neither one is wanted, neither e-cigarettes nor cigarettes are safe. As such, the focus on e-cigarettes has been to assist those already addicted, not to create a whole new group of youth becoming addicted. Thus, while this dissenting opinion is long, a short sentence could sum it up: the Petitioners here did not establish that their products

would so sufficiently assist adults that it would overcome the harm to youth.

As a result of the history of e-cigarettes, as of 2016, e-cigarettes and their component parts (including e-liquids)[1] are subject to the requirements of the TCA. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, 81 Fed. Reg. 28974 (May 10, 2016) ("Deeming Rule"). The FDA is thus *required* to deny a Premarket Tobacco Product Application ("PMTA") for an e-cigarette unless permitting the product to be marketed would be "appropriate for the protection of the public health" ("APPH"), based on an evaluation of "the risks and benefits to the population as a whole" as demonstrated by "well-controlled investigations" or other "valid scientific evidence." 21 U.S.C. § 387j(c). Contrary to the majority opinion's seeming contention that any application that has some good sounds to it must be granted, the FDA should only be granting anything that is *shown* to aid public health (i.e., the addicted adults), not create more addicted youth such that our country has much earlier deaths over time.

A body of knowledge growing over the past several years has exposed the extreme risks that flavored e-cigarettes pose to children. By any metric, our country is in the throes of a youth vaping epidemic that has reached crisis proportions. In 2020, 3.6 million kids in the United States reported using e-cigarettes, including 20% of high school students and 5% of middle school students. FDA, *Technical Project Lead (TPL) Review of*

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[1] As the majority opinion does, I use the term "e-cigarettes" throughout this opinion to refer to all forms of electronic nicotine delivery devices ("ENDS") and their component parts, including e-liquids.

PMTAs (2021), at 6. Use of these products at such an early age, "when the developing brain is most vulnerable to nicotine addiction," puts these children at much greater risk of tobacco use and dependence as adults. As the D.C. Circuit noted recently, "[t]he public health consequences are dire: Tobacco is quickly and powerfully addicting, and e-cigarettes can permanently damage developing adolescent brains, cause chronic lung diseases, and hook young users for life." *Prohibition Juice Co. v. FDA*, 45 F.4th 8, 10 (D.C. Cir. 2022).

Flavored products are a key driver of the problem.[2] According to the 2020 National Youth Tobacco Survey, 85% of high school e-cigarette users report using a flavored product, compared to 65% in 2014. Petitioners produce e-cigarettes in flavors like sour grape, pink lemonade, and pound cake with names such as "Jimmy The Juice Man Strawberry Astronaut" and "Suicide Bunny Bunny Season"—which, as one member of our sister circuit recently commented, "seem designed to have appeal to kids." *Bidi Vapor LLC v. FDA*, 47 F.4th 1191, 1212-13 (11th Cir. 2022) (Rosenbaum, J., dissenting). Indeed, the FDA has found that the availability of flavored products "is one of the primary reasons for the popularity of [e-cigarettes] among youth."

The issue for manufacturers of flavored e-cigarettes, like Petitioners, is that no counterbalancing evidence has emerged as to the product's benefits. While e-cigarettes may help some current smokers quit or switch to vaping, the research does not establish that flavored products provide an increased benefit over non-

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[2] In accordance with the FDA's guidance documents and the parties' briefs, the term "flavored" as used herein does not include tobacco- or menthol-flavored e-cigarettes.

flavored products. As the FDA noted during its review of Petitioners' PMTAs, "in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions—the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive." Thus, according to current knowledge, flavored e-cigarettes present a much higher risk to youth than non-flavored e-cigarettes, without any compensatory benefit. Such a calculus does not bode well for approval under the TCA. Still, in accordance with the guidance it has consistently given applicants, the FDA continues to conduct a case-by-case evaluation of each PMTA for flavored e-cigarettes to determine whether it contains sufficiently reliable and robust evidence to shift the balance of risks and benefits in favor of approval.

It is against this backdrop that the FDA reviewed the PMTAs of Wages and White Lion Investments, LLC, d/b/a Triton Distribution ("Triton") and Vapetasia LLC ("Vapetasia") (collectively, "Petitioners") and issued marketing denial orders ("MDOs") to Petitioners. The FDA denied Petitioners' PMTAs because they did not contain any reliable evidence suggesting the benefits of Petitioners' flavored products outweighed the significant risks to youth—an outcome that aligned with both the guidance the FDA had given to applicants and its statutory mandate under the TCA. But the majority opinion erroneously concludes that the FDA changed the evidentiary standards applied to Petitioners' PMTAs and wholly ignored Petitioners' marketing plans, and thus acted in an arbitrary and capricious manner. Unfortunately, based on a misreading of the law and a misconstruing of the relevant facts, the major-

ity opinion supersedes the FDA's work by remanding instead of denying the petition, which cuts the FDA's legs out from under it in the middle of a dangerous and constantly evolving public health crisis.

In so doing, the majority opinion also departs from all but one of our sister circuits that have addressed the same issue. *See, e.g.*, *Magellan Tech., Inc. v. FDA*, 70 F.4th 622 (2d Cir. 2023) (unanimous denial); *Liquid Labs LLC v. FDA*, 52 F.4th 533 (3rd Cir. 2022) (unanimous denial); *Avail Vapor, LLC v. FDA*, 55 F.4th 409 (4th Cir. 2022) (unanimous denial), *cert. denied*, No. 22-1112, 2023 WL 6558399 (U.S. Oct. 10, 2023); *Gripum, LLC v. FDA*, 47 F.4th 553 (7th Cir. 2022) (unanimous denial), *cert. denied*, 143 S. Ct. 2458 (2023); *Lotus Vaping Techs., LLC v. FDA*, 73 F.4th 657 (9th Cir. 2023) (unanimous denial); *Prohibition Juice*, 45 F.4th 8 (unanimous denial); *see also Breeze Smoke, LLC v. FDA*, 18 F.4th 499 (6th Cir. 2021) (denying motion for stay), *app. for stay denied*, 142 S. Ct. 638 (2021). The only circuit that granted a petition for review in a comparable context did so on much narrower grounds than the majority opinion embraces today. *See Bidi Vapor*, 47 F.4th at 1195 (remanding based on the FDA's failure to consider marketing and sales-access-restriction plans); *but see id.* at 1208-18 (Rosenbaum, J., dissenting). Despite the Eleventh Circuit's opinion, however, it is telling that the Supreme Court recently denied certiorari for two cases in which other circuits considered similar facts to those before us and *denied* the petition for review. *See Gripum, LLC v. FDA*, 143 S. Ct. 2458 (2023) (mem.); *Avail Vapor, LLC v. FDA*, No. 22-1112, 2023 WL 6558399 (U.S. Oct. 10, 2023) (mem.); *see also Breeze Smoke, LLC v. FDA*, 142 S. Ct. 638 (2021) (mem.) (denying applica-

tion for stay of FDA's denial, without any recorded dissent).

Reevaluating this case en banc, I would reach the same determination that the merits panel did and deny the petitions for review before us. *See Wages & White Lion Invs., L.L.C. v. FDA*, 41 F.4th 427, 441, 442 (5th Cir. 2022) ("*Wages II*"), *reh'g en banc granted, vacated by* 58 F.4th 233 (5th Cir. 2023). Because the majority opinion arrives at a different conclusion, I respectfully dissent.

I. Statutory, Regulatory, and Procedural Background

Before turning to the majority opinion's conclusions, it is worth briefly reviewing the relevant statutory, regulatory, and procedural background of this case.

As previously noted, Congress passed the TCA in 2009 in an effort to protect all Americans, and particularly children, from the health detriments of tobacco. *See, e.g.*, TCA § 2(34), 123 Stat. at 1779 ("Because the only known safe alternative to smoking is cessation, interventions should target all smokers to help them quit completely."); TCA § 2(1), 123 Stat. at 1777 ("The use of tobacco products by the Nation's children is a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults."). Congress decided that the FDA has the necessary "scientific expertise to . . . evaluate scientific studies supporting claims about the safety of products[] and to evaluate the impact of labels, labeling, and advertising on consumer behavior in order to reduce the risk of harm and promote understanding of the impact of the product on health." TCA § 2(44), 123 Stat. at 1780.

Accordingly, Congress gave broad authority to the FDA to regulate tobacco products, requiring that most "new tobacco product[s]" receive authorization from the FDA prior to marketing. 21 U.S.C. § 387j(a)(2)(A). The TCA applies to "all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco" as well as "any other tobacco products that the [FDA] Secretary by regulation deems to be subject to this subchapter." *Id.* § 387a(b). In 2016, the FDA used that discretion to deem e-cigarettes as tobacco products subject to the requirements of the TCA. Deeming Rule, 81 Fed. Reg. 28974.

Under the Deeming Rule, manufacturers must submit PMTAs to the FDA for any flavored e-cigarettes and their component parts, such as the e-liquids manufactured by Petitioners. The majority opinion is a switcheroo from the statute: the TCA *requires* the FDA to *deny* any PMTA if the applicant cannot show that marketing such a tobacco product "would be appropriate for the protection of the public health [APPH]." 21 U.S.C. § 387j(c)(2)(A). In determining whether a product is APPH, the FDA must consider "the risks and benefits to the population as a whole." *Id.* § 387j(c)(4). This includes considering "the increased or decreased likelihood that existing users of tobacco products will stop using such products," *id.* § 387j(c)(4)(A), as well as "the increased or decreased likelihood that those who do not use tobacco products will start using such products," *id.* § 387j(c)(4)(B). The FDA must make this determination "on the basis of well-controlled investigations" or other "valid scientific evidence" that, in the FDA's discretion, is "sufficient to evaluate the tobacco product." *Id.* § 387j(c)(5). Thus, the FDA must use its science to

evaluate the applications and cannot grant an insufficient PMTA.

Although the Deeming Rule was set to go into effect in August 2016, various events pushed out its final deadline until September 2020. In the intervening years, more information came to light regarding the prevalence of and dangers associated with e-cigarette use, particularly by youth. In case there were any doubts about the deleterious effects of e-cigarettes, research into the use of such devices has made several things clear: (1) e-cigarette usage entails myriad health risks, including lifelong addiction to e-cigarettes or traditional cigarettes, lung disease, and attention and learning deficits; (2) in most instances the use of, and addiction to, tobacco products begins during adolescence; and (3) e-cigarettes are the most popular tobacco product among youth, with flavored e-cigarettes having particular appeal.

E-cigarettes thus pose a significant public health risk, particularly to children. Concerningly, the FDA observed a "dramatic increase in the prevalence of [e-cigarette] use among U.S. youth in 2018," which caused the FDA Commissioner to label the problem a "youth vaping epidemic." The FDA responded by increasing enforcement efforts, particularly against nontobacco and non-menthol flavored e-cigarettes. In 2020, the FDA issued a guidance document announcing its new priorities and describing the underlying evidence showing that flavors were a key driver of increased youth use of e-cigarettes. FDA, "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and

Other Deemed Products on the Market Without Premarket Authorization" ("January 2020 Guidance").[3]

On September 9, 2020, Petitioners submitted PMTAs to the FDA seeking permission to market various flavored e-cigarette products. In September 2021, the FDA reviewed these PMTAs and issued MDOs to Petitioners. As to Triton, the FDA explained the "key basis" for its denial was that its "PMTAs lack[ed] sufficient evidence demonstrating that [its] flavored [e-cigarettes] will provide a benefit to adult users that would be adequate to outweigh the risks to youth." Vapetasia received a similar explanation. The FDA further elabo-

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[3] The majority opinion suggests that the January 2020 Guidance "did not apply to [P]etitioners or their liquids" because "Petitioners do *not* make e-cigarettes, vape pens, vape pods, vape cartridges or any other vaping device covered by the January 2020 Enforcement Guidance," but then cites to the January 2020 Guidance as evidence of FDA's positions on the public health standard as applied to e-cigarettes. Like the majority opinion, I find value in the January 2020 Guidance as an expression of the FDA's views on topics relevant to its assessment of whether Petitioners' products were APPH, particularly regarding the heightened risk that flavored products pose to kids. The January 2020 Guidance focused on closed-system devices, which generally come with prefilled e-liquid cartridges that are replaced after the e-liquid runs out, whereas Petitioners market flavored e-liquids that can be used to refill open-system products. However, in response to the FDA's increased enforcement efforts against flavored closed-system devices, youth responded by migrating to other device types that also had flavored e-liquids. Specifically, "when FDA changed its enforcement policy to prioritize pod-based flavored ENDS, which were most appealing to youth at the time, [it] subsequently observed a substantial rise in use of disposable flavored [e-cigarettes]—a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users." Thus, the FDA identified the "fundamental role of flavor" of any kind in driving youth appeal to e-cigarettes.

rated on its reasoning in technical project lead reports ("TPLs") it provided to Petitioners.

Petitioners timely sought review of the FDA's denials in our court. Triton moved for a stay, and the two cases were consolidated for appeal. A motions panel granted Triton's motion for a stay in October 2021, *Wages & White Lion Invs., L.L.C. v. FDA*, 16 F.4th 1130, 1144 (5th Cir. 2021) ("*Wages I*"), before a merits panel denied the petitions for review in July 2022, *see Wages II*, 41 F.4th at 442. Petitioners subsequently submitted petitions for panel rehearing and rehearing en banc. The merits panel denied the petition for panel rehearing by equal vote,[4] before we ordered the case be reheard en banc.

II. The FDA Did Not Act Arbitrarily and Capriciously

Our duty in this case is to determine whether the FDA's denials of Petitioners' PMTAs were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *See* 21 U.S.C. § 3871(b); 5 U.S.C. § 706(2)(A). The scope of our review is very narrow. *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins.*, 463 U.S. 29, 43 (1983). Critically, "[i]t is not our job as a reviewing court to redo an agency's evaluation of relevant evidence." *Avail Vapor*, 55 F.4th at 427. We are "not to substitute [our] judgment for that of the agency" and must "uphold a decision of less than ideal clarity if the agency's path may reasona-

[4] By the time all of this came into play, one of the members of the merits panel who had joined in the majority opinion had resigned from our court. Thus, the merits panel had only the original author of the majority opinion and the author of the dissenting opinion who, unsurprisingly, did not agree.

bly be discerned." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 513 (2009) (quotations omitted).

The majority opinion takes issue with two aspects of the FDA's review: (1) the evidentiary standards applied to Petitioners' PMTAs, and (2) the FDA's approach towards Petitioners' marketing plans. Both were reasonable exercises of the agency's authority.

A. Evidentiary Standards

Unlike every other circuit that has ruled on this issue,[5] the majority opinion concludes that the FDA changed

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[5] *See Magellan Tech.*, 70 F.4th at 630 ("Given that the FDA did not impose a new evidentiary standard on Magellan, the FDA did not need to provide notice or consider its reliance interests" and thus "the FDA did not act arbitrarily or capriciously."); *Liquid Labs*, 52 F.4th at 541 ("[T]he FDA did not "reverse course" and newly require randomized controlled trials and/or longitudinal cohort studies, and therefore did not upset Liquid Labs' reliance interests, provide inadequate notice, or act arbitrarily and capriciously."); *Avail Vapor*, 55 F.4th at 421 ("[W]e join the majority of our sister circuits in finding that FDA neither changed the standard nor the types of evidence required."); *Breeze Smoke*, 18 F.4th at 507 ("[T]he FDA's 2019 language and its 2021 order likely did not fail to consider reliance interests, . . . and did not introduce a new standard of review in adjudication such that it likely deprived Breeze Smoke of fair warning."); *Gripum*, 47 F.4th at 560 (agreeing with Sixth Circuit and D.C. Circuit that FDA did not shift its evidentiary standard); *Lotus Vaping Techs.*, 73 F.4th at 673 ("[T]he agency consistently advised that, in the absence of long-term data, it might rely upon sufficiently robust and reliable other evidence" and "did not act arbitrarily or capriciously by concluding that Petitioners' evidence fell short of that standard."); *Prohibition Juice*, 45 F.4th at 20 ("We hold that the FDA did not misdirect applicants."). Even the Eleventh Circuit's decision in *Bidi Vapor* was limited to consideration of the FDA's approach to the marketing and sales-access-restriction plans, and the opinion did not address the FDA's position on evidentiary require-

the evidentiary standards it applied to flavored e-cigarettes between the pre-MDO guidance and the denials of Petitioners' PMTAs. In reality, however, the FDA consistently communicated the evidentiary standard that it would apply to all PMTAs for flavored e-cigarettes, applied that standard to Petitioners' PMTAs, and rightfully concluded that Petitioners' applications did not meet it and thus must be denied—all in accordance with its mandate under the TCA.

1. Pre-MDO Communications

First and foremost, the FDA consistently communicated that it would conduct a case-by-case determination of each PMTA pursuant to the standard mandated by the TCA. *See* 21 U.S.C. § 387j(c) (PMTAs must present "well-controlled investigations" or other "valid scientific evidence" showing that "permitting such tobacco product to be marketed would be appropriate for the protection of the public health"); *see also* FDA, Premarket Tobacco Product Applications and Recordkeeping Requirements, Proposed Rule, 84 Fed. Reg. 50566, 50619 (Sept. 25, 2019) ("September 2019 Proposed Rule") ("FDA will determine . . . whether the available evidence, when taken as a whole, is adequate to support a determination that permitting the new tobacco product to be marketed would be APPH."). Each guidance documented cited by the majority opinion makes clear that the recommendations contained therein extend only insofar as they further the statutory requirements. *See, e.g.*, FDA, Premarket Tobacco Product Application Content Overview (Oct. 23, 2018), https://

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ments for PMTAs. *See Bidi Vapor LLC*, 47 F.4th at 1195 (holding limited to consideration of marketing and sales-access-restriction plans).

perma.cc/BV8DHR7H ("October 2018 Guidance") at 3-5, 31-32 (outlining statutory requirements); FDA, Premarket Tobacco Product Application (PMTA) Review Pathway, at 20 (Oct. 28, 2019), https://perma.cc/9S7Z-JQX8 ("October 2019 Guidance") at 5-6 (same); FDA, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry" ("June 2019 Guidance") at 10 ("FDA will review an ENDS PMTA consistent with the requirements of section 910(c) of the FD&C Act."); 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 Tobacco Products Submitted (Sept. 9, 2021), https://perma.cc/4F69-MRUB ("As we have said before, the burden is on the applicant to provide evidence to demonstrate that permitting the marketing of their product meets the applicable statutory standard."). As such, any suggestion that the FDA was required to accept evidence it deemed unsatisfactory under the TCA requirements "neglect[s] the forest for the trees." *See Avail Vapor*, 55 F.4th at 419.

In advance of the September 2020 deadline, as the FDA continued to gather more information about youth e-cigarette use, the agency made clear that the bar of "valid scientific evidence" was a high one. The FDA issued a document containing "Nonbinding Recommendations"[6] in June 2019 that stated, "[n]onclinical studies

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[6] The majority opinion suggests that, although it is "unquestionably true that the pre-MDO guidance documents had all manner of disclaimers, qualifiers, and cautionary language," the FDA cannot "deny that it changed its position based on th[at] qualified language." As detailed herein, the evidentiary standards that the

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." June 2019 Guidance at 12; *see also id.* at 34 (same). However, "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 is an established body of evidence regarding the health impact (individual or population) of [the] product or a similar product that can be adequately bridged to [the] product." *Id.* at 46. In order to demonstrate APPH, the June 2019 Guidance also recommended "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." *Id.* at 13. As such, the FDA made clear that evidence of comparisons between flavored and non-flavored e-cigarette products was a recommended part of a PMTA.

FDA applied to Petitioners' PMTAs align with the pre-MDO guidance, so the FDA did not change its position. The conditional language used by the FDA in its nonbinding guidance documents indicates that it never guaranteed that a certain type of evidence would be sufficient. This is a reasonable position, particularly in such a rapidly evolving area of public health concern. The cases cited by the majority opinion are inapposite. *See Physicians for Soc. Resp. v. Wheeler*, 956 F.3d 634, 646 (D.C. Cir. 2020) (explaining the EPA fully acknowledged it had changed its position and that the point of contention was whether EPA sufficiently acknowledged the reasons underlying its change in course); *Southwest Airlines Co. v. FERC*, 926 F.3d 851, 858 (D.C. Cir. 2019) (holding that "the Commission's ***consistent practice***, whether adopted expressly in a holding or established impliedly through repetition, sets the baseline from which future departures must be explained" (emphasis added)).

Notably, although the FDA never required (and still does not require) any specific type of study, it also never said that nonclinical studies *would be* sufficient to support a PMTA. Rather, the FDA has always suggested and continues to suggest that such studies might be useful, in particular where, as here, the evidence presented in a PMTA is otherwise weak. *See, e.g.*, October 2018 Guidance ("[I]t *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." (emphasis added)); June 2019 Guidance at 13 ("In addition, nonclinical in vitro assays that assess the toxicities that are seen following long-term use of tobacco products *may be* supportive of these clinical assessments." (emphasis added)), 12 (FDA "intends to review" non-clinical evidence), 47 ("Published literature reviews (including meta-analysis) or reports *may be* acceptable to support a PMTA, but are considered a less robust form of support for a PMTA." (emphasis added)); Premarket Tobacco Product Applications and Recordkeeping Requirements (Final Rule), 86 Fed. Reg. 55300, 55387 (Oct. 5, 2021) ("FDA *does not expect* that long-term clinical studies will need to be conducted for each PMTA; instead, it *expects* that it should be able to rely on other valid scientific evidence to evaluate some PMTAs." (emphasis added)). Ultimately, while the FDA "broadened the types of evidence it would consider" beyond just randomized controlled trials or longitudinal studies, it also "made clear it would not relax the scientific rigor of the requisite public health demonstration." *Prohibition Juice*, 45 F.4th at 21.

To summarize, leading up to the September 2020 deadline, the FDA published nonbinding guidance to

give applicants an insight into what the PMTA review would look like, namely: (1) a case-by-case assessment, (2) guided first and foremost by statutory requirements, with (3) the burden on applicants to provide (4) valid scientific evidence (likely in the form of randomized control trials or longitudinal studies, although other forms of similarly robust and reliable evidence *may be* sufficient) (5) showing that the public health benefits of their specific products outweighed the risks.

2. Application to Petitioners' PMTAs

Then, the FDA applied that standard to Petitioners' applications. The FDA considered whether Petitioners' PMTAs demonstrated "potential benefits to smokers from marketing [the] products with robust and reliable evidence" that was "significant enough to overcome the risk to youth." Because flavored e-cigarettes present a disproportionately high risk to children, the risk to youth was higher for Petitioners' products than for similar menthol- or tobacco-flavored e-cigarettes. The FDA rightfully factored that into its review by examining whether the applications had "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."

The FDA reasonably concluded Petitioners did not submit sufficiently robust and reliable scientific evidence to demonstrate the requisite benefit.[7] According

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[7] This appeal was filed more than two years ago. At the time it was filed, the Petitioners contended they were not given the time to do the studies the FDA sought. Thus, they originally asked this court alternatively to "vacate the MDOs and enjoin FDA from taking

to Petitioners' PMTAs, "[t]he most important consideration in deciding whether e-cigarettes produce a public health benefit is determining if using e-cigarettes is an effective cessation method for combustible cigarette use." Both Petitioners submitted a variety of published studies and articles discussing topics relevant to the APPH determination. However, Petitioners admitted their own literature reviews found "not enough evidence from well-designed studies to determine whether e-cigarette flavors aid in smoking cessation."

Vapetasia also submitted a cross-sectional survey as part of its PMTA, which the FDA similarly found did not change the risk-benefit balance. The panel opinion summarized why that was a reasonable conclusion:

> [The] survey suffered from several methodological flaws: (1) only 294 people were surveyed; (2) the survey respondents are all Vapetasia customers; and (3) it's not clear how these individuals were selected to take the survey.[] In other words, there were strong reasons to doubt the survey's results. The FDA therefore did not act arbitrarily in concluding

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further adverse action on Petitioners' PMTAs for 18 months if Petitioners will be required to conduct long-term studies to demonstrate comparative efficacy going forward." Given that this case and the "18 month request" were filed more than two years ago, Petitioners now have had plenty of time. Indeed, during that time, they could have reapplied to the FDA with whatever information they gathered. Yet, to my knowledge, and based on the lack of any information to the contrary from the Petitioners, the Petitioners have submitted no additional evidence during that time to the FDA. Given the majority opinion's remand, the Petitioners certainly will not have an argument about a lack of time.

> that Vapetasia's survey "is not sufficient to show a benefit to adult smokers."

Wages II, 41 F.4th at 436 (footnote omitted).

In both Petitioners' MDOs, the FDA explained that this evidence was not sufficient to make the requisite showing under the TCA:

> 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. We did not find such evidence in your PMTA[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.

The FDA provided an additional explanation for Vapetasia:

> Although your PMTAs contained a cross-sectional survey "Vapetasia PMTA Survey and Testimonial", this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s) or evaluate product switching or cigarette reduction resulting from use of these products over time.

The FDA thus reasonably concluded that, as compared to menthol-and tobacco-flavored products, Petitioners' flavored products posed an increased risk in seducing children to start vaping without any evidence of a heightened benefit in helping existing smokers quit. Accordingly, as the FDA said in its briefing, "FDA denied petitioners' applications *not* because they failed to include a randomized controlled trial or longitudinal cohort study but because they failed to include *any* evidence robust enough to carry petitioners' burden under the statute." This outcome is not only reasonable but required under the TCA. *See* 21 U.S.C. § 387j(c).

3. The FDA's Position Has Not Changed

So, where is the switch? The FDA's denials of Petitioners' PMTAs are a product of the same standards that the FDA shared with applicants before the September 2020 deadline and has continued to publicize since then. None of the FDA's communications or actions since September 2020 indicate otherwise.

The majority opinion suggests that the FDA announced a new "scientific-studies-or-bust standard" in an August 2021 press release that said:

> Based on existing scientific evidence and the agency's experience conducting premarket reviews, the

> evidence of benefits to adult smokers for such products would likely be in the form of a randomized controlled trial or longitudinal cohort study, although the agency does not foreclose the possibility that other types of evidence could be adequate if sufficiently robust and reliable.

See 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/LCD8-VWGQ ("Aug. 2021 Press Release"). Setting aside that the FDA has always centered its guidance on the statutory requirement for "valid *scientific* evidence," this statement is simply not a deviation from the guidance quoted above. According to its experience and expertise, the FDA believed randomized control trials or longitudinal cohort studies were most likely to provide persuasive enough evidence of benefits to adult smokers that would outweigh the high risk to youth of flavored e-cigarettes, but it was willing to consider other data if sufficiently robust and reliable. This approach aligns with the TCA and all of the FDA's pre-MDO communications.

The majority opinion faults the FDA for failing to give fair notice that "FDA will deny your application if you do not conduct long-term studies on your specific flavored product." But the FDA has never imposed a requirement for long-term studies, much less a requirement for those studies conducted on Petitioners' specific products. As demonstrated above, the FDA did not reject Petitioners' applications because they lacked a certain type of study on any certain type of product, but

rather because they lacked "*any* evidence robust enough to carry petitioners' burden under the statute."

The majority opinion also says that "[i]n its explanation for denying petitioners' applications, FDA imposed two requirements—randomized controlled trials and longitudinal cohort studies." But even a cursory read of the MDO belies that portrayal:

> 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***.

Contrary to the majority opinion's assertion, this last line cannot possibly be code for a randomized control trial or longitudinal cohort study because it is explicitly presented as an "alternat[e]" option. Nor is this a requirement for long-term scientific studies; rather, it is an emphasis on evidence regarding long-term *impact*. As our sister circuits have stated:

> [T]he "FDA never guaranteed that manufacturers could carry their evidentiary burden under the [Act] without providing long-term data." . . . And by focusing on isolated statements in the 2019 Guidance that the FDA did not expect applicants would need to conduct long-term studies, Petitioners "failed to look

> at the 2019 guidance in any depth," as "[t]he 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*."

Lotus Vaping Tech., 73 F.4th at 672 (quoting *Avail Vapor*, 55 F.4th at 422-23 (brackets in original)).

Indeed, the FDA's interest in long-term impact is rooted in the statutory APPH standard, which requires FDA to consider "the increased or decreased likelihood that existing users of tobacco products will stop using such products." 21 U.S.C. § 387j(c)(4)(A). As we explained in the panel opinion, "[n]othing can 'increase' or 'decrease' in a vacuum." *Wages II*, 41 F.4th at 434. Accordingly, although the FDA imposed no long-term studies requirement, it did emphasize the importance of valid scientific evidence demonstrating long-term impact, which should not have come as a shock to anyone given the comparative efficacy requirements in the TCA.[8]

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[8] The majority opinion states that "there is no question that petitioners compared the health risks of their products to other products as the June 2019 Guidance recommended," pointing to this quote from the FDA's en banc brief:

> Petitioners asserted in their application that "flavors are crucial to getting adult smokers to make the switch and stay away from combustible cigarettes," . . . that adult smokers prefer flavored e-cigarettes to tobacco-flavored e-cigarettes, . . . and that this preference "has powerful implications for not only the role of flavors in helping smokers' transition from smoking to vaping, but also in connection with helping vapers maintain smoking abstinence and preventing relapse to smoking."

Nor does the FDA's denial of all PMTAs it has thus far received for flavored e-liquids indicate that the FDA changed its position. The majority opinion frames this as a "categorical ban" on flavored e-liquids, which it sees as dispositive evidence that the FDA changed its position without fair notice to Petitioners. But this was a case-by-case review (so we should not review ones not before us) and, as stated before, the FDA is not obligated to *grant* but rather obligated to *deny UNLESS* the e-cigarette in question would benefit the adult health well over the harm to the youth health. Thus, there is another more likely explanation: none of these applications had sufficient evidence that their products were APPH ***because flavored e-liquids are not APPH***. That is, the high risk that these products in particular pose to youth—including increased likelihood of starting to use nicotine and tobacco products, becoming addicted, and experiencing other health problems including permanent damage to developing brains—is not out-

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Petitioners' "assert[ions]" are a far cry from valid scientific evidence. Furthermore, even cherry-picking findings from individual studies with no mention of the methodological concerns cannot refute Petitioners' own conclusion that "there is not enough evidence from well-designed studies to determine whether e-cigarette flavors aid in smoking cessation." In other words, the fact that Petitioners presented other scientific evidence in their PMTAs does not mean that such evidence was valid or persuasive. Similarly, just because Petitioners included some "bridging" information in an attempt to connect existing studies about unflavored products to their own flavored products does not mean that evidence was sufficient—indeed, the FDA apparently concluded it was not.

weighed by the benefit they may provide in helping adult smokers quit.[9]

Of course, it is not the court's role to make this determination. Congress has provided that authority to the FDA.[10] Drawing on its scientific expertise (far greater than ours), the FDA has evaluated each PMTA for flavored e-liquids individually and concluded it did not provide sufficient evidence to demonstrate its product was APPH. The agency presumably will continue this case-by-case evaluation, remaining open to the possibility that a PMTA for a flavored e-liquid product could provide sufficiently robust and reliable evidence to tip the APPH balance in favor of approval, unless and until it announces a change in its position.[11] But the FDA is not required to approve an unsatisfactory application to market a flavored e-liquid just to prove that it has not imposed a categorical ban on these products—in fact, it

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[9] No applicant has submitted reliable evidence to the contrary. As mentioned above, the Petitioners have now had plenty of time to get more information but have not, at least based upon the information in our court, bothered to do so.

[10] Contrary to the majority opinion's assertion, it is also neither our nor the FDA's responsibility to "say what 'other evidence' petitioners might have supplied to win approval." As detailed herein, both the statute and the FDA's guidance provide recommendations for what types of valid scientific evidence might be sufficient. But the statute places the burden on ***applicants*** to present such evidence showing their product is APPH, and it requires the FDA to deny any PMTA that fails to do so. *See* 21 U.S.C. § 387j(c)(2)(A).

[11] The majority opinion's statement that a "categorical ban" would have "other statutory problems," including requiring adherence to notice-and-comment obligations, underscores the point that the FDA has never imposed such a ban.

is prohibited by the statute from doing so. *See* 21 U.S.C. § 387j(c).

The majority opinion's portrayal of Petitioners' PMTA denials as a categorical ban on the use of data involving unflavored products in flavored-product PMTAs similarly ignores the facts of this case and the APPH balancing standard mandated by the TCA. The FDA consistently advised applicants that data regarding other products should only be included in a PMTA to the extent it is appropriate to show the product at issue is APPH. *See, e.g.*, October 2018 Guidance at 11 (advising that, if a PMTA "[c]ompare[s] the new tobacco product to a representative sample of tobacco products on the market," it should "[i]nclude justification for why using evidence or data from other products is appropriate"); June 2019 Guidance at 48 (advising applicants who rely on literature reviews to "[p]rovide adequate justification for bridging data from the new product studied to your new product"). Further, as the FDA was acutely aware, the risks associated with flavored products are higher than those associated with non-flavored products, which means evidence of benefits for flavored products must be stronger than for non-flavored products to satisfy the APPH standard. *See* 21 U.S.C. § 387j(c)(2) and (4). That necessarily suggests evidence about the benefits of non-flavored products, by itself, would not be sufficient for the FDA to approve a PMTA for a flavored product. Nevertheless, as promised, the FDA continues to conduct a case-by-case assessment of each PMTA, including whether an applicant has presented sufficiently robust "bridging" evidence justifying its use of other products' data. Based on the

FDA's scientific expertise, Petitioners simply failed to do so here.[12]

In this case, Petitioners failed to show that their products were APPH. As our sister circuits have held, "[t]he Agency's finding that the evidence was insufficiently rigorous does not reflect a changed standard, but the manufacturers' failure to meet the standard the agency consistently applied." *Prohibition Juice*, 45 F.4th at 21; *see also Lotus Vaping Techs.*, 73 F.4th at 673 ("[W]e join the Second, Third, Fourth, Seventh, and D.C. Circuits in determining that the agency consistently advised that, in the absence of long-term data, it might rely upon sufficiently robust and reliable other evidence. The agency did not act arbitrarily or capriciously by concluding that Petitioners' evidence fell short of that standard."). Because "FDA did not 'reverse course' and newly require randomized controlled trials and/or longitudinal cohort studies," we should safely conclude that it "did not upset [Petitioners'] reliance interests . . . or act arbitrarily and capriciously" and deny the petitions. *Liquid Labs LLC*, 52 F.4th at 541.

B. Marketing Plans

The majority opinion also concludes that the FDA acted arbitrarily and capriciously because it entirely failed to consider Petitioners' sales and marketing plans

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[12] Remember, even Petitioners admitted their own literature reviews found "not enough evidence from well-designed studies to determine whether e-cigarette flavors aid in smoking cessation"—a glaring admission to which the majority opinion provides no response.

in its review of their PMTAs, but the record demonstrates that is not the case.

In their PMTAs, Petitioners included summaries of their marketing plans, which provided that their products "w[ould] continue to be strictly marketed and sold to adults in adult-only retailers and through age-verified online websites," and that Petitioners and third parties would not promote these products "on social media, radio or television." Petitioners also averred that they would use "robust age-verification software," such as "a pop-up 'age-gate.'" As part of these age-verification measures, Petitioners also described their implementation of "AgeCheckner.Net . . . which provides state-of-the-art age verification services to online stores that sell age restricted products such as vaporizers and tobacco related products."

In its MDOs and TPLs to Petitioners, the FDA explained that it had reviewed Petitioners' PMTAs, and that its "assessment includes evaluating the appropriateness of the proposed marketing plan[s]." However, in a footnote, the FDA also discussed the fact that, "to date, none of the [e-cigarette] PMTAs that the FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns . . . regarding youth use." Accordingly, the FDA stated, "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."

As the record makes clear, the FDA was not mistaken in its approach to Petitioners' sales and marketing

plans. The FDA determined that it would not fully consider Petitioners' marketing plans in light of the fact that, although "[i]t is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal," it had not once evaluated a marketing plan that actually did so. This conclusion accords with guidance the FDA published in 2020, which noted that youth use of e-cigarettes continued to rise despite the FDA's prior efforts to curb predatory marketing. Based on its expertise, the FDA determined that traditional marketing schemes like those Petitioners submitted —which rely on customers self-verifying their age at the point of sale—are inadequate to prevent young people from starting to use e-cigarettes. Indeed, the FDA explained that, based on "the most recent data that youth use of [e-cigarette] products continues to increase," it "believes that age verification alone is not sufficient to address this issue," and "focusing on how the product was sold would not be sufficient to address youth use of these products." In contrast, the FDA has pointed to proposed plans that use "biometric locking mechanism[s]" to prevent youth use as an example of "novel" marketing plans that could adequately address youth access.

The majority opinion characterizes the FDA as having effectively misled applicants, including Petitioners, as to the potential significance that marketing plans would play in the agency's review of PMTAs. However, this description is at odds with the aforementioned guidance, which provides readers with clear insight into the FDA's data-backed determination that traditional marketing schemes are inadequate to stem the tide of youth misuse of e-cigarettes. *See Prohibition Juice Co.*, 45 F.4th at 25 (highlighting where petitioners'

"plans—to require customers' self-verification of age at the point of sale and to use what they characterize as less vibrant marketing unappealing to youth—track measures the FDA in its 2020 guidance deemed inadequate"); *Lotus Vaping Techs.*, 73 F.4th at 674 (reviewing FDA's 2020 Guidance in the context of petitioners' marketing plan challenge and noting FDA's conclusion that, based on the inadequacies of manufacturers' proposed measures to restrict youth access to e-cigarettes, efforts related to how e-cigarette products are sold are insufficient to deter youth use).

It is certainly true that the FDA previously acknowledged that marketing plans are a relevant factor to its overall review of PMTAs. *See* Premarket Tobacco Product Applications and Recordkeeping Requirements (Proposed Rule), 84 Fed. Reg. 50566, 50581 (Sept. 25, 2019) ("The applicant's marketing plans will help FDA determine whether permitting the marketing of the new tobacco product would be [appropriate for the protection of public health]"); Premarket Tobacco Product Applications and Recordkeeping Requirements (Final Rule), 86 Fed. Reg. 55300, 55324 (Oct. 5, 2021) ("FDA has rationally concluded that the required descriptions of marketing plans will directly inform . . . its consideration of the potential impact on youth initiation and use."). However, these acknowledgments do not obviate the clear "Guidance for Industry" the FDA provided in 2020 that traditional marketing plans would be inadequate for purposes of PMTAs. Put differently, what the FDA made clear through its various announcements was that marketing plans were *necessary* for PMTAs, but traditional marketing plans were not *sufficient* to justify approval of such applications. This is a particularly salient distinction in the context of flavored e-cigarettes,

where an incremental decrease in the alarmingly high risk to youth cannot compensate for the utter lack of evidence of the product's benefits.

If the FDA had not actually reviewed *any* documentation regarding the content of the marketing plans, the FDA arguably could not have known that Petitioners' plans aligned with the traditional, ineffective plans and were not unique. But that is not the case here. Rather, the FDA clarified at oral argument that it *did* review summaries of Petitioners' marketing plans contained within their PMTAs, and thus reasonably concluded that Petitioners' plans contained no novel proposals that would have changed FDA's analysis. *See Wages II*, 41 F.4th at 441.

Of course, we do not accept post hoc justifications for agency actions, and the FDA "must defend its actions based on the reasons it gave *when it acted*." *Dep't of Homeland Sec. v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020) (emphasis added). But the FDA's explanation at oral argument is not the same as a situation in which an agency submits an *entirely new*, post hoc argument for why a previous action was justified. On the contrary, in its MDOs and TPLs, the FDA explained that its "evaluation of the marketing plans in applications will not occur at this stage of review" only after *separately* stating that its "assessment [of PMTAs] includes evaluating the appropriateness of the proposed marketing plan." The FDA had clearly stated that it reviewed the PMTA; that document clearly includes a summary of the marketing. Within the context of these two, at-first-seemingly contradictory stances, the FDA's oral argument statements are not a newly fabricated post hoc justification but instead a *clarification* of

the FDA's approach to reviewing marketing materials (i.e. reviewing the marketing plan summaries rather than the full marketing plans themselves).

This clarification is not inconsistent with the FDA's explanations in the MDOs and TPLs, and the panel opinion properly considered it. Indeed, this is exactly the type of factual clarification we seek at oral argument. *See, e.g.*, *Cooper Cameron Corp. v. U.S. Dep't of Lab., OSHA*, 280 F.3d 539, 542 (5th Cir. 2002) ("Given the gaps in the record, we attempted to clarify at oral argument what kinds of documents OSHA had withheld . . . Counsel for the DOL, to his credit, conceded that the withheld material included some newspaper articles."); *Schofield v. Saul*, 950 F.3d 315, 322 (5th Cir. 2020) (noting that counsel at oral argument asserted the agency had not relied on the decision of the appeals council, so the panel declined to consider it); *Pennzoil Co. v. FERC*, 789 F.2d 1128, 1139 & n.28 (5th Cir. 1986) (relying on FERC counsel's responses to questions at oral argument when concluding that the FERC Commissioner decided the case at issue on procedural grounds).[13] Other circuit courts facing cases similar to this have also taken into consideration the explanations

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[13] The majority is correct that none of these cases stands for the proposition that an agency can use oral argument to provide post hoc rationalizations that contradict its past positions; that is because, as we clearly state herein, an agency is not permitted to do so. *See Regents of the Univ. of Cal.*, 140 S. Ct. at 1909. But the FDA did not do that in this case. Here, the FDA made two seemingly contradictory express statements in the record: first, it said that it reviewed the PMTA, which included a summary of the marketing plan; then, it said that it did not evaluate any marketing plan submitted with the application during its review. The oral argument comments simply clarified this point.

and other concessions made during oral arguments. *See, e.g.*, *Avail Vapor, LLC*, 55 F.4th at 425 (discussing the FDA's explanation "in oral argument" that "a PMTA is like a driver's test, in that it has two components"); *Bidi Vapor LLC*, 47 F.4th at 1208 (distinguishing the case before the court with this case while noting that "the statements made before the Fifth Circuit at oral argument by the [FDA] . . . were not made before this Court").

Common sense makes clear that we must be able to consider these types of clarifications—otherwise, we should have far fewer oral arguments. Put simply, we are free, and indeed often choose, to ask questions of agencies during oral argument and account for their answers that are consistent with or explain the evidence. This process allows us to ground our conclusions in the most-accurate facts of a given case. Doing so here makes clear that the FDA's approach to Petitioners' marketing plans was not arbitrary and capricious.

* * *

The facts of this case and the applicable law, as confirmed by our sister circuits, make the conclusion in this case clear: the FDA properly fulfilled its statutory mandate by considering the relevant portions of Petitioners' PMTAs and coming to a reasonable conclusion that marketing Petitioners' products is not appropriate for public health. Because the majority comes to a different conclusion, I respectfully dissent.

JAMES E. GRAVES, JR., *Circuit Judge*, joining the dissent in part:

I agree with the dissent that the FDA did not act arbitrarily or capriciously when it denied Petitioners' Premarket Tobacco Product Applications. I also agree with most, but not all, of the dissent's analysis. I write separately as to the FDA's treatment of Petitioners' sales and marketing plans.

In determining "whether the marketing of a tobacco product . . . is appropriate for the protection of the public health," the FDA must consider (A) the "increased or decreased likelihood that existing users of tobacco products will stop using such products" and (B) "the increased or decreased likelihood that those who do not use tobacco products will start using such products." 21 U.S.C. § 387j(c)(4)(A)-(B). It is the applicant's burden to demonstrate to the FDA that its product meets that standard. § 387j(c)(2)(A); *see supra* at 58. As to part (B) in this case, Petitioners were required to submit a marketing plan to explain to the FDA how they would avoid attracting new or youth tobacco users. *See*, *e.g.*, 84 Fed. Reg. 50581.

I fully agree with the dissent that the FDA correctly concluded that Petitioners failed to present any satisfactory evidence as to part (A). The issue, then, is whether the FDA acted arbitrarily and capriciously by failing to consider the marketing plans that Petitioners submitted to satisfy part (B). The majority concludes that the FDA did not consider the plans, and that its decision not to do so was arbitrary and capricious. The dissent concludes that the FDA *did* consider the plans, and that the FDA's experience with, and data about, similar marketing plans was a sufficient basis on which to deny them.

The majority correctly concludes that the FDA did not consider the marketing plans to any significant degree. The FDA told Petitioners as much when it denied their applications, writing that "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."

The dissent concludes that the FDA clarified at oral argument that it reviewed summaries of Petitioners' marketing plans, and from the summaries could tell that the plans were inadequate. I agree that this court may, and often does, seek clarification at oral argument. But the FDA's statement does not clarify. Among other things, the statement raises the question of why, if the FDA did review the summaries, it told Petitioners that it had "not evaluated any marketing plans." As it stands, the FDA's statement at oral argument is at odds with the record. For that reason alone, the court should disregard it.

Nor can I agree that the FDA would have been justified to "not fully consider" the marketing plans because its data and experience showed that traditional marketing schemes, generally, are not adequate to curb youth access to e-cigarettes. Just because no applicant has introduced a satisfactory marketing scheme does not mean that one cannot exist. Moreover, as the dissent notes, 21 U.S.C. § 387j(c)(2) sets forth a framework for case-by-case analysis of applications. While general scientific understanding of the dangers of flavored tobacco products will no doubt inform the FDA's consideration of each application, the agency also must not re-

ject a marketing plan on the basis that it judged some other plans to be deficient.

In my view, however, the FDA correctly declined to evaluate the marketing plans. It appears that only the Eleventh and Fourth Circuits have reached the merits of this issue. The Eleventh Circuit concluded that the FDA's decision not to review the plans was arbitrary and capricious because the FDA represented that the plans were "critical" and "necessary." *Bidi Vapor LLC v. FDA.*, 47 F.4th 1191, 1203-04 (11th Cir. 2022).

The Fourth Circuit reached the opposite conclusion. It analogized:

> [A Premarket Tobacco Product Application] 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.

Avail Vapor, LLC v. FDA, 55 F.4th 409, 425 (4th Cir. 2022).

That analogy is apt because part (A) and part (B) are "pass-fail" tests—an applicant either satisfies them or it does not—that are bound by the conjunctive "and," such that each represents a "critical" and "necessary" showing that is nevertheless insufficient on its own to carry an applicant's burden.

The majority poses a hypothetical involving an application for an e-cigarette product "that gets only one existing smoker to quit, but has a marketing plan so restrictive that no non-smokers could access it and use it to start vaping." *Supra* at p. 50. The majority reasons that such a product would seemingly score poorly on part (A) of the test, but that because of its obvious public health benefit, the FDA "could not reject a PMTA for it." *Id.* But that hypothetical fails to capture the essence of § 387j(c)(2), which concerns long-term "risks" and "likelihoods" and is necessarily predictive. When an applicant submits its application, no one knows for certain whether its product will cause one smoker or 100,000 smokers to quit smoking; the best an applicant can do is present scientific evidence to aid the FDA in making a prediction. If an applicant furnishes enough evidence to support "the increased . . . likelihood that existing users of tobacco products will stop using such products," part (A) is satisfied. If not, the applicant fails part (A), and consequently, the larger test.

Here, Petitioners failed to submit reliable evidence that their products provide any benefit to adult smokers. Once the FDA made that determination, Petitioners' marketing plans, and any other aspect of part (B), became irrelevant, because even the most promising plans would not have helped them show that their products are appropriate for the protection of the public

health. For that reason alone, the FDA's decision not to review the plans was justified. There was no error.

In sum, the FDA did not act arbitrarily or capriciously when it denied Petitioners' applications.

APPENDIX B

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

No. 21-60766

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

CONSOLIDATED WITH

No. 21-60800

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION;
VAPETASIA, L.L.C., PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

[Filed: July 18, 2022]

Petitions for Review of an Order of the
Food and Drug Administration

Before JONES, HAYNES, and COSTA, *Circuit Judges*.

HAYNES, *Circuit Judge*:

Petitioners Wages and White Lion Investments, LLC, d/b/a Triton Distribution ("Triton") and Vape-

tasia, LLC ("Vapetasia") sought to market flavored nicotine-containing e-liquids for use in open-system e-cigarette devices. To do so, Petitioners needed to submit premarket tobacco product applications as required by 21 U.S.C. § 387j—which the Food and Drug Administration ("FDA") deemed applicable to e-cigarette tobacco products in 2016. FDA denied the requested marketing authorizations, finding that Petitioners failed to offer reliable and robust evidence (such as randomized controlled trials or longitudinal studies) to overcome the risks of youth addiction and show a benefit to adult smokers.

Petitioners seek review of those marketing denial orders ("MDOs"), and prior to the consolidation of the two cases, Triton requested a stay pending that review. Without (of course) the benefit of full merits briefing, a prior panel of this court granted the stay, determining (as any court granting a stay application must determine) that there was "a strong likelihood of success on the merits." *Wages & White Lion Invs., L.L.C. v. FDA*, 16 F.4th 1130, 1136, 1144 (5th Cir. 2021). But having now had the opportunity to review the merits briefing followed by oral argument, we DENY the petitions for review.

I. Statutory & Regulatory Landscape

To fully appreciate the events that gave rise to the petitions before us, we begin with a careful review of the statutory and regulatory background. Nearly a century ago, Congress passed the Food, Drug, and Cosmetics Act ("FDCA"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 301, *et seq.*), which established broad regulatory authority—such as a premarket "new drug" authorization requirement—to protect the public

against the dangers of "adulterated and misbranded food, drugs, devices, and cosmetics." 52 Stat. at 1040, 1052; *see generally id.* at 1040-59.

The FDCA developed substantially over the next fifty-eight years, but tobacco remained unregulated through the Act and its accompanying regulations. That is, until 1996, when FDA determined that it could regulate tobacco given its existing authority to regulate drugs and devices. Nicotine in Cigarettes and Smokeless Tobacco Is a Drug, 61 Fed. Reg. 44,619 (Aug. 28, 1996). "Like the products that FDA traditionally regulates," tobacco products are "placed within the human body; like many of these products, they deliver a pharmacologically active substance to the bloodstream; and like these products, they have potentially dangerous effects. Indeed, no products cause more death and disease. . . . " *Id.* at 44,628. On that basis, FDA determined that it had jurisdiction to regulate tobacco products. *Id.*

The Supreme Court disagreed. In a landmark decision, the Court held that "Congress . . . precluded the FDA's jurisdiction to regulate tobacco products." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). The Court's reasoning centered on Congress's failure to amend the FDCA to give FDA that authority, Congress's enactment of several tobacco statutes, and FDA's prior assertion that it lacked jurisdiction. *Id.* at 155-57. Following *Brown & Williamson Tobacco Corp.*, if Congress wanted FDA to regulate tobacco, it would have to grant the agency that authority expressly.

So Congress did precisely that. In 2009, it passed the Family Smoking Prevention and Tobacco Control

Act ("TCA"), Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified at 21 U.S.C. § 387, *et seq.*), which amended the FDCA to include the regulation of tobacco. Section 2 of the Act laid out myriad congressional findings, which pointed to the dangerous effects of tobacco on both adults and children. *See, e.g.*, TCA § 2(34), 123 Stat. at 1779 ("Because the only known safe alternative to smoking is cessation, interventions should target all smokers to help them quit completely."); *id.* § 2(1), 123 Stat. at 1777 ("The use of tobacco products by the Nation's children is a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults."). "Obviously," given the extensive congressional record, "the TCA's purpose sounds in (1) protecting public health and (2) preventing young people from accessing (and becoming addicted to) tobacco products." *Big Time Vapes, Inc. v. FDA*, 963 F.3d 436, 444 (5th Cir. 2020), *cert. denied*, 141 S. Ct. 2746 (2021) (mem.).

Congress also found that FDA had the relevant "scientific expertise to . . . evaluate scientific studies supporting claims about the safety of products[] and to evaluate the impact of labels, labeling, and advertising on consumer behavior in order to reduce the risk of harm and promote understanding of the impact of the product on health." TCA § 2(44), 123 Stat. at 1780. To that end, Congress gave FDA broad authority to regulate tobacco products, requiring that most "new tobacco product" receive authorization from the FDA prior to marketing. 21 U.S.C. § 387j(a)(2)(A).

The TCA defines "new tobacco product" (in relevant part) as "any tobacco product . . . that was not commercially marketed in the United States as of February

15, 2007." *Id.* § 387j(a)(1)(A). The Act lists specific categories of tobacco products subject to regulation—"all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco"—but it also provides that the Act will apply "to any other tobacco products that the Secretary by regulation deems to be subject to this subchapter." *Id.* § 387a(b).[1] In 2016, FDA used that authority to deem e-cigarettes and their component parts (including e-liquids) as tobacco products subject to the requirements of the TCA. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, 81 Fed. Reg. 28,974 (May 10, 2016) ("Deeming Rule").[2]

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[1] We recently rejected the argument that this provision constitutes an unlawful delegation of congressional power. *Big Time Vapes*, 963 F.3d at 447. In reaching that decision, this court extensively examined the TCA's purpose and relevant background. *Id.* at 444.

[2] As Petitioners showcased at oral argument, e-cigarettes can come in various forms. FDA provided a helpful explanation in its briefing:

> Some devices have "pods" or "cartridges" that hold nicotine-containing liquid known as "e-liquid." Some pods or cartridges (known as closed systems) come pre-filled with e-liquid and are replaced after the e-liquid is used up, while others (known as open systems) can be refilled by the user. Tank or "mod" (short for "modifiable") devices can also be refilled by users and are also usually customizable. Disposable e-cigarettes come prefilled with the e-liquid, and the entire device is designed to be discarded after the e-liquid runs out.

Collectively, these devices are referred to as electronic nicotine delivery systems ("ENDS"), but the term "ENDS" is sometimes used interchangeably with e-cigarettes. We mimic one of our sister courts in simply using the term "e-cigarettes" for ease of reference. *See Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 273 n.1 (D.C. Cir. 2019)

Relevant here, the Deeming Rule subjected e-cigarette manufacturers to the TCA's prior authorization requirement—manufacturers of "new tobacco product[s]" must submit premarket tobacco product applications ("PMTAs"). *See* 21U.S.C. § 387j(a)(2). FDA reviews the PMTAs and is statutorily required to decline them if "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." *Id.* § 387j(c)(2)(A). In determining whether a product is appropriate for the protection of the public health (referred to as the "APPH" standard), FDA must consider "the risks and benefits to the population as a whole." *Id.* § 387j(c)(4). This includes considering "the increased or decreased likelihood that existing users of tobacco products will stop using such products," *id.* § 387j(c)(4)(A), as well as "the increased or decreased likelihood that those who do not use tobacco products will start using such products," *id.* § 387j(c)(4)(B).

The Deeming Rule was set to go into effect on August 8, 2016, but FDA delayed enforcement of the regulation as to existing e-cigarette manufacturers. 81 Fed. Reg. at 28,977. Instead, manufacturers would have a two- to three-year period to come into compliance. *Id.* at 28,977-78. In 2017, the FDA pushed that deadline to 2022.[3] But shortly after extending the deadline, the

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("We use the term 'e-cigarettes' to refer to the full range of products that the Industry calls 'vapor products' and the FDA calls Electronic Nicotine Delivery Systems, or ENDS. They go by many other names as well. . . . ").

[3] FDA, Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry

American Academy of Pediatrics sued the FDA for granting the extension. *See Am. Acad. of Pediatrics v. FDA*, 399 F. Supp. 3d 479 (D. Md. 2019). A federal court vacated FDA's 2017 guidance and required FDA to set a new deadline at ten months after the issuance of its order. *Id.* at 480-81, 487. The deadline shifted once again due to the COVID-19 pandemic, making the final deadline September 9, 2020.

II. The Petitions

Waiting to file until the deadline date, on September 9, 2020, Petitioners submitted PMTAs in an effort to manufacture and sell various flavored e-cigarette products.[4] Specifically, they sought approval for products that came in flavors like sour grape, pink lemonade, crème brulee, peachy strawberry, milk & cookies, and pound cake and with names such as "Jimmy The Juice Man Strawberry Astronaut" and "Suicide Bunny Bunny Season."

On September 14 and 16, 2021, FDA issued marketing denial orders to Petitioners. FDA listed the following as the "key basis" for Triton's MDO (with emphasis on the language Petitioners take issue with):

> 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

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5 (2020) ("2020 Guidance"), https://www.fda.gov/media/133880/download.

[4] Triton and Vapetasia submitted nearly identical PMTAs because Triton operates as a contract manufacturer for Vapetasia and the two worked together extensively (as they continue to do in this litigation). Triton prepared Vapetasia's PMTAs, and the two jointly filed Vapetasia's petition for review.

> 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. We did not find such evidence in your PMTA[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.

Vapetasia received a very similar basis for denial, but for Vapetasia, FDA added:

> Although your PMTAs contained a cross-sectional survey "Vapetasia PMTA Survey and Testimonial", this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s) or evaluate product switching or cigarette reduction resulting from use of these products over time.

Along with each MDO, FDA provided a Technical Project Lead report that described their reasoning in much greater detail.

Petitioners timely sought review of the MDOs in this court. They argue, primarily, that FDA lacks the authority to impose a comparative efficacy requirement and that FDA acted arbitrarily and capriciously by "requiring" scientific studies. Triton moved for a stay. After the stay was granted, the two cases were consolidated for appeal.

III. Jurisdiction & Standard of Review

We have jurisdiction under 21 U.S.C. § 387*l*(a)(1)(B), which authorizes federal court review of the denial of premarket tobacco product applications in a U.S. Court of Appeals "for the circuit in which" the individual or entity that received such a denial "resides or has their principal place of business." Triton's principal place of business is Richardson, Texas, giving us jurisdiction over its petition and the petition it jointly filed with Vapetasia.

The FDA's denial of Petitioners' premarket authorizations is reviewed under the standards set by the Administrative Procedure Act ("APA"). *See* 21 U.S.C. § 387*l*(b). The APA allows a reviewing court to set aside an agency determination if that determination was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). "The scope of review under the 'arbitrary and capricious' standard is narrow[,] and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

IV. Discussion

Petitioners advance two primary arguments: (1) FDA acted arbitrarily and capriciously by pulling a

"surprise switcheroo" on Petitioners and failing to consider important aspects of the PMTAs; and (2) FDA lacks statutory authority to impose a comparative efficacy requirement.[5] We are unpersuaded by either argument.

A. FDA Authority

We begin with the simpler matter. Petitioners argue that FDA "lacks authority . . . to impose a requirement that Triton demonstrate its flavored ENDS products are more effective at promoting smoking cessation than its tobacco flavored ENDS products." Petitioners are blatantly wrong—the TCA authorizes FDA to consider comparative cessation evidence, if not expressly then impliedly.

Beginning with the express authority. 21 U.S.C. § 387j is the relevant provision: subsection (b) sets out the requirements for a premarket tobacco application, and subsection (c) outlines the actions FDA may take with regards to the application. *Id.* § 387j(b), (c). Under subsection (b), applicants are *required* to include in their applications "full reports . . . 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*."

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[5] Upon success on the first argument (that FDA acted arbitrarily and capriciously) but failure on the second (that FDA lacks statutory authority), Petitioners request that the court grant them an eighteen-month-long injunction against the agency so that they could conduct randomized controlled trials and longitudinal studies. FDA rejects this request as incongruent with the APA, arguing that remand is the only appropriate remedy. Because we deny the petitions for review, we need not address the propriety of the requested relief.

Id. § 387j(b)(1)(A) (emphasis added). Under subsection (c), FDA is then *required* to consider "the information submitted to the Secretary as part of the application," which necessarily includes the comparative efficacy reports that applicants must provide. *Id.* § 387j(c)(2).

Petitioners ask us to ignore these provisions, arguing that the word "risk" in § 387j(b)(1)(A) "refers to physiological *health* risks, not some broader concept of risk that encompasses initiation and cessation behaviors." This argument is unpersuasive. Initiation and cessation behaviors *are* physiological health risks. In fact, as Petitioners themselves note, cessation is one of the reasons Congress enacted the TCA in the first place. TCA § 3(9), 123 Stat. at 1782; *see also* TCA § 2(34), 123 Stat. at 1779 ("Because the only known safe alternative to smoking is cessation, interventions should target all smokers to help them quit completely.").

Moreover, subsection (c) provides further express authority for FDA to consider comparative efficacy. The statute provides that to determine compliance with the APPH standard, FDA must consider "the increased or decreased likelihood that existing users of tobacco products will stop using such products." 21 U.S.C. § 387j(c)(4)(A). The phrase "increased or decreased likelihood" necessarily implies a comparative analysis. Nothing can "increase" or "decrease" in a vacuum.[6] Petitioners surely understood as much because, as FDA

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[6] If someone smoked 10 cigarettes today, you could not say that she "increased" or "decreased" her smoking ritual without having evidence of her prior smoking habits—that is, evidence that would allow you to *compare* her smoking today to her smoking yesterday and before.

points out, Petitioners actually included evidence of comparative cessation in their PMTAs.

But even if Petitioners are right that FDA lacks the express authority to consider such evidence, FDA certainly has implied authority to do so. In addition to the provisions cited above, FDA may consider "any other information before the Secretary with respect to [the] tobacco product," 21 U.S.C. § 387j(c)(2), may commission an investigation to determine whether a product meets the APPH standard, *id.* § 387j(c)(5)(A), and may consider other "valid scientific evidence," *id.* § 387j(c)(5)(B). Therefore, FDA's consideration of the lack of cessation as a risk and comparing that risk between new tobacco products and old tobacco products "fall[s] squarely within the ambit of the FDA's expertise and merit[s] deference." *Cf. Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995).

B. Arbitrary and Capricious

We now turn to the core issue upon which our motions panel relied to grant a stay. Petitioners argue that they relied on FDA's statements that scientific studies were not necessary, but that FDA seemed to consider the lack of studies the only relevant factor in its decision, ignoring all the reasons it should have authorized their products. The motions panel largely agreed. It determined that FDA pulled a "surprise switcheroo" and either inadequately considered or failed to consider altogether several relevant aspects of Petitioners' applications, including: "(1) Triton's marketing plan; (2) Triton's reliance interests; (3) less disruptive alternatives; (4) device-type preferences; and (5) evidence on the potential benefits of flavored e-cigarettes." *Wages & White Lion*, 16 F.4th at 1136.

Notably, after our court entered that decision, the Sixth Circuit denied a stay application of a similar MDO. *Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 506 (6th Cir. 2021) ("Considering all of Breeze Smoke's evidence, we disagree with Breeze Smoke, and with our colleagues on the Fifth Circuit, who say that the FDA orchestrated a 'surprise switcheroo.'").[7] Examining largely the same factors our court pointed out, our sister court determined that FDA appropriately considered this evidence and reached a contrary conclusion. *Id.* at 506-08.

Before diving into these specific issues, we should note that our job here is quite limited. We are not tasked with determining whether we *agree* with FDA's decision (that is, whether we would have granted authorization if the PMTAs were submitted to us in the first instance). Instead, we review the MDOs for whether they were arbitrary and capricious. There are only narrow circumstances under which we would consider an agency action 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.

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[7] Other circuits have granted stays but provide little in the way of explanation that addresses the considerations herein. *See Gripum LLC v. FDA*, No. 21-2840 (7th Cir. Nov. 4, 2021) (order granting stay pending review); *Bidi Vapor LLC v. FDA*, No. 21-13340 (11th Cir. Feb. 1, 2022) (same); *Johnny Copper, L.L.C. v. FDA*, No. 21-13438 (11th Cir. Feb. 1, 2022) (same); *Vapor Unlimited LLC v. FDA*, No. 21-13454 (11th Cir. Feb. 1, 2022) (same).

Motor Vehicle Mfrs., 463 U.S. at 43.

Moreover, where the parties disagree on the science, we owe the FDA deference. After all, Congress deemed only the FDA as the scientific expert here—not the federal courts. *See* TCA § 2(44), 123 Stat. at 1780 ("The Food and Drug Administration is a regulatory agency with the scientific expertise to . . . evaluate scientific studies supporting claims about the safety of products[]. . . . "). With those general caveats in place, we now address the relevant specifics.

(1) Evidence on Potential Benefits

Petitioners argue that FDA dismissed their evidence regarding benefits to adults because the evidence did not consist of the specific studies FDA recommended. We are unpersuaded by Petitioners. As FDA aptly summarized in its briefing before this court: "FDA denied petitioners' applications *not* because they failed to include a randomized controlled trial or longitudinal cohort study but because they failed to include *any* evidence robust enough to carry petitioners' burden under the statute." The key piece of evidence that Petitioners focus on in their briefing is a cross-sectional survey conducted by Vapetasia. Petitioners emphasize that according to this study, 82.99% of survey respondents indicated that e-cigarettes helped them quit smoking combustible tobacco. But that survey suffered from several methodological flaws: (1) only 294 people were surveyed; (2) the survey respondents are all Vapetasia customers; and (3) it's not clear how these individuals were selected to take the survey.[8] In other words,

[8] As the Sixth Circuit explained given a similar customer survey:

there were strong reasons to doubt the survey's results. The FDA therefore did not act arbitrarily in concluding that Vapetasia's survey "is not sufficient to show a benefit to adult smokers."[9]

> On this record, Breeze Smoke's survey presents methodological issues. The FDA's 2019 guidance suggested that applicants include studies "with robust rationale, acute toxicological endpoints or other clinical endpoints that may relate to long-term health impacts." Breeze Smoke's study, submitted via Google Form, contained responses from customers "solicited . . . by request in the retail stores."

Breeze Smoke, 18 F.4th at 506 (citations omitted).

[9] The motions panel discussed a study cited by Triton (and conducted by the Consumer Advocates for Smoke-Free Alternatives Association) as key evidence that the FDA ought to have considered. The panel noted:

> Triton urged the FDA to consider a 2015 survey of 20,000 e-cigarette users showing that nearly a third of the respondents "started out using tobacco or menthol flavors" and then began using other flavored e-cigarettes. Similarly, Triton asserted that flavored e-cigarettes "could serve an important role in transitioning existing adult users away from more harmful, combustible cigarette products." But in the Order, the FDA ignored the first point altogether and gave the second short shrift.

Wages & White Lion, 16 F.4th at 1140 (citations omitted).

Petitioners do not actively discuss this study in their briefing, only referring to it a couple of times in passing. Regardless, the Technical Project Lead reports explain that FDA "reviewed the application for any acceptably strong evidence." It found none. At most, Petitioners fault FDA for not *mentioning* the study in the MDO (unlike how it handled the Vapetasia study). But unlike the Vapetasia study, Triton did *not* conduct or commission this survey, and in any event, FDA not mentioning the study is not the same as "entirely fail[ing] to consider an important aspect of the problem." *State Farm*, 436 U.S. at 43.

(2) Device-Type Preferences

Petitioners argue that FDA failed to consider device-type preferences amongst youth. E-cigarettes can come in various forms: "closed systems," which are e-cigarettes designed to have cartridges inserted into the device; "open systems," which are e-cigarettes with built-in tanks that are filled by the user; and disposables, which are e-cigarettes where the entire device is thrown out when the e-liquid runs out (as opposed to just the empty cartridge being thrown out in a closed-system device).[10] In 2019, FDA witnessed the highest level ever recorded of youth e-cigarette use. *See* Enforcement Priorities for Electronic Nicotine Delivery Systems and Other Deemed Products on the Market Without Premarket Authorization, 85 Fed. Reg. 720, 722 (Jan. 7, 2020) ("Data from the 2019 NYTS also show that 2019 was the second consecutive year in which current (past 30-day) e-cigarette use among youth reached unprecedented levels.").

FDA's 2020 Guidance explained that, based on 2019 data, youth were particularly attracted to closed-system devices. 2020 Guidance at 19. ("[D]ata from the 2019 NYTS indicate that youth overwhelmingly prefer cartridge-based ENDS products. These products are easy to conceal, can be used discreetly, may have a high nicotine content, and are manufactured on a large scale." (footnote omitted)). Given this data, FDA began to ramp up its enforcement efforts against closed-

[10] The motions panel inadvertently confused closed-system devices with disposable devices. *See Wages & White Lion*, 16 F.4th at 1130. To clarify, the distinction is whether the device as a whole is thrown out (disposable) as opposed to a component part being thrown out (closed system).

system devices. Former FDA Commissioner Scott Gottlieb even made a speech after he no longer served as Commissioner in which Gottlieb called for a complete ban on closed-system devices and noted that open-system devices are not as popular with youth. Nicholas Florko, *Former FDA Commissioner Calls for A Full Ban on Pod-Based E-Cigarettes*, STAT (Nov. 12, 2019), https://www.statnews.com/2019/11/12/gottlieb-ban-pod-based-e-cigarettes/.

Petitioners rely heavily on the Gottlieb statement and FDA's enforcement efforts against closed-system devices. They argue that FDA acted arbitrarily and capriciously because it failed to consider that their e-cigarettes are open-system devices. But in reality, Petitioners fault FDA for refusing to turn a blind eye to all the evidence that has emerged since 2019. Particularly, after FDA increased enforcement actions against closed-system devices, the youth-smoking epidemic did *not* end; instead, youth smokers migrated to *other* device types with flavored e-liquids: "[W]hen 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—a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users." *See* Triton TPL Report at 8; Vapetasia TPL Report at 8.[11] To the extent Petitioners rely on the Gottlieb statement and the 2020 Guidance, their reliance is misplaced. Both were based on data from 2019—that is, data from *before* the FDA's subsequent enforce-

[11] The notion in the dissenting opinion that Petitioners only received the TPLs via FOIA was not an argument raised adequately by Petitioners in their briefing.

ment actions and the observed youth migration.[12] As well, Gottlieb was no longer the FDA Commissioner, so his comments have no greater weight than anyone else's thoughts. In contrast to the evidence on device-type preference, FDA concluded that "across these different device types, the role of flavor is consistent." In other words, FDA *did* consider Petitioners' device type, and it concluded (reasonably) that what truly impacts youth smokers is flavor preference, not device preference.

(3) Reliance Interests

Petitioners argue, and the motions panel concluded, that FDA "pulled a surprise switcheroo" in "requir[ing] the very studies it originally expected it didn't need." *Wages & White Lion*, 16 F.4th at 1138 (internal quotation marks, brackets, and citation omitted). But the FDA does not now—and has not ever—*required* studies of smoking cessation. Contrary to the motion panel's determination that FDA made a "radical" change, *id.* at 1138-39, FDA has always suggested and continues to suggest that such studies *might* be useful, in particular where, as here, the evidence presented in an application is otherwise weak. *See Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 282 (D.C. Cir. 2019) ("The FDA has *expressed willingness* to accept scientific literature reviews instead of commissioned studies in support of

[12] While Petitioners cite two studies that purport to include data from 2020 and 2021, these studies do not show (or at least, Petitioners fail to explain how they show) what the percentage breakdown across devices is, what effect the FDA enforcement actions had on this usage, or how these statistics map on to statistics regarding flavor. The evidence provided on device-type preferences is, therefore, unpersuasive.

e-cigarette applications *in appropriate circumstances*." (emphasis added)).

One needs to look no further than the FDA's own conditional language over the last several years to reach that conclusion. The record is replete. *See, e.g.*, Premarket Tobacco Product Applications and Recordkeeping Requirements (Final Rule), 86 Fed. Reg. 55,300, 55,387 (Oct. 5, 2021) ("FDA does not expect that long-term clinical studies will need to be conducted for each PMTA; instead, it expects that it *should be able* to rely on other *valid* scientific evidence to evaluate some PMTAs." (emphasis added)); Premarket Tobacco Product Applications and Recordkeeping Requirements (Proposed Rule), 84 Fed. Reg. 50,566, 50,619 (Sept. 25, 2019) ("FDA will determine . . . whether the available evidence, *when taken as a whole*, is adequate to support a determination that permitting the new tobacco product to be marketed would be APPH." (emphasis added)); FDA, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS): Guidance for Industry 13 (2019), https://www.fda.gov/media/127853/download ("[I]nstead of conducting clinical studies that span months or years to evaluate potential clinical impact, applicants *could* demonstrate possible long-term health impact by including existing longer duration studies in the public literature with the appropriate bridging information. . . . " (emphasis added)); *id.* at 46 ("[T]hese data *may* be sufficient to support a PMTA. . . . " (emphasis added)); 81 Fed. Reg. at 28,997 ("[I]n *some cases*, it *may be* possible for an applicant to obtain a PMTA marketing authorization order without conducting any new nonclinical or clinical studies where there is an established body of ev-

idence regarding the public health impact of the product." (emphasis added)).

The evidence cited by the dissenting opinion to the contrary ignores the FDA's continuous use of conditional language. For example, quoting the TPLs, the dissenting opinion frames FDA as stating that longitudinal "studies are 'most likely' to provide reliable and robust evidence to satisfy the APPH standard." But the dissenting opinion ignores the next line in the TPL: "other types of evidence could be adequate[] and will be evaluated on a case-by-case basis." Similarly, per the dissenting opinion, "FDA announced that it would authorize the flavored ENDS products *only if* the PMTAs included previously purely optional studies." Dissenting Op. at 3-4. For this argument, the dissenting opinion relies on an FDA press release, while ignoring the line in that press release that says, "the agency does not foreclose the possibility that other types of evidence could be adequate if sufficiently robust and reliable." *See* 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://bit.ly/2YsYmzd. Finally, the dissenting opinion's reliance on a subsequently retracted internal FDA memo does not alter any of the conditional language that FDA continued to provide.

Having reviewed this record, we agree with the Sixth Circuit's conclusion regarding the lack of any scientific study "requirement." *See Breeze Smoke*, 18 F.4th at 506-07. *Breeze Smoke* was decided after *Wages & White Lion*, and following the *Breeze Smoke* decision, Petitioners presented an application for a stay (i.e., a

stay of the FDA's denial) to Justice Kavanaugh, who referred the application to the Court. *See Breeze Smoke, LLC v. FDA*, 142 S. Ct. 638 (2021) (mem.). The application was denied, without any recorded dissent from the Supreme Court. *Id.* Having had the benefit of these subsequent developments as well as full briefing and oral argument, we take a different view from the stay panel.[13]

The fact that Petitioners presented other scientific evidence does not make that scientific evidence valid, and it is entirely consistent with FDA's prior statements to reject that evidence. Moreover, Petitioners' attempts to distinguish *Breeze Smoke* are unavailing. Petitioners make two arguments: (1) "the Sixth Circuit's motions panel considered only one excerpt from FDA's 2019 Guidance, and not the representations made by FDA at the two public meetings with applicants or the Final PMTA Rule"; and (2) "*Breeze Smoke* . . . dealt exclusively with disposable ENDS products, not bottled e-liquids." As to the first argument, as noted above, all the representations made by the FDA consistently said that other evidence *might* be accepted. As to the second argument, the device-type distinction is unpersuasive for the reasons set out earlier, and that distinction has no impact on the FDA's prior statements regarding scientific studies. Therefore, we (like our sister court) conclude that FDA has not pulled an imper-

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[13] It should go without saying, but the dissenting opinion wrongly implies that four judges of this court have "found" the merits lacking. Dissenting Op. at 1. Our precedent makes clear that a stay panel's determination regarding the likelihood of success on the merits is *not* itself a determination on the merits. That determination is for this panel to make alone.

missible "surprise switcheroo." *See Breeze Smoke*, 18 F.4th at 506-07.[14]

(4) Marketing Plan

Finally, Petitioners argue that FDA did not appropriately consider their marketing scheme. Instead, FDA stated that "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." The motions panel rebuked this statement, noting that "'efficiency' is no substitute for 'reasoned decisionmaking.'" *Wages & White Lion*, 16 F.4th at 1137 (quoting *Michigan v. EPA*, 576 U.S. 743, 750 (2015)). After careful consideration, we have determined that the FDA did not act arbitrarily and capriciously in not reviewing the marketing plans, and if they did, such error was harmless.

As an initial matter, FDA did not consider the marketing plan because although "[i]t is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal," FDA had not once evaluated a marketing plan that actually did so. This was not a novel observation on the FDA's part. In fact, part of the reason Congress passed the TCA is *because*

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[14] For these same reasons, we disagree with the dissenting opinion's attempt to distinguish *Breeze Smoke* and specifically disagree with the dissenting opinion's accusation that the Sixth Circuit "fail[ed] to acknowledge the abundant administrative record concerning FDA's public engagement with ENDS product suppliers, FDA's Sept. 2019 proposed rule, and the Final Rule, all of which are inconsistent with its perfunctory denial orders." Dissenting Op. at 5 n.4. The Sixth Circuit considered each extensively. *See Breeze Smoke*, 18 F.4th at 505-08.

marketing restrictions simply were not working: "Because past efforts to restrict advertising and marketing of tobacco products have failed adequately to curb tobacco use by adolescents, comprehensive restrictions on the sale, promotion, and distribution of such products are needed." TCA § 2(6), 123 Stat. at 1777.

Moreover, Petitioners should have known that marketing plans on their own are not particularly useful.[15] FDA explained as much in its 2020 Guidance, in which it noted that youth usage continued to rise *despite* FDA's 2018 efforts to curb predatory marketing, such as its issuance of "warning letters to manufacturers, distributors, and retailers for selling e-liquids with labeling and/or advertising that resemble kid-friendly food products, such as juice boxes, candy, or cookies." 2020 Guidance at 6-9. This finding by FDA directly refutes the dissenting opinion's claim that, until the MDOs, "[e]very single statement by the agency . . . reasonably led petitioners to believe that if they devised marketing arrangements that would prevent underage persons from purchasing their flavored e-liquids . . . they would have surmounted a significant requirement for marketing approval." Dissenting Op. at 8. The record not only undermines this statement, it contravenes it entirely—FDA stating that marketing plans would "help FDA determine" whether the new tobacco product meets the APPH standard is *not* the same as FDA stating that *if*

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[15] To be clear, in saying this we do not "blame" Petitioners for not knowing that their marketing plans would not be useful. *See* Dissenting Op. at 8. Instead, the record shows that it would have been unreasonable for Petitioners to believe that marketing plans in and of themselves would suffice for FDA to grant their PMTAs. An unreasonable belief on the part of an applicant is not the same as arbitrary and capricious action on the part of an agency.

marketing plans exist *then* market authorization was a step away.[16]

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[16] The dissenting opinion does not address the substance of FDA's finding that youth usage continued despite FDA's 2018 efforts to curb predatory marketing, focusing instead on the *source* in which FDA issued that finding: the 2020 Guidance. Dissenting Op. at 7-8. Instead, it provides four reasons the 2020 Guidance should not be considered. We address each in turn.

First, the dissenting opinion takes issue with the 2020 Guidance not "amending" the earlier Guidance. But both the 2020 Guidance and the earlier 2019 Guidance (which the dissenting opinion calls the "definitive" and "final" guidance) contained *nonbinding recommendations*. Lest anyone get confused, each document had a header that said, in bold print, "Contains Nonbinding Recommendations." Nothing in the record suggests that it is necessary or even common for FDA to amend a document no one was ever bound by.

Second, the dissenting opinion notes that "there is no evidence at all that these petitioners marketed or sold to youth." Dissenting Op. at 7. But there is no statutory requirement that for FDA to deny authorization, it must (or even should) have evidence that a particular applicant marketed or sold to youth.

Third, the dissenting opinion states that the 2020 Guidance is not referenced in the MDOs. This statement is technically true, but misleading. After all, the MDOs also didn't mention the 2019 Guidance. Nor is that the purpose of an MDO. An MDO is merely a short letter stating FDA's conclusion. Its reasoning is described more fully in the TPLs, which, of course, discuss the 2020 Guidance at length.

Fourth, the dissent's final concern—"the high level of youth vaping that spawned the 2020 Guidance had been underway since 2018, yet FDA did not adjust its PMTA Guidance materials significantly during this period"—asks FDA to do the impossible and analyze something that did not yet exist. Although vaping was a large issue amongst youth in 2018, the primary study FDA relied on for that data was not released until *November* 2018. FDA then quickly implemented new enforcement priorities. It then studied the effect of its new enforcement priorities in 2019 and developed updated guidance based on that data in 2020. Asking FDA to have provided data ear-

Instead, based on its expertise, FDA determined that traditional marketing schemes do not work and that absent a "novel or materially different" scheme, youth appeal would continue. Of course, one could argue that without having actually reviewed the marketing plans, FDA could not have known that Petitioners' plans would not have been unique. But at oral argument, FDA clarified that what it did review included a summary of the marketing plans.[17] We, therefore, do not believe that the agency acted arbitrarily and capriciously—Petitioners' plans were not unique; FDA did not need to go any further.

Quoting the stay panel, the dissenting opinion objects to this line of reasoning, analogizing FDA's actions to a judge that "stopped reading briefs because she previously found them unhelpful" and arguing that FDA only did so because it was inundated with a backlog of PMTAs. Dissenting Op. at 7. With this framing in mind, it's no wonder that the dissenting opinion calls the FDA's conduct "obviously illogical and unreasonable." Dissenting Op. at 7. But that framing does not appropriately capture what happened here.

We offer a different analogy. Consider a district court, inundated with a backlog of motions. Of course the court will not consider a summary judgment motion on the merits if it concludes that it must grant a motion

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lier would be asking FDA to release guidance with potentially no actual data. *That* would be an arbitrary and capricious agency action.

[17] Parties clarify factual matters before appellate courts all the time—it's one of the benefits of oral argument. Clarifying what happened factually is not, by any stretch of the imagination, "judicial post hoc reasoning about a post hoc justification." *See* Dissenting Op. at 8.

to dismiss for lack of jurisdiction because it doesn't matter how good of a merits argument a plaintiff has, such an argument cannot cure a jurisdictional defect. We recognize that, for efficiency, a district court need not review every single motion before it when a motion will have no effect on the outcome of the litigation, and we understand that not addressing every issue is not the same as a failure of reasoned decision making.

We cannot hold a federal agency, operated by a co-equal branch of government, to a higher standard than we hold the federal courts. FDA, per its expertise, understood that whatever the specific details of Petitioners' marketing plans were, those details could not cure the other defects in Petitioners PMTAs. It did not need to assess the details of the marketing plan, and its failure to do so is not a failure of reasoned decision making.

In any event, nothing in Petitioners' briefing to this court indicates that their marketing plan was in fact unique. Instead, "Triton and Vapetasia's PMTA marketing plans called for their products to be only sold in age-gated vape and specialty tobacco shops and through age-gated online sales." But FDA had already explained that such attempts do *not* work:

> FDA has been focusing enforcement efforts on age verification as a strategy to address youth use of tobacco products, and FDA continues to enforce age restrictions. However, FDA 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. FDA determined that focusing on how the product was sold would not be sufficient to address youth use of these products

> given the many sources of products available for youth access. The reality is that youth have continued access to ENDS products in the face of legal prohibitions and even after voluntary actions by some manufacturers.

2020 Guidance at 44.

The burden falls on Petitioners to show that they would have received authorization had FDA considered these plans. *See, e.g.*, *Shinseki v. Sanders*, 556 U.S. 396, 409 (2009); *Am. Airlines, Inc. v. Dep't of Transp.*, 202 F.3d 788, 797 (5th Cir. 2000). They have not done so. Given that the TCA incorporates the APA's harmless error rule—*see* 21 U.S.C. § 387*l*(b); 5 U.S.C. § 706—Petitioners' failure to show harm necessitates the denial of relief.

* * *

Congress passed the TCA in an active effort to protect public health. In serving that purpose, we cannot say that FDA acted arbitrarily and capriciously by disagreeing with Petitioners as to the significance of the evidence they presented. Of course, nothing prevents Petitioners from reapplying with further evidence (and then seeking judicial review after further agency action). But as to the present state, we conclude that the petitions are DENIED.

EDITH H. JONES, *Circuit Judge*, dissenting:

Six judges of this court have reviewed the FDA's "reasons" for removing from the market and destroying the business for these petitioners' electronic nicotine delivery system ("ENDS") products. Four of us have found the agency's decisions seriously inadequate, but at least the debate with my colleagues is founded on known standards. Not so FDA's actions. 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. *See DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020). Kafka would have understood the FDA all too well. The agency's decisions are arbitrary and capricious. I dissent.

I. BACKGROUND

Petitioners' flavored nicotine-flavored liquids are among a host of "tobacco products" (although they contain no tobacco) that have fallen within the regulatory purview of the FDA since 2016. *See* 81 Fed. Reg. 28974 (May 10, 2016) ("the deeming rule").[1] To continue selling their flavored liquids, Petitioners had to submit a premarket tobacco product application ("PMTA") to the FDA by September 9, 2020. *See* 21 U.S.C. § 387j; *Va-*

[1] Petitioners' products are used in "open system" e-cigarettes, which are distinct from "closed system" cartridge-type and disposable e-cigarettes. According to FDA's studies, disposable or cartridge-based products are overwhelmingly more attractive to youthful users because they are discreet, easy to operate and conceal.

por Tech. Ass'n v. FDA, 97 F.3d 496, 498-501 (6th Cir. 2020). If the FDA issues a marketing denial order ("MDO") in response to a PMTA, sales of the products become unlawful. Given that ENDS product companies' very existence depended on securing marketing approval, petitioners had significant incentives to get the applications right. Recognizing this, the FDA put an extensive amount of information out to the public about what was relevant to a successful application, and what was not.

Toward that end, in October 2018 the FDA held a two-day public meeting to "improve public understanding . . . on the process for the submission and review of [PMTAs]." Tobacco Product Application Review—A Public Meeting (October 22, 2018), https://bit.ly/3FhPxJi. In relaying the types of studies that could support a PMTA, 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." Premarket Tobacco Product Application Content Overview: Iilun Murphy—OS/Division of Individual Health Science (October 23, 2018) (emphasis added).

In June 2019, the FDA issued final guidance on PMTAs for ENDS products, the purpose of which was to "assist persons submitting [PMTAs] for [ENDS]" products and to "enable ENDS manufacturers to consider and strengthen their applications." FDA, Guidance for Industry, Premarket Tobacco Applications for Electronic Nicotine Delivery Systems (June 2019); Triton-FDA2-004408, 004411. The FDA's guidance made four

salient points. First, "in general, *FDA does not expect that applicants will need to conduct long-term studies to support an application*." Triton FDA2-004423 (emphasis added). Second, although randomized clinical studies "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*." Triton-FDA2-004448 (emphasis added). Third, FDA intended to review each PMTA and weigh all the benefits and risks from the product. Fourth, FDA would specifically pay attention to marketing restrictions that could restrict distribution to underage users.

In September 2019, FDA's proposed rule governing PMTAs reinforced all of these points. In particular, the agency stated once again that long-term studies were *not* expected. In addition, the FDA re-emphasized that marketing plans *were* critical:

> *"[t]he applicant's marketing plans* will help FDA determine whether permitting the marketing of the new tobacco product would be [appropriate for the protection of the public health] because they *will provide input that is critical* to FDA's determination of the likelihood of changes in tobacco product use behavior, especially when considered in conjunction with other information contained in the application. *FDA 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."

84 Fed. Reg. 50566, 50581 (Sept. 25, 2019) (emphasis added).

Petitioners assumed that these guidelines governed their applications, and accordingly prepared applications that emphasized their restrictive marketing but did not include long-term studies on smoking cessation behavior. The PMTAs were timely filed on September 9, 2020.

1. The New Rules.

Ten months later, when FDA was inundated by literally millions of PMTAs, the agency circulated an internal memorandum providing a new "standard of evidence" for some PMTAs for flavored ENDS products. *See* Triton-FDA2-005144-005155 (July 9, 2021). This memo was not publicly released, though its intent was to facilitate "final action on as many applications as possible by September 10, 2021." *See* Triton-FDA2-005144. Given the "large number of applications that remain[ed] to be reviewed by September 9, 2021," the memo explained that in lieu of reviewing applications on an individualized basis, the 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*[]." Triton-FDA2-005145 (emphasis added). The "fatal flaw" would be the absence of studies—that is to say, long-term studies that the agency previously stated were neither necessary nor expected. Triton-FDA2-005144-45. Put bluntly, the memo ensured that even if an applicant followed FDA's pre-deadline public statements and proposed rule, the FDA would nonetheless deny a PMTA because it failed to satisfy the internal non-public requirement for "the necessary type of studies" crafted in July 2021. FDA asserts that the Fatal Flaw memo was rescinded, but its approach appears to have been fol-

lowed in a check-box "scientific review" form that indicated only whether a PMTA included a randomized controlled trial or longitudinal cohort study. Triton FDA1-000247-000260.

Similarly, FDA changed its mind about reviewing marketing plans and decided not to do so "for the sake of efficiency." Significant sections of that internal memo, though also claimed by FDA to be rescinded,[2] are copied word-for-word in the TPLs for petitioners' products.

2. The Late Notice.

The FDA revealed its new *modus operandi* concerning long-term studies on August 26, 2021 in a press release when it denied 55,000 ENDS products PMTAs in one day. Thus, nearly a year after the PMTA deadline, FDA announced that it would authorize the flavored ENDS products only if the PMTAs included previously purely optional studies, *i.e.*, long-term studies showing that the applicant's flavored ENDS products effectively promoted cessation from cigarette smoking in a manner that outweighs the potential risk to youth. 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://bit.ly/2YsYmzd.

Petitioners' PMTAs were not among the first batch of denials. *Id.* In an attempt to adjust to the new requirement, petitioners submitted a letter to the FDA on September 1, 2021, stating that they intended to conduct additional behavioral studies on adult smoking cessation

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[2] PMTA Review: Evidence to Demonstrate Benefit of Flavored ENDS to Adult Smokers. FDA, Aug. 25, 2021.

and long-term studies of their products to supplement their PMTAs.

3. Rubber-stamped denials.

Their prompt reaction was in vain. On September 14, FDA issued MDOs denying them the right to sell their flavored liquids in the United States. The MDOs refused to consider, much less evaluate the petitioners' marketing plans "for the sake of efficiency."[3] TRITON-FDA 1-000279. Petitioners were denied any attempt to comply with the new rule, FDA informed them, because the September 1, 2021 letter was "received near the completion of scientific review." Triton-FDA1-000123. The MDOs perfunctorily concluded that their evidence failed to demonstrate "robustly" and "reliably" the magnitude of their flavored products' potential benefit to adult smokers. Such evidence, however, "could have been provided using a randomized controlled trial and/or longitudinal study that demonstrated the benefit of your flavored ends products over an appropriate tobacco-flavored ends." Triton-FDA1-000124.

The TPLs furnished to petitioners as alleged backup for the MDOs is more egregiously out of step with all of FDA's pre-deadline policies, as it states that, "[b]ased on existing scientific evidence and our experiences in

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[3] This MDO also states that "none of the ENDS PMTAs that FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use." Because FDA had not seen a successful marketing plan on past applications, it generalized, all future applications must lack worthwhile marketing plans. So much for individualized consideration of marketing plans.

conducting premarket review employing the APPH standard *over the last several years*, FDA has determined. . . . most likely product specific evidence from a randomized controlled trial (RCT) or longitudinal controlled study" will be adequate. Triton-FDA1-000271. Later, the TPL recounts, contrary to the agency's previous representations, that the types of studies it earlier promoted must also be conducted "over time."

4. The Post Mortem Rule

FDA published its final PMTA Rule on October 4, 2021, a rule consistent with its prior pre-August 2021 policies but inconsistent with the process described in petitioners' MDOs. FDA, Premarket Tobacco Product Applications and Recordkeeping Requirements, Final Rule, 86 Fed. Reg. 55300. The Final Rule, yet again, states that the FDA does "not expect that applicants will need to conduct long-term clinical studies to support an application." 86 Fed. Reg. 55300, 55387. Contrary to the fatal flaw approach, the final rule states that the "FDA declines to create a series of criteria that either all products or a specific subset of products must meet in order for marketing of such products to be considered as part of this rule." *Id.* at 55386. Instead, FDA assured that it would "consider[] many factors," *id.* at 55314, would not rely on "one static set of requirements" *id.* at 55385, does not assign weight to different types of evidence, *id.* at 55335, and carefully "balances" risks and benefits, *id.* at 55384.

Concerning marketing plans, the FDA's Final Rule repeatedly contradicts the MDOs' flat refusal to consider them, as it explains that "FDA has rationally concluded that the required descriptions of marketing plans

will directly inform its 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.[4]

II. DISCUSSION

As noted, the majority and I agree that according to the Administrative Procedure Act, we must decide whether the FDA's decisions are "arbitrary and capricious . . . or not in accordance with law." 5 U.S.C. § 706(2)(A). The Supreme Court has succinctly explained that "[t]he APA's arbitrary and capricious standard requires that agency action be reasonable and reasonably explained." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021); *see also Motor Vehicle Mfs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 50, 103 S. Ct. 2856, 2870 (1983). We know our rules; I disagree that FDA followed those rules.

Although courts may not substitute our policy view for that of the agency, we must ensure the agency turns

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[4] Several other courts have ruled on motions to stay FDAs MDOs concerning other ENDS products. Two courts granted stays, like the motions panel here, and one denied a stay. *See Gripum LLC v. FDA*, No. 21-2840, ECF No. 18 (7th Cir. Nov. 4, 2021); *Bidi Vapor LLC v. FDA, et al.*, No. 21-13340, Per Curiam Order (11th Cir. Feb 1, 2022); *Breeze Smoke, LLC v. United States Food & Drug Admin.*, 18 F.4th 499 (6th Cir. 2021) (denying motion to stay similar MDOs). In particular, I would distinguish the Sixth Circuit's ruling, touted by the panel, because it fails to acknowledge the abundant administrative record concerning FDA's public engagement with ENDS product suppliers, FDA's Sept. 2019 proposed rule, and the Final Rule, all of which are inconsistent with its perfunctory denial orders.

square corners[5] in dealing with the public to whom it is subservient. Consequently, agency action may not be justified to a court based on *post hoc* rationalization; the agency must "defend its actions based on the reasons it gave when it acted." *DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020). Nor may an agency wholly fail to consider "relevant factors" and "important aspect[s] of the problem." *Michigan v. EPA*, 576 U.S. 743, 752, 135 S. Ct. 2699, 2707 (2015). Nor may an agency thwart legitimate reliance interests by pulling a "surprise switcheroo" by changing its requirements too late for the petitioners to respond. *See Env't Integrity Project v. EPA*, 425 F.3d 992, 996 (D.C. Cir. 2005) (Sentelle, J.); *accord Azar v. Allina Health Servs.*, 139 S. Ct. 1804, 1810 (2019) (citing the "surprise switcheroo" doctrine).

The majority's analysis of these MDOs looks almost exclusively at the bottom-line result of FDA's decisions and finds nothing to criticize. But the facts recited above speak for themselves. FDA refused to review petitioners' marketing restrictions, which it had repeatedly stated were key to discouraging youthful use of the products and were thus critical components of the PMTAs. FDA repeatedly counselled applicants that long term studies were likely unnecessary and it said nothing about comparative efficacy studies—until the PMTA deadline was long gone; and then it refused peti-

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[5] Square corners is a turn of phrase used by Justice Robert Jackson. *See Fed. Crop Ins. Corp. v. Merrill*, 332 U.S. 380, 387-88, 68 S. Ct. 1, 5 (1947) (J. Jackson dissenting) (observing that regulatory law is a two-way street and that agencies when dealing with the regulated, just as much as citizens subject to their regulations, must turn square corners).

tioners the opportunity to conduct such studies. Finally, FDA's defense against petitioners on the merits of their applications is loaded with *post hoc* rationalizations. Any of these errors is a "fatal flaw." Taken together, they are mortal wounds.

The MDOs should be vacated, and the case remanded to FDA with instructions to allow these petitioners to develop and offer further evidence in support of the PMTAs.

A. Marketing Plans

The majority holds that the FDA's decision to ignore and not review the petitioners' plans was not arbitrary and capricious. To do this, the majority must themselves ignore the MDOs' only stated reason for ignoring the plans: "for the sake of efficiency." The majority does not deny that "'efficiency' is no substitute for 'reasoned decisionmaking.'" *Wages & White Lion Invs., L.L.C. v. FDA*, 16 F.4th 1130, 1137 (5th Cir. 2021) (quoting *Michigan v. EPA,* 576 U.S. 743, 750, 135 S. Ct. at 2706). Instead, the majority relies on FDA's *post hoc* justifications for ignoring the marketing plans.

First, the majority accepts FDA's assertion that it had not in the past evaluated a marketing plan that discouraged youth from using ENDS products. This is not a "reason" for refusing to even look at these petitioners' MDOs. As the stay panel noted, this excuse is akin to a judge's saying, "she stopped reading briefs because she previously found them unhelpful." *Wages & White Lion,* 16 F.4th at 1137. It is obviously illogical and unreasonable to infer from the general to the particular, especially when FDA acknowledged its duty to consider each PMTA individually and holistically. Nor

is the mere invocation of agency "expertise" a non-arbitrary substitute for an explanation how such expertise was brought to bear on the particular PMTA. "The requirement of explanation presumes the expertise and experience of the agency and still demands an adequate explanation in the particular matter." *CS Wind Viet. Co., Ltd. v. United States,* 832 F.3d 1367, 1377 (Fed. Cir. 2016) (citations omitted). The agency's failure to meaningfully consider an aspect of the petitioners' PMTAs that it had previously deemed essential is quintessentially arbitrary and capricious. *Univ. of Texas M.D. Anderson Cancer Ctr. v HHS,* 985 F.3d 472, 475 (5th Cir. 2021).

Second, the majority makes much of an FDA 2020 Guidance that decried increasing adolescent use of tobacco products starting in 2018 even after the agency cracked down on vape companies that marketed and sold ENDS products in packaging that looked like juice boxes and candy cartons. The 2020 Guidance, however, has nothing to do with this case because (a) it discussed enforcement priorities, and it did not purport in any way to amend the definitive PMTA Guidance documents that emphasized the importance of marketing plans; (b) there is no evidence at all that these petitioners marketed or sold to youth directly or indirectly, knowingly or objectionably; (c) the 2020 Guidance was not referenced at all in the MDOs and is therefore an inadmissible *post hoc* explanation; and (d) the high level of youth vaping that spawned the 2020 Guidance had been underway since 2018, yet FDA did not adjust its PMTA Guidance materials significantly during this pe-

riod.[6] Moreover, recourse to the 2020 Guidance as a basis for FDA's having disregarded the marketing plans is flatly contradicted by the Final PMTA Rule, which continued to stress the importance of such plans as a "critical factor" in FDA's approval decisions.

Third, the majority admits that since FDA never reviewed the marketing plans, "one could argue" it had no basis to find them neither "novel or materially different" from others. But wait—the majority relies on FDA's statement—in oral argument to *this court*—that its review actually included a summary of the marketing plan. This is judicial post hoc reasoning about a post hoc justification.

Fourth, and most objectionably, the majority blames *petitioners* for not knowing that "marketing plans on their own are not particularly useful." That statement stands the requirement of reasoned *agency* decision-making on its head. Every single statement by the agency, until it issued its MDOs to these petitioners, reasonably led petitioners to believe that if they devised marketing arrangements that would prevent underage persons from purchasing their flavored e-liquids for

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[6] The 2020 Guidance also focuses almost exclusively on the continuing attractiveness to youth of closed-system ENDS products, and very little if at all on bottled e-liquids for use in open systems. These petitioners produce bottled e-liquids. To the extent FDA means to say that youth will migrate to any flavored ENDS products if other avenues are closed off, it provided no evidence of that migration toward petitioners' products during the periods in question. In fact, the 2020 Guidance stated that it "should have minimal impact on those vape shops that primarily sell non-cartridge ENDS products and ensure that purchasers are of the requisite age and are not purchasing for resale[.]" Triton FDA-2-000321-000322.

open systems, they would have surmounted a significant requirement for marketing approval.

Finally, to assert that the agency's deliberate lapse amounted to "harmless error" is simply incorrect. Prejudice in the administrative law context does not involve a "complex system of 'burden shifting' rules or a particularly onerous requirement." *Shinseki v. Sanders,* 556 U.S. 396, 410, 129 S. Ct. 1696, 1706 (2009). An "APA deficiency is not prejudicial only when it is one that clearly had no bearing on the procedure used or the substance of decision reached." *United States v. Johnson,* 632 F.3d 912, 930 (5th Cir. 2011). Taken in conjunction with the agency's violation of other administrative norms through its failures of notice and ignoring petitioners' reliance interests, the majority has no basis for claiming harmless error.

For all these reasons, the agency cannot run away from individually reviewing petitioners' marketing plans when, for two years, it assured the public that properly tailored marketing of flavored ENDS products could protect youth from exposure and abuse while the products also helped those who need to stop smoking. It is the epitome of agency hubris to pull the rug out from entities whose very existence depends on the agency's careful balancing of all factors relevant to this public health issue.

B. Notice and Reliance Interests

The majority puts down petitioners' claimed "reliance interests" and denies that FDA pulled a "surprise switcheroo" by rejecting their PMTAs for lack of "randomized controlled trials" or "longitudinal cohort studies" showing the benefits of their products in enabling

smoking cessation. The majority reads FDA's pronouncements to have consistently conditioned its criteria for APPH studies or evidence and *never* to have *required* comparative efficacy studies of smoking cessation.

This is surprising, because petitioners were only advised in the TPLs underlying their MDOs[7]—when it was too late—that such studies are "most likely" to provide reliable and robust evidence to satisfy the APPH standard.[8] And only then were they advised that studies "over time" should have been included. From October 2018 through the September 2020 PMTA deadline, and until August 2021, the FDA continually repeated that such studies were neither necessary nor expected.[9] Instead, FDA stated that other forms of evidence, including observational and consumer-perception studies, as well as scientific literature reviews, could be acceptable. In August 2021, contrary to those pronouncements, FDA announced that it had denied 55,000 PMTAs precisely because they lacked "the evidence of benefits to adult smokers for such products [that] would likely be in

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[7] Petitioners did not receive TPLs automatically; they obtained them only through FOIA requests.

[8] 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" and takes into account the likelihood that existing users of tobacco products will stop using such products; and the likelihood that those who do not use tobacco products will start using such products. 21 U.S.C. § 387j(c)(4).

[9] As has been explained, FDA also steadfastly represented the critical importance of marketing plans that would prevent underage youth from obtaining petitioners' products—until it backtracked on that requirement in the TPLs.

the form of a randomized controlled trial or longitudinal cohort study. . . . "

If this meandering administrative course is not an "administrative switcheroo," it is hard to know what is. For one thing, from FDA's denials of 55,000 PMTAs one might reasonably infer that other manufacturers besides these petitioners were fooled by FDA's previous instructions. And that legitimate reliance interests were built into the previous FDA announcements is attested by an affidavit of petitioners' executive in charge of filing their PMTAs. Moreover, petitioners' business was generating $15 to 20 million annual revenues. Petitioners invested a half million dollars to complete their PMTAs and filed 9 gigabytes of information, including hundreds of files, with FDA in seeking marketing approval. They had every reason to file PMTAs most conscientiously and comprehensively because the existence of the company depended on agency approval of their products.

In light of all the circumstances, there are two ways to look at the MDOs in this case. Under one scenario, FDA changed its policies: from individualized consideration of PMTAs and flexibility as to the type of scientific evidence it would hold acceptable,[10] to perfunctory disapproval of PMTAs lacking longitudinal studies.[11]

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[10] *See Nicopure Labs, LLC v. FDA,* 944 F.3d 267, 282 (D.C. Cir. 2019)("[t]he FDA has expressed willingness to accept scientific literature reviews instead of commissioned studies in support of e-cigarette applications in appropriate circumstances").

[11] The Triton MDO indicates that to be acceptable, the petitioner's "other evidence" had to "evaluat[e] the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction *over time*." (emphasis added). Triton-

The majority nowhere acknowledges that during the entire pre-deadline process, FDA kept stating that it did not "expect" long-term studies to be necessary.

Viewed as a policy change, FDA acted arbitrarily and capriciously by failing to inform petitioners and by failing to consider their legitimate reliance interests. After all, "[t]hose 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, 135 S. Ct. 1199 (2015)). Agencies must provide fair warning of conduct the agency "prohibits or requires" and cannot "unfair[ly] surprise" a party by penalizing it for "good-faith reliance" on the agency's prior positions. *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156-57, 132 S. Ct. 2156, 2167-68 (2012). The fair notice requirement applies as much to agencies' other public pronouncements as to its regulations. *See Gen. Elec. Co. v. EPA,* 53 F.3d 1324, 1329 (D.C. Cir. 1995) ("in many cases the agency's pre-enforcement efforts to bring about compliance will provide adequate notice," such as notifying regulated entities of process requirements). Serious reliance interests, moreover, must be taken into account when an agency changes longstanding policies. *See DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913 (2020). FDA's disregard for the principles of fair notice and consideration of reliance interests is exacerbated here by its refusal to allow petitioners to supplement their applications according to the new requirements.

FDA1-000115. This looks like a requirement of a commissioned, longitudinal study of some kind.

This is not to say that FDA could not have formally changed its APPH requirement from the earlier Guidance documents and declared that *only* long-term, specific product studies would be acceptable, but it did not do that. *See Regents, id.* at 1914 ("[m]aking that difficult decision was the agency's job, but the agency failed to do it").

The second scenario posits that FDA's carefully crafted Guidance language authorized maximum agency discretion to approve or disapprove PMTAs as circumstances evolved. The "circumstances" entailed the increasing underage use of ENDS products, which resulted in the 2020 Guidance on which the majority rests much of its analysis.[12] Relying on snippets of Guidance language, FDA does not admit that it changed its evaluation policy, and the majority agrees. But this scenario is of no use in defending the MDOs. To begin, it is counterfactual. The MDOs rested on rejecting the types of evidence the agency had previously found likely sufficient, while requiring product-specific studies conducted "over time" that it had previously found unnecessary. But laying that aside, the Supreme Court holds that "[w]hen an agency changes its existing position, it . . . must at least display awareness that it is changing position and show that there are good reasons for the new policy." *Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 136 S. Ct. 2117, 2125-26 (2016) (quotation omitted). It follows that "unexplained incon-

[12] To repeat, however, the 2020 Guidance made no mention of and did not consider the elements necessary for petitioners to file successful PMTAs, nor did it alter agency policy regarding PMTAs; and it presumed "minimal impact" on shops selling products like those of petitioners.

sistency in agency policy is a reason for holding an [action] to be an arbitrary and capricious change from agency practice." *Id.* at 2126 (quotation omitted). FDA's migration from stating that "in general, FDA does not expect that applicants will need to conduct long-term studies to support an application" to denying petitioners' MDOs because they lacked long-term studies of comparative efficacy is "unexplained" and "inconsistent" and therefore arbitrary and capricious.

FDA, in sum, sealed the petitioners' doom by changing its evaluation rules without giving them notice and by ignoring individualized consideration of their plan for marketing restrictions to prevent underage youth access. Even with the noblest of motives in mind, a federal agency does not have license to run companies out of business without adhering to fixed rules of fair procedure. I respectfully dissent.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

No. 21-60766

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION, PETITIONER

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, RESPONDENT

[Filed: Oct. 26, 2021]

Petition for Review of an Order of the
Food and Drug Administration

Before ELROD, OLDHAM, and WILSON, *Circuit Judges*.

ANDREW S. OLDHAM, *Circuit Judge*:

The Food and Drug Administration denied Triton's application to market flavored e-cigarettes. Triton moved for a stay pending disposition of its petition for review. We grant the stay.

I.

A.

In 2009, Congress enacted the Family Smoking Prevention and Tobacco Control Act ("TCA") to regulate tobacco products. Pub. L. No. 111-31, 123 Stat. 1776 (2009). The TCA authorizes the Secretary of Health

and Human Services to implement the Act through the Food and Drug Administration ("FDA"). *See* 21 U.S.C. §§ 387a(b), 393(d)(2). The TCA prohibits manufacturers from selling any "new tobacco product" without authorization. *See id.* § 387j(a). In 2016, the FDA deemed electronic nicotine delivery systems ("ENDS")—colloquially called "electronic cigarettes" or "e-cigarettes"—a "new tobacco product." 81 Fed. Reg. 28,973 (May 10, 2016) ("Deeming Rule"); *see also Big Time Vapes, Inc. v. FDA*, 963 F.3d 436, 443 (5th Cir. 2020) ("In the TCA, Congress delegated to the Secretary the power to 'deem' which tobacco products should be subject to the Act's mandates."). Thus, the TCA and the Deeming Rule generally prohibited the marketing of e-cigarettes.

This created a serious and obvious problem because, by the time the FDA got around to issuing the Deeming Rule, manufacturers were widely marketing e-cigarettes throughout the United States. To avoid an overnight shutdown of the entire e-cigarette industry, the FDA delayed enforcement of the Deeming Rule. Then the FDA forced e-cigarette makers to meet a series of requirements and staggered deadlines to keep their products on the market.

As relevant here, the FDA required e-cigarette manufacturers to submit premarket tobacco applications ("PMTAs"). The PMTA process is "onerous," to put it mildly. *See Big Time Vapes*, 963 F.3d at 439 ("The PMTA process is onerous, requiring manufacturers to gather significant amounts of information."). A manufacturer must submit to the FDA information on the product's health risks, ingredients, and manufacturing process. The manufacturer also must include samples

of the product and its proposed labeling. 21 U.S.C. § 387j(b)-(c).

In the months and years following the Deeming Rule, the FDA moved its regulatory goalposts in at least two important ways. First, it moved the PMTA deadline. Originally, the FDA demanded that all PMTAs must be filed within 24 months of the Deeming Rule—*i.e.*, by 2018. The FDA later purported to extend the PMTA deadline to 2022. But then, in response to litigation from anti-smoking groups, the FDA moved the deadline up to September 9, 2020. Second, and crucial to this case, the FDA changed the regulatory requirements for PMTAs. Initially, the FDA's guidance stated that "in general, FDA does not expect that applicants will need to conduct long-term studies to support an application." A.74; *see also* A.92 (same). As Triton's case illustrates, however, the FDA later changed its mind and required the very thing it said it would not—namely, long-term studies of e-cigarettes.

B.

Wages and White Lion Investments, LLC, doing business as Triton Distribution ("Triton"), is a Texas-based manufacturer of e-cigarettes. Some of its e-cigarette products have been on the market since August 4, 2016—before the Deeming Rule's effective date. Triton submitted a timely PMTA for certain flavored e-cigarettes. So did many other e-cigarette manufacturers.

On August 26, 2021, the FDA announced that it would deny the PMTAs for 55,000 flavored e-cigarettes. In its press release, the FDA explained that it would do so because it "likely" needed evidence from long-term studies to grant a PMTA for flavored e-cigarettes.

Less than a week after the FDA changed its regulatory requirements, Triton submitted a letter stating that it intended to conduct long-term studies of its products.

About two weeks later, on September 14, the FDA issued a marketing denial order ("Order") to Triton. *See* 21 U.S.C. § 387j(c)(2). The FDA acknowledged that it did not consider Triton's letter in its determination because the FDA "received [the letter] near the completion of scientific review." A.14-15. The "key basis" for the denial, wrote the FDA, was that Triton's PMTA lacked "robust and reliable evidence" from long-term studies, such as a "randomized controlled trial," a "longitudinal cohort study," or "other evidence . . . evaluat[ing] the impact of the new flavored vs. Tobacco-flavored products on adult smokers' switching or cigarette reduction over time." A.49.

Triton then petitioned for review and moved to stay the Order pending that review.[1] We granted a temporary administrative stay to prevent the FDA from shutting down Triton's business. Now we enter a full stay pending disposition of Triton's petition.

II.

For a stay pending review, we must consider four factors: (1) whether the requester makes a strong showing that it's likely to succeed on the merits; (2) whether the requester will be irreparably injured without a stay; (3) whether other interested parties will be irreparably injured by a stay; and (4) where the public interest lies. *Nken v. Holder*, 556 U.S. 418, 426 (2009). "The first

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[1] Triton did not first ask the FDA for a stay. But it's common ground that it would have been "impracticable" for Triton to do so. *See* FED. R. APP. P. 18(a)(2)(i).

two factors are the most critical." *Valentine v. Collier*, 956 F.3d 797, 801 (5th Cir. 2020) (per curiam). "'The party seeking the stay bears the burden of showing its need.'" *Tex. League of United Latin Am. Citizens v. Hughs*, 978 F.3d 136, 143 (5th Cir. 2020) (quoting *Clinton v. Jones*, 520 U.S. 681, 708 (1997)); *see also Nken*, 556 U.S. at 433-34 ("The party requesting a stay bears the burden of showing that the circumstances justify an exercise of that discretion."). Triton has met its burden: The first three factors support a stay, while the fourth is at worst neutral.

A.

First, likelihood of success. The Administrative Procedure Act ("APA") directs courts to "hold unlawful and set aside agency action[s]" that are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2). "The APA's arbitrary-and-capricious standard requires that agency action be reasonable and reasonably explained." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). We must not "substitute" our "own policy judgment for that of the agency." *Ibid.* Still, we must ensure that "the agency has acted within a zone of reasonableness and, in particular, has reasonably considered the relevant issues and reasonably explained the decision." *Ibid.*; *see also Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) ("[T]he agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" (quoting *Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962))). "Put simply, we must set aside any action premised on rea-

soning that fails to account for 'relevant factors' or evinces 'a clear error of judgment.'" *Univ. of Tex. M.D. Anderson Cancer Ctr. v. HHS*, 985 F.3d 472, 475 (5th Cir. 2021) (quoting *Marsh v. Or. Nat. Res. Council*, 490 U.S. 360, 378 (1989)).

In reviewing an agency's action, we may consider only the reasoning "articulated by the agency itself"; we cannot consider *post hoc* rationalizations. *State Farm*, 463 U.S. at 50; *see also DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020) ("An agency must defend its actions based on the reasons it gave when it acted."). Our review is "not toothless." *Sw. Elec. Power Co. v. EPA*, 920 F.3d 999, 1013 (5th Cir. 2019). In fact, after *Regents*, it has serious bite. *See* 140 S. Ct. at 1907-15; *see also, e.g.*, *Texas v. Biden*, 10 F.4th 538, 552-57 (5th Cir. 2021) (per curiam); *Biden v. Texas*, No. 21A21, 2021 WL 3732667, at *1 (U.S. Aug. 24, 2021).

Triton has shown a strong likelihood of success on the merits. That's because the FDA failed to "reasonably consider[] the relevant issues and reasonably explain[]" the Order. *Prometheus*, 141 S. Ct. at 1158; *see also Michigan v. EPA*, 576 U.S. 743, 750, 752 (2015) ("[A]gency action is lawful only if it rests on a consideration of the relevant factors" and "important aspect[s] of the problem." (quotation omitted)). The relevant factors the FDA inadequately addressed or explained include: (1) Triton's marketing plan; (2) Triton's reliance interests; (3) less disruptive alternatives; (4) device-type preferences; and (5) evidence on the potential benefits of flavored e-cigarettes. The FDA's counterarguments (6) are unavailing.

1.

The FDA failed to reasonably consider Triton's proposed marketing plan. The FDA repeatedly stated that a marketing plan is "a critical factor in[] FDA's statutorily required determination." Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. 55,300, 55,324 (Oct. 5, 2021) ("Final Rule"); *see also* 84 Fed. Reg. 50,566, 50,581 (Sept. 25, 2019) ("Proposed Rule") ("The applicant's marketing plans . . . will provide input that is *critical* to FDA's determination of the likelihood of changes in tobacco product use behavior, especially when considered in conjunction with other information contained in the application." (emphasis added)); A.45 n.xix ("Limiting youth access and exposure to marketing is a *critical* aspect of product regulation." (emphasis added)); A.45 (Premarket "assessment includes evaluating the appropriateness of the proposed marketing plan."). Here, however, the FDA simply ignored Triton's plan. It stated: "[F]or the sake of efficiency, the evaluation of the marketing plan in applications will not occur at this stage of review, and we have not evaluated any marketing plans submitted with these applications." A.45 n.xix.

The FDA's excuses for ignoring the "critical factor" of Triton's marketing plan are unpersuasive. First, the FDA says it didn't evaluate Triton's plan for "the sake of efficiency." *Ibid.* But "efficiency" is no substitute for "reasoned decisionmaking." *Michigan*, 576 U.S. at 750; *see also Judulang v. Holder*, 565 U.S. 42, 64 (2011) (emphasizing that "cheapness alone cannot save an arbitrary agency policy").

Second, the FDA claimed that its purported expertise and experience showed that no marketing plan would be sufficient, so it stopped looking:

> 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 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.

A.45 n.xix. This statement is insufficient. For one thing, it's unreasonable for the FDA to stop looking at proposed plans because past ones have been unpersuasive. That's like an Article III judge saying that she stopped reading briefs because she previously found them unhelpful.

For another, reliance on expertise and experience, like efficiency, is no substitute for "reasoned decisionmaking." *Michigan*, 576 U.S. at 750. Of course, "[a]gencies . . . have expertise and experience in administering their statutes that no court can properly ignore." *Judulang*, 565 U.S. at 53. But here that hurts, not helps, the FDA. That's because experience and expertise bring responsibility:

> [A]n agency's "experience and expertise" presumably enable the agency to provide the required expla-

> nation, but they do not substitute for the explanation, any more than an expert witness's credentials substitute for the substantive requirements applicable to the expert's testimony under [Federal Rule of Evidence] 702. The requirement of explanation presumes the expertise and experience of the agency and still demands an adequate explanation in the particular matter.

CS Wind Viet. Co., Ltd. v. United States, 832 F.3d 1367, 1377 (Fed. Cir. 2016) (citations omitted).

The FDA did not meet its obligation. Its statement on marketing plans is conclusory, unsupported, and thus wholly insufficient. *See, e.g.*, *United Techs. Corp. v. U.S. Dep't of Def.*, 601 F.3d 557, 562 (D.C. Cir. 2010) ("We do not defer to the agency's conclusory or unsupported suppositions." (quotation omitted)); *Texas v. Biden*, 10 F.4th at 556 (collecting cases).[2] This "omission alone [likely] renders [the FDA's] decision arbitrary and capricious." *Regents*, 140 S. Ct. at 1913.

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[2] The FDA's failure to meaningfully consider Triton's marketing plan is even more unreasonable because part of Triton's plan was endorsed by a former FDA commissioner. *See* Statement from FDA Commissioner Scott Gottlieb, M.D., On Proposed New Steps to Protect Youth by Preventing Access to Flavored Tobacco Products and Banning Menthol in Cigarettes (Nov. 15, 2018) ("The changes I seek would protect kids by having all flavored ENDS products (other than tobacco, mint and menthol flavors or non-flavored products) sold in age-restricted, in-person locations and, if sold online, under heightened practices for age verification."); *ibid.* (calling some of Triton's proposed marketing restrictions "best practices").

2.

The FDA also failed to reasonably consider Triton's legitimate reliance interests. Between the Deeming Rule's effective date and the deadline for PMTAs, the FDA held public meetings and issued guidance on how e-cigarette manufacturers could get premarket authorization. In its "final guidance," the FDA stated that it did not "expect" that tobacco manufacturers would need to conduct long-term studies to support their PMTA. *See, e.g.*, A.73-74; A.92; *see also Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 282 (D.C. Cir. 2019) ("The FDA has expressed willingness to accept scientific literature reviews instead of commissioned studies in support of e-cigarette applications in appropriate circumstances."). The FDA's expectation did not deviate in its Proposed Rule issued before the Order or the Final Rule issued a couple weeks after the Order. *See* Final Rule, 86 Fed. Reg. at 55,387 ("FDA does not expect that long-term clinical studies will need to be conducted for each PMTA; instead, it expects that it should be able to rely on other valid scientific evidence to evaluate some PMTAs."); Proposed Rule, 84 Fed. Reg. at 50,619 (similar). Many e-cigarette companies relied on the FDA's repeated insistence that it did "not expect that applicants will have to conduct long-term studies to support an application" and did not perform or submit such evidence. A.74.

Then the FDA "pull[ed] a surprise switcheroo on regulated entities." *Env't Integrity Project v. EPA*, 425 F.3d 992, 996 (D.C. Cir. 2005) (Sentelle, J.); *accord Azar v. Allina Health Servs.*, 139 S. Ct. 1804, 1810 (2019) (citing the "surprise switcheroo" doctrine). Almost a year after the PMTA deadline, the FDA issued its first mar-

keting denial orders for various flavored e-cigarettes and announced that it required the very studies it originally expected it didn't need. *See* Press Release, FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health (Aug. 26, 2021). It explained: "[T]he evidence of benefits to adult smokers for such products would likely be in the form of a randomized controlled trial or longitudinal cohort study, although the agency does not foreclose the possibility that other types of evidence could be adequate if sufficiently robust and reliable" and performed over time. *Ibid.* About two weeks later, the FDA maintained its long-term-study requirement in the Order denying Triton premarket authorization. *See* A.49; A.37 (materially identical language to Press Release). Despite the radical difference, the FDA never mentioned, let alone reasonably considered, whether e-cigarette manufacturers, like Triton, could've reasonably relied on the FDA's prior meetings and guidance.

The law requires more. "When an agency changes course, . . . it must be cognizant that longstanding policies may have engendered serious reliance interests that must be taken into account." *Regents*, 140 S. Ct. at 1913 (quotation omitted). This does not mean that the FDA could not have "determine[d], in the particular context before it, that other interests and policy concerns outweigh any reliance interests. Making that difficult decision was the agency's job, but the agency failed to do it." *Id.* at 1914. This reinforces that the Order was likely arbitrary, capricious, or otherwise unlawful.

3.

The FDA insufficiently addressed alternatives to issuing the Order as well. "[W]hen an agency rescinds [or alters] a prior policy[,] its reasoned analysis must consider the alternatives that are *within the ambit of the existing policy*." *Regents*, 140 S. Ct. at 1913 (emphasis added) (quotation omitted). While considering less disruptive alternatives, the FDA "was required to assess whether there were reliance interests, determine whether they were significant, and weigh any such interests against competing policy concerns." *Id.* at 1915. The FDA did not consider alternatives when changing from its no-long-term-studies-necessary policy to its apparent long-term-studies-required policy.

And even if the FDA did, it failed to adequately assess reliance interests. "So it would be impossible for the [Order] to properly weigh the relevant interests against competing policy concerns while considering alternatives." *Texas v. Biden*, 10 F.4th at 555.

4.

The FDA also failed to adequately address Triton's contention that its reusable e-cigarette will reduce youth popularity compared to disposable e-cigarettes. In January 2020 guidance, the FDA found that "youth overwhelmingly prefer [disposable] ENDS products" because they "are easy to conceal" and "can be used discreetly." Enforcement Priorities for Electronic Nicotine Delivery Systems and Other Deemed Products on the Market Without Premarket Authorization; Guidance for Industry; Availability, 85 Fed. Reg. 720, 722 (Jan. 7, 2020). By contrast, the FDA found in the Order that the type of system didn't matter. Specifically,

the FDA found that "preference for device types and popularity of certain styles is likely fluid and affected by the marketplace" and "that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired flavor option, underscoring the fundamental role of flavor in driving appeal." A.42.

Because its "new policy rest[ed] upon factual findings that contradict those which underlay its prior policy," the FDA had to provide "a more detailed justification." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009). The FDA initially said that *disposable* e-cigarettes pose risks to youths. When Triton said that concern doesn't apply to its *reusable* e-cigarettes, the FDA turned around and ignored its prior disposable-reusable distinction. The FDA failed to adequately explain this change. This further reinforces that the Order is likely arbitrary, capricious, or otherwise unlawful.

5.

In announcing its rule that the manufacturer must provide long-term studies to get approval for flavored e-cigarettes, the FDA resorted entirely to experience and expertise from reviewing applications other than Triton's PMTA. *See* A.45. In so doing, the FDA used "generalized language to reject" Triton's PMTA. *See Siddiqui v. Holder*, 670 F.3d 736, 744 (7th Cir. 2012) ("Where, as here, the agency uses only generalized language to reject the evidence, we cannot conclude that the decisions rest on proper grounds."). The consequence is that the FDA failed to reasonably consider relevant issues that *Triton* brought up in its PMTA but that others might not have.

The FDA responded to much of Triton's evidence for the first time before our court. But "[i]t is a fundamental precept of administrative law that an administrative agency cannot make its decision first and explain it later." *Texas v. Biden*, 10 F.4th at 558-59; *see also Sherley v. Sebelius*, 689 F.3d 776, 784 (D.C. Cir. 2012) (Sentelle, C.J.) ("The failure to respond to comments is significant only insofar as it demonstrates that the agency's decision was not based on a consideration of the relevant factors." (quotation omitted)); *Circus Circus Casinos, Inc. v. NLRB*, 961 F.3d 469, 476 (D.C. Cir. 2020) ("New rules set through adjudication must meet the same standard of reasonableness as notice and comment rulemaking." (citing *Allentown Mack Sales & Serv., Inc. v. NLRB*, 522 U.S. 359, 374 (1998))).

For example, Triton urged the FDA to consider a 2015 survey of 20,000 e-cigarette users showing that nearly a third of the respondents "started out using tobacco or menthol flavors" and then began using other flavored e-cigarettes. A.296. Similarly, Triton asserted that flavored e-cigarettes "could serve an important role in transitioning existing adult users away from more harmful, combustible cigarette products." *Ibid.* But in the Order, the FDA ignored the first point altogether and gave the second short shrift. The FDA cannot cure those deficiencies by offering *post hoc* rationalizations before our court. The very fact that the FDA perceived the need to rehabilitate its Order with new and different arguments before our court underscores that the Order itself omitted a reasoned justification for the agency's action. This further confirms that the Order is likely arbitrary, capricious, or otherwise unlawful.

6.

The FDA makes four other counterarguments. They fail.

First, the FDA argues that its consistency "in reviewing other manufacturers' similar applications to market flavored e-cigarette products is a hallmark of good government, not a reason to fault the agency." Opp. at 23 (citation omitted). Consistency is great—but only when the agency is consistently following the law. As the Supreme Court has made clear: "Arbitrary agency action becomes no less so by simple dint of repetition." *Judulang*, 565 U.S. at 61; *see also ibid.* ("[L]ongstanding capriciousness receives no special exemption from the APA.").

Second, the FDA insists that the reasoning in the Order is consistent with its prior guidance. According to the FDA, it didn't make a rule requiring long-term studies because it left open that "other types of evidence could be adequate[] and will be evaluated on a case-by-case basis." A.37.

But the administrative record makes clear that the FDA now requires direct evidence through studies performed "over time" for flavored e-cigarettes. A.46; *see also, e.g.*, A.37 n.vi; A.47 n.xxiii. And it's clear the FDA expressly rejected reliance on evidence it approved of in its pre-Order guidance, such as observational and consumer-perception studies. *Compare* A.46-47, *with* A.99. The FDA did not have to completely flip flop for there to be a change in position. *Cf. Sw. Airlines Co. v. Fed. Energy Regul. Comm'n*, 926 F.3d 851, 856 (D.C. Cir. 2019) ("A full and rational explanation becomes especially important when, as here, an agency elects to

shift its policy or depart from its typical manner of administering a program." (quotation omitted)). It is enough that the FDA's guidance indicated long-term studies were likely unnecessary, while the FDA's Order at the very least created a strong presumption that such evidence is required.

Plus, if we accepted the FDA's current position that it did not acknowledge a change in policy in the Order, then the Order would obviously be arbitrary and capricious. That's because "[w]hen an agency changes its existing position, it . . . must at least display awareness that it is changing position and show that there are good reasons for the new policy." *Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2125-26 (2016) (quotation omitted); *see also id.* at 2126 (explaining that an "unexplained inconsistency in agency policy is a reason for holding an [action] to be an arbitrary and capricious change from agency practice" (quotation omitted)); *Fox*, 556 U.S. at 515 ("[T]he requirement that an agency provide reasoned explanation for its action would ordinarily demand that it display awareness that it *is* changing position. An agency may not . . . depart from a prior policy *sub silentio*."). It would be impossible for the FDA to display awareness that it was changing position if it believed it wasn't.

Third, the FDA argues that Triton should not have relied on the agency's pre-Order guidance. This is because, the FDA claims, 21 U.S.C. § 387j(c)(5) "directs FDA to make that finding based on 'clinical investigations by experts qualified by training and experience to evaluate the tobacco product' or other 'valid scientific evidence' that FDA determines is sufficient." Opp. at 19; *see also id.* at 20 (The "2019 guidance does not and

could not relax the statute's requirements."). Of course, an agency cannot issue guidance on the meaning of a statute, encourage its regulated entities to rely on the guidance, and then blame *the statute* for pulling the rug out from under the entities. And in any event, the FDA mischaracterizes § 387j(c)(5). Paragraph (5) does not require the FDA to base *all* of its appropriate-for-the-protection-of-the-public-health findings on long-term studies; instead, it requires the FDA to base its decision on "well-controlled investigations" "*when appropriate*" and provides that those investigations "*may* include 1 or more *clinical* investigations." 21 U.S.C. § 387j(c)(5)(A) (emphases added). And the consideration of other "valid scientific evidence" is likewise discretionary. *See id.* § 387j(c)(5)(B) ("may authorize"). The FDA's "final guidance" reflected its "expect[ation]" that, at the time, it would not deem it "appropriate" to base its decision on long-term studies. A.74; A.92. The guidance also stated that the FDA would consider the type of evidence Triton presented "valid scientific evidence." So of course, the statute might have *permitted* the FDA to demand the evidence it ultimately did. But it does not follow that the statute *required* the FDA to jettison the guidance it previously offered regulated entities.

Fourth and last, the FDA argues that Triton's reliance interests shouldn't matter because Triton has been breaking the law and the FDA's non-enforcement was entirely discretionary. *Regents* squarely forecloses this argument. There, the Department of Homeland Security ("DHS") tried to rescind the Deferred Action for Childhood Arrivals ("DACA") program because of "the Attorney General's conclusion that DACA was unlawful." *Regents*, 140 S. Ct. at 1910. The United

States argued that justified ignoring potential reliance interests. *Id.* at 1913-14. The Supreme Court rejected that argument. *Ibid.* The Court instead required reasonable consideration of the relevant issues and the "important aspects of the problem." *Id.* at 1910 (quotation omitted). That was because, the Court explained, "deciding how best to address a finding of illegality moving forward can involve important policy choices." *Ibid.* The same is true here. The FDA was free to make that policy choice, but it had to address Triton's reliance interests in a reasonable and reasonably explained decision.

For these reasons, Triton has shown a likelihood of success based on its APA challenge. So this critical factor favors granting a stay. We therefore need not address Triton's argument that the FDA violated the Due Process Clause for not giving "fair warning" of its change in position on what evidence would be required in its PMTA.

B.

Next, irreparable injury. Triton alleges that because of the Order, it "has stopped production of all of its flavored ENDS products, representing 90 percent of its annual revenue, thereby requiring the company to make plans to lay off its employees within approximately two weeks and threatening the company's very existence." Stay Mot. at 21; *see also* A.15-16 (Declaration of Triton's General Manager). The FDA does not contest that allegation.

Triton's alleged injury is irreparable for two independent reasons. First, we've explained that "substantial financial injury" may be "sufficient to show irrepa-

rable injury." *Texas v. EPA*, 829 F.3d 405, 433 (5th Cir. 2016). Triton's alleged financial injury "threatens the very existence of [its] business." *Id.* at 434. Even assuming the financial costs are recoverable, this suffices to show irreparable injury. *See id.* at 434 n.41 ("Even recoverable costs may constitute irreparable harm where the loss threatens the very existence of the movant's business." (quotation omitted)).

Second, the costs are likely unrecoverable. "Indeed, complying with [an agency order] later held invalid almost *always* produces the irreparable harm of nonrecoverable compliance costs." *Id.* at 433 (quotation omitted). The FDA does not contend that Triton has an avenue to recover costs from complying with the Order. That's probably because federal agencies generally enjoy sovereign immunity for any monetary damages. *See, e.g.*, *Alabama-Coushatta Tribe of Texas v. United States*, 757 F.3d 484, 488 (5th Cir. 2014); *Louisiana v. United States*, 948 F.3d 317, 320 (5th Cir. 2020); *Muniz-Muniz v. U.S. Border Patrol*, 741 F.3d 668, 671 (6th Cir. 2013) ("Sovereign immunity extends to agencies of the United States." (quotation omitted)). At bottom, Triton's lack of a "guarantee of eventual recovery" is another reason that its alleged harm is irreparable. *Alabama Ass'n of Realtors v. Dep't of Health & Hum. Servs.*, 141 S. Ct. 2485, 2489 (2021).

The FDA makes no developed argument contesting irreparable harm. *See* Opp. at 11, 13 (mentioning "irreparable injury" in passing). So such arguments are forfeited. *See, e.g.*, *DeVoss v. Sw. Airlines Co.*, 903 F.3d 487, 490 n.1 (5th Cir. 2018) (concluding that an argument was "forfeited" because it wasn't "structured"); *Texas v. EPA*, 829 F.3d at 435 ("Because EPA offers

nothing beyond this cursory comment, it has waived any argument about the scope of the stay.").

In these circumstances, given Triton's uncontested allegations of injury and the FDA's failure to make a developed argument challenging this factor, we conclude that Triton has met its burden of showing irreparable harm. Thus, the two most critical factors favor granting a stay.

C.

Now, the balance of harms and public interest.

The balance of the harms favors a stay. We've explained that "the maintenance of the *status quo* is an important consideration in granting a stay." *Barber v. Bryant*, 833 F.3d 510, 511 (5th Cir. 2016) (quotation omitted). And staying the Order will preserve the *status quo ante*. *Cf. Turning Point Brands, Inc. v. FDA*, No. 21-3855, ECF No. 19 at 9-10 (6th Cir. Oct. 8, 2021) (FDA letter rescinding a marketing denial order and stating the "FDA has no intention of initiating an enforcement action against any of your tobacco products identified in" the relevant PMTA). "Given the great likelihood that [Triton] will ultimately succeed on the merits, combined with the undeniable, irreparable harm that [the Order] would inflict on" Triton and the FDA's failure to make a developed argument on this factor, we conclude, in these circumstances, "that the balance of harms weighs in favor of" Triton. *Tex. Democratic Party v. Abbott*, 961 F.3d 389, 412 (5th Cir. 2020).

The public-interest factor is at worst neutral. The "public interest is in having governmental agencies abide by the federal laws that govern their existence and operations." *Texas v. Biden*, 10 F.4th at 559 (quotation

omitted). "And 'there is generally no public interest in the perpetuation of unlawful agency action.'" *Id.* at 560 (alteration omitted) (quoting *League of Women Voters of U.S. v. Newby*, 838 F.3d 1, 12 (D.C. Cir. 2016)). Although the FDA fails to argue this factor, *amici curiae* do. They argue that the public interest cuts against a stay because continued sale of flavored e-cigarettes will endanger the youth much more than it might help adults. "But our system does not permit agencies to act unlawfully even in pursuit of desirable ends." *Alabama Ass'n of Realtors*, 141 S. Ct. at 2490. So we conclude that this factor is at best neutral, or, in all events, outweighed by the three other factors favoring a stay.

III.

Finally, the FDA argues that Triton requests relief we cannot give. We have no authority, says the FDA, to permit Triton to continue marketing and selling the products denied in the Order. But again, the APA says otherwise. Under 5 U.S.C. § 705, we may, under certain "conditions[,] . . . and to the extent necessary to prevent irreparable injury, . . . issue all necessary and appropriate process to postpone the effective date of an agency action or to preserve status or rights pending conclusion of the review proceedings."

The immigration context is instructive. Consider an alien that is unlawfully present in the United States. Suppose the Government attempts to remove the alien. Then the alien argues that he should not be removed because he deserves asylum, and he asks us to stay the removal pending our review of his petition. Under the FDA's logic, we couldn't do anything. After all, we couldn't order the Board of Immigration Appeals to grant the alien asylum or otherwise adjust his immigra-

tion status to make his presence lawful. But of course, we could grant a stay of the removal, giving the alien interim relief. *See generally Tesfamichael v. Gonzales*, 411 F.3d 169 (5th Cir. 2005) (granting a stay of removal pending the court of appeals' consideration of the party's petition for review); *see also Nken*, 556 U.S. at 429 ("An alien seeking a stay of removal pending adjudication of a petition for review does not ask for a coercive order against the Government, but rather for the temporary setting aside of the source of the Government's authority to remove. Although such a stay acts to bar Executive Branch officials from removing the applicant from the country, it does so by returning to the *status quo*—the state of affairs before the removal order was entered." (quotation omitted)).

Triton's request is not materially different. It merely seeks to preserve the *status quo ante*, before the FDA issued the Order. In other words, "the relief sought here would simply suspend *administrative* alteration of the *status quo*." *Nken*, 556 U.S. at 430 n.1. So we reject the FDA's argument that we lack authority to grant a stay that provides interim relief.

* * *

Three factors—including the two most critical—favor granting a stay, while one factor is at worst neutral. Triton has thus met its burden. Contrary to the FDA's suggestion, we have the authority to give Triton relief pending review. For the foregoing reasons, Triton's motion for a stay pending review of its petition is GRANTED.

APPENDIX D

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Sept. 14, 2021

DENIAL

Wages & White Lion Investments LLC
dba Triton Distribution
Attention: Jon Rose, General Manager
789 North Grove Road Suite 111
Richardson, TX 75081

FDA Submission Tracking Numbers (STNs): Multiple STNs, see Appendix A

Dear Mr. Rose:

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.

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

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

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 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 evalu-

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

> ated the impact of the new flavored vs. Tobacco-flavored products on adult smokers' switching or cigarette reduction over time. We did not find such evidence in your PMTAS. 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.

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.

If you have any questions, please contact Sammrawit Girma, Regulatory Health Project Manager, at (301) 796-5313 or Sammrawit.Girma@fda.hhs.gov.

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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

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2021.09.14 16:46:09 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

Enclosures: **(if provided electronically, the Appendix is 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 A[7]

New Tobacco Products Subject of This Letter

Common Attributes of PMTAs	
Date of Submission	September 9, 2020
Date of receipt	September 9, 2020
Product Manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Product Category	ENDS (Electronic Nicotine Delivery System)
Product Sub-Category	ENDS Component

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

[FOLDOUT]

[FOLDOUT]

[FOLDOUT]

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Appendix B

Amendments Received for These Applications

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
September 1, 2021	September 1, 2021	PM0004979	No. Amendment not reviewed because it was received near the completion of the scientific review.	Other—outline for intended submission of further product testing
September 1, 2021	September 2, 2021	PM0004982	No. Amendment not reviewed because it was received near the completion of the scientific review.	Other—outline for intended submission of further product testing

APPENDIX E

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking numbers (STNs)	PM0003790, see Appendix A
Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Wages & White Lion Investments LLC dba Triton Distribution
Product manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

[i] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application. Scientific references are listed at the end of this document and referred to with Arabic numerals; general footnotes are referred to with Roman numerals.

Recommendation
Issue marketing denial orders for the new tobacco products subject of this review.

Technical Project Lead (TPL):

Digitally signed by Bridget K. Ambrose -S
Date: 2021.09.14 16:05:55 -04'00'

Bridget Ambrose, Ph.D., M.P.H.
Director
Division of Population Health Science

Signatory Decision: **Concur with TPL recommendation and basis of recommendation**

Digitally signed by Matthew R. Holman -S
Date: 2021.09.14 16:44:10 -04'00'

Matthew R. Holman
Director
Office of Science

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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.

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

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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.

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 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.

[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 prespecified 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 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.

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 subject PMTAs do not contain evidence from a randomized controlled trial, longitudinal cohort study, or other evidence 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. 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.

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 April 12, 2021. FDA issued Filing letters to the applicant on June 24, 2021, and August 2, 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]

[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 de-

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 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 Market without Premarket Authorization" (2020 Enforcement Priorities Guidance). In this guidance, 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]

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crease 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, 2011-2018," Morbidity and Mortality Weekly Report, 67(45); 1276-1277, 2018.

[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

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 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

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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 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.

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 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 al-

ways 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 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

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[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.

[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.

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 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.

[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.

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, 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 in-

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

creased reward-seeking and risk-taking 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 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) relat-

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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.

ing 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 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 car-

diovascular health effects. This evidence demonstrates that flavored ENDS pose a significant risk to youth.

— **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 assessment of how a new product may be used by current smokers can be derived from a variety of sources. FDA may consider direct behav-

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[xvii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

ioral 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-controlled investigations are "appropriate" for 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.

[xviii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

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]

[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 significant enough to ad-

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-

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dress 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.

world use 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 that would enable a com-

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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 products to one or more of their other products (not included in the study).

parison 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]

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 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.

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 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/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

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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.

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] evidence to demonstrate a potential for benefit to adult smokers that could justify that risk.

[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 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.

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.

3. SCIENTIFIC REVIEW

Reviews were completed by Sean Dolan and Robert Garcia on September 14, 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 appropri-

ate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes. Our review also did not identify other evidence that supports this finding.

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 review, we determined that the PMTAs for 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.

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. We did not find such evidence in your PMTAS. 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[xxvi,xxvii]

Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Wages & White Lion Investments LLC dba Triton Distribution
Product manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

Appendix B. Amendments Received

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
September 1, 2021	September 1, 2021	PM0004979	All[xxvii]	No. Amendment not reviewed because	Other—outline for intended submission of

[xxvi] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.

[xxvii] Brand/sub-brand or other commercial name used in commercial distribution.

				it was received near the completion of the scientific review.	further product testing
September 1, 2021	September 2, 2021	PM0004982	All[xxviii]	No. Amendment not reviewed because it was received near the completion of the scientific review.	Other—outline for intended submission of further product testing

[xxviii] This amendment applies to all STNs subject of this review.

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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 Customiza-

ble 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 character-

ized 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 F

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Sept. 14, 2021

DENIAL

Wages & White Lion Investments LLC dba Triton Distribution
Attention: Jon Rose, General Manager
789 North Grove Road Suite 111
Richardson, TX 75081

FDA Submission Tracking Numbers (STNs): Multiple STNs, see Appendix A

Dear Mr. Rose:

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.

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

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

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 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 evalu-

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

> ated the impact of the new flavored vs. Tobacco-flavored products on adult smokers' switching or cigarette reduction over time. We did not find such evidence in your PMTAS. 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.

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.

If you have any questions, please contact Sammrawit Girma, Regulatory Health Project Manager, at (301) 796-5313 or Sammrawit.Girma@fda.hhs.gov.

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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

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2021.09.14 16:46:57 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

Enclosures: **(if provided electronically, the Appendix is 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 G

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking numbers (STNs)	PM0003790, see Appendix A
Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Wages & White Lion Investments LLC dba Triton Distribution
Product manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

[i] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application. Scientific references are listed at the end of this document and referred to with Arabic numerals; general footnotes are referred to with Roman numerals.

Recommendation
Issue marketing denial orders for the new tobacco products subject of this review.

Technical Project Lead (TPL):

Digitally signed by Bridget K. Ambrose -S
Date: 2021.09.14 16:06:50 -04'00'

Bridget Ambrose, Ph.D., M.P.H.
Director
Division of Population Health Science

Signatory Decision: **Concur with TPL recommendation and basis of recommendation**

Digitally signed by Matthew R. Holman -S
Date: 2021.09.14 16:44:47 -04'00'

Matthew R. Holman
Director
Office of Science

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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.

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

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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.

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 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.

[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 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.

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 subject PMTAs do not contain evidence from a randomized controlled trial, longitudinal cohort study, or other evidence 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. 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.

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 April 12, 2021. FDA issued Filing letters to the applicant on June 24, 2021, and August 2, 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]

[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 de-

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 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 Market without Premarket Authorization" (2020 Enforcement Priorities Guidance). In this guidance, 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]

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crease 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, 2011-2018," Morbidity and Mortality Weekly Report, 67(45); 1276-1277, 2018.

[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

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 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

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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 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.

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 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.

2.3.1. 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 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

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[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.

[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.

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 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

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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.

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, 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 develop-

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

mental period consisting of major neurobiological and psychosocial changes and is characterized by increased reward-seeking and risk-taking 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 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-ciga-

rette 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,

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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.

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 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 un-

derstood, 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.

2.3.2. 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 assessment of how a new product may

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[xvii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

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-controlled investigations are "appropriate" for 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 conduct-

[xviii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

ing an RCT to demonstrate adequate benefit is a longitudinal cohort study.

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]

[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.

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 con-

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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 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.

trast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions—the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive.[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 that would enable a com-

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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 justifi-

parison 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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able 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.

[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 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 im-

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 smokers arises from a combination of its product features—including labeled characteristics like

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pact it would have on initiation, experimentation, or progression to regular use.

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/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

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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.

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] evidence to demonstrate a potential for

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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 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 in-

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.

3. SCIENTIFIC REVIEW

Reviews were completed by Sean Dolan and Robert Garcia on September 14, 2021.

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formation, bridging from a different set of products (not the subject of the application) would not be appropriate here.

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. Our review also did not identify other evidence that supports this finding.

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 review, we determined that the PMTAs for 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.

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. We did not find such evidence in your pmtas. 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. APENDIX

Appendix A. New Products[xxvi,xxvii]

Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Wages & White Lion Investments LLC dba Triton Distribution
Product manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

Appendix B. Amendments Received

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
September 1, 2021	September 1, 2021	PM0004979	All[xxvii]	No. Amendment not reviewed because	Other—outline for intended submission of

[xxvi] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.

[xxvii] Brand/sub-brand or other commercial name used in commercial distribution.

				it was received near the completion of the scientific review.	further product testing
September 1, 2021	September 2, 2021	PM0004982	All[xxviii]	No. Amendment not reviewed because it was received near the completion of the scientific review.	Other—outline for intended submission of further product testing

[xxviii] This amendment applies to all STNs subject of this review.

STN	PD Number	Product Name	Category	Subcategory	Package Type	Package Quantity	Characterizing Flavor	Additional Property
PM0003790	PD227	Teleos Boo 0mg	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Boo	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL,120mL
PM0003790	PD228	Teleos Boo 3mg	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Boo	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL,120mL
PM0003790	PD229	Teleos Boo 6mg	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Boo	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL,120mL
PM0003790	PD230	Teleos Boo 12mg	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Boo	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL,120mL

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 Customiza-

ble 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 character-

ized 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 H

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Sept. 16, 2021

DENIAL

Vapetasia LLC
Attention: Jon Rose, General Manager
Wages & White Lion Investments LLC dba Triton Distribution
789 North Grove Road Suite 111
Richardson, TX 75081

FDA Submission Tracking Numbers (STNs): PM0003531, see Appendix A

Dear Mr. Rose:

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.

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 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

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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

> 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 a cross-sectional survey "Vapetasia PMTA Survey and Tesimonial", this evidence is sufficient to show a benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s) or evaluate product switching or cigarette reduction resulting from use of these products over time.
>
> 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.

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

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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

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.

If you have any questions, please contact Crystal Caesar, Regulatory Health Project Manager, at (240) 402-4793 or Crystal.Caesar@fda.hhs.gov.

Sincerely,

Digitally signed by Matthew R. Holman -5
Date: 2021.09.16 14:38:30 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

Enclosure (if provided electronically, the Appendix is not included in physical mail):

Appendix A—New Tobacco Products Subject of This Letter

Appendix B—Amendments Received for These Applications

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

Appendix A[7]

New Tobacco Products Subject of This Letter

Common Attributes of PMTAs	
Date of Submission:	September 9, 2020
Date of receipt:	September 9, 2020
Applicant:	Vapetasia LLC
Product Manufacturer:	Vapetasia LLC
Product Category:	ENDS (VAPES)
Product Sub-Category:	ENDS Component

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

Appendix B

Amendments Received for These Applications

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
September 1, 2021	September 1, 2021	All	No. Amendment not reviewed because it was received near the completion of the scientific review.	Additional information regarding plans for further product testing, and studies.
September 1, 2021	September 1, 2021	All	No. Amendment not reviewed because it was received near the completion of the scientific review.	Additional information regarding plans for further product testing, and studies.

APPENDIX I

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking numbers (STNs)	PM0003531, see Appendix A
Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Vapetasia LLC
Product manufacturer	Vapetasia LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submissions	
All new products	MF0000068, MF000262, MF0000363, MF0000384,

[i] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application. Scientific references are listed at the end of this document and referred to with Arabic numerals; general footnotes are referred to with Roman numerals.

	MF0000397, MF0000401, MF0000403, MF0000447
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review	

Technical Project Lead (TPL):

Digitally signed by Luis G. Valerio -S
Date: 2021.09.16 13:12:22 -04'00'

Luis G. Valerio, Jr., Ph.D., ATS
Associate Director
Division of Nonclinical Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2021.09.16 14:37:30 -04'00'

Matthew R. Holman
Director
Office of Science

TABLE OF CONTENTS

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.

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

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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.

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 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.

[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 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.

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 subject PMTAs do not contain evidence from a randomized controlled trial, longitudinal cohort study, or other evidence 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. 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.

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 April 12, 2021. FDA issued Filing letters to the applicant on June 24, 2021, and August 2, 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]

[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 de-

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 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 Market without Premarket Authorization" (2020 Enforcement Priorities Guidance). In this guidance, 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]

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crease 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, 2011-2018," Morbidity and Mortality Weekly Report, 67(45); 1276-1277, 2018.

[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

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 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

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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 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.

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 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 al-

ways 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 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

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[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.

[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.

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 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.

[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.

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, 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 in-

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

creased reward-seeking and risk-taking 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 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) relat-

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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.

ing 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 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 car-

diovascular health effects. This evidence demonstrates that flavored ENDS pose a significant risk to youth.

— **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 assessment of how a new product may be used by current smokers can be derived from a variety of sources. FDA may consider direct behav-

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[xvii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

ioral 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-controlled investigations are "appropriate" for 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.

[xviii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

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]

[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 significant enough to ad-

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-

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dress 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.

world use 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 that would enable a com-

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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 products to one or more of their other products (not included in the study).

parison 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]

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 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.

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 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/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

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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.

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] evidence to demonstrate a potential for benefit to adult smokers that could justify that risk.

[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 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.

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.

3. SCIENTIFIC REVIEW

Reviews were completed by Sean Dolan and Robert Garcia on September 14, 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 appropri-

ate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes. Our review also did not identify other evidence that supports this finding.

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 review, we determined that the PMTAs for 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.

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 a cross-sectional survey "Vapetasia PMTA Survey and Testimonial", this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it does not evaluate the specific products in the application(s) or evaluate product switching or cigarette reduction resulting from use of these products over time.

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. APENDIX

Appendix A. New Products

Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Vapetasia LLC
Product manufacturer	Vapetasia LLC
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

Appendix B. Amendments Received

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
September 1, 2021	September 1, 2021	PM0004981	All[xxvi]	No. Amendment not reviewed because it was received near the completion of the scientific review.	Additional information regarding plans for further product testing, and studies.
September 1, 2021	September 2, 2021	PM0004978	All[xxvi]	No. Amendment not reviewed because it was received near the completion of the sci-	Additional information regarding plans for further product testing, and studies.

[xxvi] This amendment applies to all STN subject of this review.

				entific review.	

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 Customiza-

ble 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 character-

ized 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 J

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

No. 21-60766

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

CONSOLIDATED WITH

No. 21-60800

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION;
VAPETASIA, L.L.C., PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

Filed: Mar. 12, 2024

Petition for Review from an Order of the
Food and Drug Administration
Agency Nos. 21 USC 3871, PM0003531

UNPUBLISHED ORDER

Before RICHMAN, *Chief Judge*, and JONES, SMITH, STEWART, ELROD, SOUTHWICK, HAYNES, GRAVES, HIGGINSON, WILLETT, HO, DUNCAN, ENGELHARDT, OLDHAM, WILSON, and DOUGLAS, *Circuit Judges*.[*]

IT IS ORDERED that Petitioners' unopposed motion for modification, amendment, or clarification of the en banc majority opinion, issued on January 3, 2024, is DENIED.[†]

The record shows: "In April 2019, FDA authorized the marketing of a menthol-flavored IQOS heat-not-burn cigarette product through the PMTA pathway." A.217; *see also* A.217 n.101 (citing https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway). The en banc majority relied on this document in noting that "FDA has approved menthol-flavored e-cigarette products notwithstanding its ban on 'flavored' products." 90 F.4th 357, 373. And as noted in the opinion, the en banc majority used the term "e-cigarette products" as a catch-all term to refer to a wide array of products, including but not limited to ENDS. *See id.* at 363 n.1.

It is also true, as the unopposed motion notes (at 5), that "Respondent Food and Drug Administration ('FDA') has not approved menthol-flavored electronic nicotine delivery systems ('ENDS') through the premarket tobacco application ('PMTA') process." Noth-

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[*] JUDGE RAMIREZ joined the court after this case was submitted and did not participate in the decision.

[†] Because the motion is directed only to the en banc majority opinion, this order is joined only by those judges who joined the underlying majority opinion.

ing in the en banc majority opinion is to the contrary. And nothing in the en banc majority opinion should be read to prejudice petitioners' arguments in other cases that FDA unlawfully created a new product standard banning menthol-flavored, liquid-based ENDS products. *See, e.g.*, Nos. 23-60037, 23-60128, 23-60545, *R.J. Reynolds Vapor Co. v. FDA*.

APPENDIX K

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

No. 21-60766

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

CONSOLIDATED WITH

No. 21-60800

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION;
VAPETASIA, L.L.C., PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

Filed: Jan. 19, 2023

Petitions for Review from an Order of the
Food and Drug Administration
Agency No. 21 USC 3871
Agency No. PM0003531

ON PETITION FOR REHEARING EN BANC
(Opinion July 18, 2022, 5 CIR. 2022, 41 F.4th 427)

Before RICHMAN, *Chief Judge*, and JONES, SMITH, STEWART, ELROD, SOUTHWICK, HAYNES, GRAVES, HIGGINSON, WILLETT, HO, DUNCAN, ENGELHARDT, OLDHAM, WILSON, and DOUGLAS, *Circuit Judges*.

PER CURIAM:

A member of the court having requested a poll on the petition for rehearing en banc, and a majority of the circuit judges in regular active service and not disqualified having voted in favor,

IT IS ORDERED that this cause shall be reheard by the court en banc with oral argument on a date hereafter to be fixed. The Clerk will specify a briefing schedule for the filing of supplemental briefs. Pursuant to 5th Circuit Rule 41.3, the panel opinion in this case dated July 18, 2022, is VACATED.

APPENDIX L

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

No. 21-60766

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

CONSOLIDATED WITH

No. 21-60800

WAGES AND WHITE LION INVESTMENTS, L.L.C., DOING BUSINESS AS TRITON DISTRIBUTION;
VAPETASIA, L.L.C., PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

Filed: Sept. 20, 2022

Petitions for Review from an Order of the
Food and Drug Administration
Agency No. 21 USC 3871

ON PETITION FOR PANEL REHEARING

Before JONES and HAYNES, *Circuit Judges*.

PER CURIAM:

The petition for panel rehearing is DENIED. The petition for rehearing en banc remains pending.

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[*] Judge Costa was a member of the original panel but resigned from the Court on August 31, 2022, and, therefore, did not participate in this decision. Due to his departure, the panel is equally divided such that panel rehearing cannot be granted.

APPENDIX M

1. 21 U.S.C. 387j provides:

Application for review of certain tobacco products

(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 387e(j) of this title; 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 chapter; or

(ii) the tobacco product is exempt from the requirements of section 387e(j) of this title pursuant to a regulation issued under section 387e(j)(3) of this title.

(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 June 22, 2009; and

(ii) for which a report was submitted under section 387e(j) of this title 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.

(3) Substantially equivalent defined

(A) In general

In this section and section 387e(j) of this title, the term "substantially equivalent" or "substantial equivalence" means, with respect to the tobacco product being compared to the predicate to-

bacco product, that the Secretary by order has found that the tobacco product—

(i) has the same characteristics as the predicate tobacco product; or

(ii) has different characteristics and the information submitted contains information, including clinical data if deemed necessary by the Secretary, that demonstrates that it is not appropriate to regulate the product under this section because the product does not raise different questions of public health.

(B) Characteristics

In subparagraph (A), the term "characteristics" means the materials, ingredients, design, composition, heating source, or other features of a tobacco product.

(C) Limitation

A tobacco product may not be found to be substantially equivalent to a predicate tobacco product that has been removed from the market at the initiative of the Secretary or that has been determined by a judicial order to be misbranded or adulterated.

(4) Health information

(A) Summary

As part of a submission under section 387e(j) of this title respecting a tobacco product, the person required to file a premarket notification under such section shall provide an adequate summary of any health information related to the tobacco

product or state that such information will be made available upon request by any person.

(B) Required information

Any summary under subparagraph (A) respecting a tobacco product shall contain detailed information regarding data concerning adverse health effects and shall be made available to the public by the Secretary within 30 days of the issuance of a determination that such tobacco product is substantially equivalent to another tobacco product.

(b) Application

(1) Contents

An application under this section shall contain—

(A) full reports of all information, published or known to, or which should reasonably be known to, the applicant, 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;

(B) a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;

(C) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product;

(D) an identifying reference to any tobacco product standard under section 387g of this title which would be applicable to any aspect of

such tobacco product, and either adequate information to show that such aspect of such tobacco product fully meets such tobacco product standard or adequate information to justify any deviation from such standard;

(E) such samples of such tobacco product and of components thereof as the Secretary may reasonably require;

(F) specimens of the labeling proposed to be used for such tobacco product; and

(G) such other information relevant to the subject matter of the application as the Secretary may require.

(2) Referral to Tobacco Products Scientific Advisory Committee

Upon receipt of an application meeting the requirements set forth in paragraph (1), the Secretary—

(A) may, on the Secretary's own initiative; or

(B) may, upon the request of an applicant,

refer such application to the Tobacco Products Scientific Advisory Committee for reference and for submission (within such period as the Secretary may establish) of a report and recommendation respecting the application, together with all underlying data and the reasons or basis for the recommendation.

(c) Action on application

(1) Deadline

(A) In general

As promptly as possible, but in no event later than 180 days after the receipt of an application under subsection (b), the Secretary, after considering the report and recommendation submitted under subsection (b)(2), shall—

(i) issue an order that the new product may be introduced or delivered for introduction into interstate commerce if the Secretary finds that none of the grounds specified in paragraph (2) of this subsection applies; or

(ii) issue an order that the new product may not be introduced or delivered for introduction into interstate commerce if the Secretary finds (and sets forth the basis for such finding as part of or accompanying such denial) that 1 or more grounds for denial specified in paragraph (2) of this subsection apply.

(B) Restrictions on sale and distribution

An order under subparagraph (A)(i) may require that the sale and distribution of the tobacco product be restricted but only to the extent that the sale and distribution of a tobacco product may be restricted under a regulation under section 387f(d) of this title.

(2) Denial of application

The Secretary shall deny an application submitted under subsection (b) if, upon the basis of the infor-

mation submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product, the Secretary finds that—

(A) 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;

(B) the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of such tobacco product do not conform to the requirements of section 387f(e) of this title;

(C) based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular; or

(D) such tobacco product is not shown to conform in all respects to a tobacco product standard in effect under section 387g of this title, and there is a lack of adequate information to justify the deviation from such standard.

(3) Denial information

Any denial of an application shall, insofar as the Secretary determines to be practicable, be accompanied by a statement informing the applicant of the measures required to remove such application from deniable form (which measures may include further research by the applicant in accordance with 1 or more protocols prescribed by the Secretary).

(4) Basis for finding

For purposes of this section, the finding as to whether the marketing of a tobacco product for which

an application has been submitted is appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account—

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

(5) Basis for action

(A) Investigations

For purposes of paragraph (2)(A), 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, which may include 1 or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product.

(B) Other evidence

If the Secretary determines that there exists valid scientific evidence (other than evidence derived from investigations described in subparagraph (A)) which is sufficient to evaluate the tobacco product, the Secretary may authorize that the determination for purposes of paragraph (2)(A) be made on the basis of such evidence.

(d) Withdrawal and temporary suspension

(1) In general

The Secretary shall, upon obtaining, where appropriate, advice on scientific matters from the Tobacco Products Scientific Advisory Committee, and after due notice and opportunity for informal hearing for a tobacco product for which an order was issued under subsection (c)(1)(A)(i), issue an order withdrawing the order if the Secretary finds—

(A) that the continued marketing of such tobacco product no longer is appropriate for the protection of the public health;

(B) that the application contained or was accompanied by an untrue statement of a material fact;

(C) that the applicant—

(i) has failed to establish a system for maintaining records, or has repeatedly or deliberately failed to maintain records or to make reports, required by an applicable regulation under section 387i of this title;

(ii) has refused to permit access to, or copying or verification of, such records as required by section 374 of this title; or

(iii) has not complied with the requirements of section 387e of this title;

(D) on the basis of new information before the Secretary with respect to such tobacco product, evaluated together with the evidence before the Secretary when the application was reviewed,

that the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or installation of such tobacco product do not conform with the requirements of section 387f(e) of this title and were not brought into conformity with such requirements within a reasonable time after receipt of written notice from the Secretary of nonconformity;

(E) on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when the application was reviewed, that the labeling of such tobacco product, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary of such fact; or

(F) on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when such order was issued, that such tobacco product is not shown to conform in all respects to a tobacco product standard which is in effect under section 387g of this title, compliance with which was a condition to the issuance of an order relating to the application, and that there is a lack of adequate information to justify the deviation from such standard.

(2) Appeal

The holder of an application subject to an order issued under paragraph (1) withdrawing an order issued pursuant to subsection (c)(1)(A)(i) may, by petition filed on or before the 30th day after the date

upon which such holder receives notice of such withdrawal, obtain review thereof in accordance with section 387*l* of this title.

(3) Temporary suspension

If, after providing an opportunity for an informal hearing, the Secretary determines there is reasonable probability that the continuation of distribution of a tobacco product under an order would cause serious, adverse health consequences or death, that is greater than ordinarily caused by tobacco products on the market, the Secretary shall by order temporarily suspend the authority of the manufacturer to market the product. If the Secretary issues such an order, the Secretary shall proceed expeditiously under paragraph (1) to withdraw such application.

(e) Service of order

An order issued by the Secretary under this section shall be served—

(1) in person by any officer or employee of the department designated by the Secretary; or

(2) by mailing the order by registered mail or certified mail addressed to the applicant at the applicant's last known address in the records of the Secretary.

(f) Records

(1) Additional information

In the case of any tobacco product for which an order issued pursuant to subsection (c)(1)(A)(i) for an application filed under subsection (b) is in effect, the applicant shall establish and maintain such records,

and make such reports to the Secretary, as the Secretary may by regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination of, whether there is or may be grounds for withdrawing or temporarily suspending such order.

(2) Access to records

Each person required under this section to maintain records, and each person in charge of custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(g) Investigational tobacco product exemption for investigational use

The Secretary may exempt tobacco products intended for investigational use from the provisions of this subchapter under such conditions as the Secretary may by regulation prescribe.

2. 21 U.S.C. 387*l* provides:

Judicial review

(a) Right to review

(1) In general

Not later than 30 days after—

(A) the promulgation of a regulation under section 387g of this title establishing, amending, or revoking a tobacco product standard; or

(B) a denial of an application under section 387j(c) of this title,

any person adversely affected by such regulation or denial may file a petition for judicial review of such regulation or denial with the United States Court of Appeals for the District of Columbia or for the circuit in which such person resides or has their principal place of business.

(2) Requirements

(A) Copy of petition

A copy of the petition filed under paragraph (1) shall be transmitted by the clerk of the court involved to the Secretary.

(B) Record of proceedings

On receipt of a petition under subparagraph (A), the Secretary shall file in the court in which such petition was filed—

(i) the record of the proceedings on which the regulation or order was based; and

(ii) a statement of the reasons for the issuance of such a regulation or order.

(C) Definition of record

In this section, the term "record" means—

(i) all notices and other matter published in the Federal Register with respect to the regulation or order reviewed;

(ii) all information submitted to the Secretary with respect to such regulation or order;

(iii) proceedings of any panel or advisory committee with respect to such regulation or order;

(iv) any hearing held with respect to such regulation or order; and

(v) any other information identified by the Secretary, in the administrative proceeding held with respect to such regulation or order, as being relevant to such regulation or order.

(b) 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 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.

(c) Finality of judgment

The judgment of the court affirming or setting aside, in whole or in part, any regulation or order shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification, as provided in section 1254 of title 28.

(d) Other remedies

The remedies provided for in this section shall be in addition to, and not in lieu of, any other remedies provided by law.

(e) Regulations and orders must recite basis in record

To facilitate judicial review, a regulation or order issued under section 387f, 387g, 387h, 387i, 387j, or 387p of this title shall contain a statement of the reasons for the issuance of such regulation or order in the record of the proceedings held in connection with its issuance.