APPENDIX

APPENDIX

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APPENDIX A

UNITED STATES COURT OF APPEALS

FOR THE SECOND CIRCUIT

August Term 2022

Argued: February 6, 2023
Decided: June 16, 2023

No. 21-2426

[Filed June 16, 2023]

MAGELLAN TECHNOLOGY, INC.,	)
	)
Petitioner,	)
	)
v.	)
	)
UNITED STATES FOOD AND DRUG ADMINISTRATION,	)
	)
	)
Respondent.	)
	)

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

Before: JACOBS, PÉREZ, and MERRIAM, *Circuit Judges*.

Petitioner Magellan Technology, Inc. ("Magellan"), the distributor of various electronic nicotine delivery

systems ("ENDS") products, petitions for review of a marketing denial order issued by Respondent, the United States Food and Drug Administration (the "FDA"). In September 2021, the FDA denied Magellan's premarket tobacco application, concluding that the application lacked sufficient evidence to demonstrate that the marketing of Magellan's flavored ENDS products was appropriate for the protection of the public health. Because we conclude that the FDA's denial of Magellan's application did not violate the Administrative Procedure Act and was well within the FDA's statutory authority under the Family Smoking Prevention and Tobacco Control Act, we deny Magellan's petition.

ERIC N. HEYER (Joseph A. Smith, Jessica Tierney, *on the brief*), Thompson Hine LLP, Washington, D.C., *for Petitioner Magellan Technology, Inc.*

DAVID H. HIXSON, Trial Attorney, Consumer Protection Branch (Brian M. Boynton, Principal Deputy Assistant Attorney General, Civil Division, Arun G. Rao, Deputy Assistant Attorney General, Civil Division, Gustav W. Eyler, Director, Consumer Protection Branch, Hilary K. Perkins, Assistant Director, Consumer Protection Branch, *on the brief*), U.S. Department of Justice, Washington, D.C. (Samuel R. Bagenstos, General Counsel, U.S. Department of Health and Human Services, Wendy S. Vicente, Acting Deputy Chief Counsel for Litigation, U.S. Food and Drug

Administration, William D. Thanhauser, Associate Chief Counsel, Office of the Chief Counsel, U.S. Food and Drug Administration, Silver Spring, MD, *of counsel*), *for Respondent United States Food and Drug Administration.*

J. Gregory Troutman, Troutman Law Office, PLLC, Louisville, KY, *for Amici Curiae 38 National and State Electronic Nicotine Delivery System Product Advocacy Associations, in support of Petitioner.*

Mary G. Bielaska, Zanicorn Legal PLLC, New York, NY, *for Amici Curiae Dr. David B. Abrams, Clive D. Bates, and Professor David T. Sweanor, in support of Petitioner.*

Shawn Naunton, Zuckerman Spaeder LLP, New York, NY, *for Amici Curiae Medical and Public Health Groups, in support of Respondent.*

MYRNA PÉREZ, *Circuit Judge*:

This case concerns the United States Food and Drug Administration's (the "FDA") efforts to regulate electronic nicotine delivery systems ("ENDS") products, more commonly known as e-cigarettes. ENDS are a relatively new type of tobacco product that deliver aerosolized liquid containing nicotine derived from tobacco ("e-liquids") when a user inhales. They have rapidly become popular—especially among young people, who have overwhelmingly adopted flavored ENDS products as their tobacco products of choice.

Magellan Technology, Inc. ("Magellan") distributes ENDS products, including replaceable cartridges,[1] also known as "pods." Magellan's pods contain e-liquids at four different nicotine strengths in fruit and dessert flavors—"Mango," "Pretzel Graham," and "Blue Razz"—as well as tobacco and menthol flavors. The FDA differentiates between e-liquids in fruit and dessert flavors ("flavored ENDS products" or "flavored pods") and e-liquids in tobacco and menthol flavors. *See* Joint App'x at 84.

Magellan sought authorization from the FDA to market its ENDS products under the Family Smoking Prevention and Tobacco Control Act (the "TCA"), Pub. L. No. 111-31, 123 Stat. 1776 (2009). The FDA denied Magellan's premarket tobacco application ("PMTA") with respect to its flavored pods, finding insufficient evidence showing that marketing the pods would be appropriate for the protection of the public health, a finding that requires denial of a PMTA under the TCA. *See* 21 U.S.C. § 387j(c)(2)(A). Magellan now petitions for review. It argues that the FDA's denial of its PMTA was arbitrary and capricious because (1) the FDA departed from its stated standard of review without providing notice to or considering the reliance interests of applicants; and (2) despite previously emphasizing the potential importance of marketing plans to its PMTA assessment, the FDA failed to consider Magellan's. Magellan also argues that the FDA

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[1] A cartridge is a "small, enclosed unit . . . designed to fit within or operate as part of an electronic nicotine delivery system" that "holds liquid that is to be aerosolized through product use." Joint App'x at 83.

exceeded its statutory authority by requiring applicants to demonstrate that their flavored ENDS products are more effective than tobacco-flavored products at promoting cessation or switching from combustible cigarettes to ENDS products. For the reasons stated herein, we uphold the FDA's decision and deny Magellan's petition.

I. Background

A. Statutory Framework

In enacting the TCA in 2009, Congress found that the use of tobacco products was "the foremost preventable cause of premature death in America" and, in particular, that youth use "is a pediatric disease of considerable proportions." TCA §§ 2(1), (13), 123 Stat. at 1777. To combat the public's use of and dependence on tobacco, the TCA "provide[s] authority to the Food and Drug Administration to regulate tobacco products under the Federal Food, Drug, and Cosmetic Act . . . , by recognizing it as the primary Federal regulatory authority with respect to the manufacture, marketing, and distribution of tobacco products." *Id.* § 3(1), 123 Stat. at 1781.

The TCA requires the FDA's premarket review of "new tobacco products" (defined in 21 U.S.C. § 387j(a)(1) as, inter alia, tobacco products not commercially marketed in the United States as of

February 15, 2007).[2] *Id.* § 387j(a)(2). Accordingly, unless an exemption applies, a manufacturer must submit a PMTA and obtain premarket authorization from the FDA to introduce a new tobacco product into interstate commerce. *Id.* §§ 387j(a)(1)–(2), (c)(1)(A)(i). As relevant here, to obtain FDA approval, an applicant must show that allowing its tobacco product to be marketed would be "appropriate for the public health" ("Appropriate"). *Id.* § 387j(c)(2)(A).

In determining whether the marketing of a tobacco product is Appropriate, the FDA considers the "risks and benefits to the population as a whole, including users and nonusers of the tobacco product." *Id.* § 387j(c)(4). The FDA must take 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." *Id.* §§ 387j(c)(4)(A)–(B). Thus, the FDA must weigh the potential benefits of the new tobacco product in promoting smoking cessation against the risks of the product contributing to smoking initiation. *See Avail Vapor, LLC v. FDA*, 55 F.4th 409, 414 (4th Cir. 2022). The FDA bases this finding on "well-controlled investigations" or other "exist[ing] valid scientific evidence . . . which is sufficient to evaluate the tobacco product." 21 U.S.C. §§ 387j(c)(5)(A)–(B).

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[2] The TCA "grandfathered tobacco products on the market as of February 15, 2007, excusing them from the premarket authorization requirement." *Prohibition Juice Co. v. FDA*, 45 F.4th 8, 13 (D.C. Cir. 2022) (citing 21 U.S.C. § 387j(a)(1)).

B. Regulatory Framework

The TCA also empowers the FDA to deem "tobacco products" as being subject to the TCA's requirements. *Id.* § 387a(b). In 2016, the FDA issued a rule deeming all tobacco products to be subject to the requirements of the Federal Food, Drug, and Cosmetic Act, as modified by the TCA. *See* Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products, 81 Fed. Reg. 28,974, 28,975 (May 10, 2016) (codified at 21 C.F.R. §§ 1100, 1140, 1143).

The "Deeming Rule" applied to tobacco products, including ENDS products, which were brought to market after Congress passed the TCA. The practical effect of the Deeming Rule was that ENDS products already on the market could no longer be sold legally without the FDA's approval, as they were now subject to the TCA's premarket authorization requirement. *See* Joint App'x at 78. Instead of requiring ENDS applicants to recall their newly deemed tobacco products, however, the FDA permitted them to continue marketing their products pending review. The deadline for submission of PMTAs for all deemed tobacco products was September 9, 2020.

C. The FDA's Pre-Deadline Preparation

In anticipation of the application deadline, the FDA published several nonbinding guidance documents aimed at helping ENDS applicants prepare their

PMTAs. Relevant here, the FDA issued one such document in June 2019 (the "June 2019 Guidance"), which was intended to "assist applicants in submitting an ENDS PMTA that could support a showing that the marketing of a new tobacco product would be [Appropriate]." Joint App'x at 211. To that end, the FDA explained that, as part of its consideration, it would review the "health risks associated with changes in tobacco product use behavior (e.g., initiation, switching, dual use, cessation)" and recommended that applicants compare their products with other products in relevant categories. *Id.* at 212–13.

The June 2019 Guidance also outlined what could be considered sufficient scientific evidence demonstrating that an ENDS product was Appropriate. The FDA acknowledged that "[g]iven the relatively new entrance of ENDS on the U.S. market, . . . limited data may exist from scientific studies and analyses." *Id.* at 211. As a result, the FDA would not limit its review to "well-controlled investigations," such as clinical randomized control trials ("RCTs") and longitudinal cohort studies but would consider other valid scientific evidence as well. *Id.* The FDA cautioned, however, that "[n]onclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be [Appropriate]." *Id.*

The FDA also issued internal guidance (that was promptly superseded) detailing how it intended to manage the PMTA review process. Central to Magellan's claims is the FDA's July 2021 internal memorandum (the "July 2021 Memorandum"). The

July 2021 Memorandum laid out the FDA's plan "to take final action on as many [non-tobacco flavored ENDS product] applications as possible by September 10, 2021." *Id.* at 46. Specifically, it stated that the FDA would engage in a preliminary "fatal flaw review" of the non-tobacco-flavored ENDS PMTAs not yet in the substantive scientific review phase. The FDA would review these submissions for "fatal flaw[s]," which it identified as the absence of an RCT or a longitudinal cohort study. *Id.* at 46–47. "[A]ny application lacking this evidence w[ould] likely receive a marketing denial order . . . ." *Id.* at 47.

The July 2021 Memorandum was superseded by another internal memorandum (the "August 2021 Memorandum"). *Id.* at 58–59. The August 2021 Memorandum stated that, in addition to RCTs and longitudinal cohort studies, the FDA would also consider evidence from other study types, provided that those studies "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." *Id.* at 59 n.ix.

D. Procedural History

Magellan submitted a PMTA for various ENDS products, including its flavored pods ("Mango," "Pretzel Graham," and "Blue Razz"), on September 8, 2020, which was after the FDA issued the June 2019 Guidance, but before it internally circulated the July 2021 Memorandum.

To demonstrate that its ENDS products were Appropriate, Magellan submitted four nonclinical studies: (1) a focus group of only two dozen subjects, in which participants were asked about their perceptions of and intentions for ENDS products generally, and about the packaging and marketing of Magellan's specific products; (2) a two-week online diary study that examined the behavior of only twenty users of Magellan ENDS products, of whom eighteen completed the study; (3) a "human factors stud[y]" involving only fifteen participants that aimed to measure consumer comprehension of product labeling and instructions for Magellan's products; and (4) an online cross-sectional perception and intent survey of 400 current smokers and 1,002 nonsmokers.

Notably, none of Magellan's studies robustly "evaluat[ed] the effects of the ENDS on users, including effects on initiation, switching behavior, cessation, and dual use; and on nonusers' initiation of the product," as the June 2019 Guidance recommended. Joint App'x at 237. Three of Magellan's four studies included no more than two dozen participants. The diary study—the only study that documented actual ENDS usage—was completed by just eighteen participants over a two-week period. Although it reflected some participants' intent to use ENDS products to quit smoking combustible cigarettes, it did not measure the actual effectiveness of Magellan's products at promoting cessation. The focus group study and online survey similarly focused on participants' intent with respect to ENDS products rather than outcomes.

As part of its PMTA, Magellan also submitted a marketing plan outlining its strategy to restrict youth access to its products and to limit youth exposure to its marketing, as well as a systematic literature review that summarized scientific data about the use of ENDS products.

On September 8, 2021, the FDA issued a Marketing Denial Order (an "MDO") to Magellan for its flavored pods.[3] The FDA concluded that Magellan's PMTAs "lack[ed] sufficient evidence demonstrating that [its] flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth." *Id.* at 7. Specifically, the FDA determined that Magellan had not shown the comparative efficacy of its flavored ENDS products over tobacco-flavored ENDS products in helping smokers completely switch to ENDS products or stop smoking altogether.

Because the FDA found Magellan's evidence to be "insufficient," it did not proceed "to assess other aspects of the[] application[]." *Id.* at 8. After the FDA issued the MDO, Magellan timely petitioned this Court for review.

II. Standard of Review

The TCA incorporates by reference the standard of review established by the Administrative Procedure Act (the "APA"). *See* 21 U.S.C. § 387l(b) (citing 5 U.S.C. § 706(2)(A)). Under the APA, we must "hold unlawful

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[3] As of the date of Magellan's opening brief, the FDA had not issued marketing decisions for Magellan's tobacco- and menthol-flavored pods.

and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Agency action is "arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

"Under the arbitrary-and-capricious standard, judicial review of agency action is necessarily narrow. A reviewing court may not itself weigh the evidence or substitute its judgment for that of the agency." *Islander E. Pipeline Co. v. McCarthy*, 525 F.3d 141, 150 (2d Cir. 2008) (citations omitted); *see also FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021) ("A court simply ensures that the agency has acted within a zone of reasonableness and, in particular, has reasonably considered the relevant issues and reasonably explained the decision.").

Judicial review of agency action incorporates the APA's prejudicial error rule. *See* 5 U.S.C. § 706. Under the prejudicial error rule, a court will not disturb an agency's decision if it determines that the outcome of the agency action would be the same absent agency error. *See Nat'l Ass'n of Home Builders v. Defs. of Wildlife*, 551 U.S. 644, 659–60 (2007) ("'In administrative law, as in federal civil and criminal

litigation, there is a harmless error rule.'" (quoting *PDK Lab'ys Inc. v. U.S. Drug Enf't Admin.*, 362 F.3d 786, 799 (D.C. Cir. 2004))); *see also Green Island Power Auth. v. FERC*, 577 F.3d 148, 165 (2d Cir. 2009) ("[W]e will not disturb [agency action] if we can determine that the outcome . . . w[ould] be the same absent [agency] error."). "[T]he burden of showing that an error is harmful normally falls upon the party attacking the agency's determination." *Shinseki v. Sanders*, 556 U.S. 396, 409 (2009).

III. Discussion

A. Magellan's Challenge to the FDA's Standard of Review

Contrary to Magellan's claims, the FDA did not apply a new standard of review in evaluating Magellan's PMTA. Therefore the FDA was not obligated to notify Magellan or consider its reliance interests, as it would be if the FDA had applied a new standard of review.

When an agency changes course, it must provide notice, *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) ("An agency may not . . . depart from a prior policy *sub silentio* or simply disregard rules that are still on the books."), and consider the reliance interests of the governed parties, *Dep't of Homeland Sec. v. Regents of Univ. of Cal.*, 140 S. Ct. 1891, 1913 (2020) (where an agency policy has engendered a reliance interest among the governed, the agency must be "cognizant" of that fact and take potential reliance interests "into account" (quotation marks omitted)).

But here the record shows that the FDA never changed its position: that it might accept evidence other than long-term studies to demonstrate that an ENDS product was Appropriate *if* that evidence had sufficient scientific underpinnings. Consistent with its position, the FDA considered Magellan's weak scientific evidence and found it insufficient to support an Appropriate finding.

In support of its argument, Magellan points to a statement in the June 2019 Guidance that the FDA did not "expect that applicants will need to conduct long-term studies to support an application"; but this out-of-context fragment does very little to help Magellan. Joint App'x at 212. There is no dispute that the June 2019 Guidance contemplated that evidence besides long-term studies *might* be sufficient, but it did not guarantee that other scientific evidence *would be* sufficient. *See Prohibition Juice Co. v. FDA*, 45 F.4th 8, 21 (D.C. Cir. 2022) ("The FDA did not reverse course. . . . The text of the FDA's 2019 Guidance makes that clear."). The June 2019 Guidance consistently used conditional language when describing acceptable evidence (as set out in the margin[4]). It also cautioned

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[4] Specifically, the June 2019 Guidance states:

- Other evidence might be acceptable if "it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be [Appropriate]." Joint App'x at 211.
- "[I]n some cases, it may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies." *Id.* at 245.
- "In cases where a product has not yet been sufficiently reviewed, new nonclinical and clinical studies may be necessary to support a marketing order." *Id.*

that "[n]onclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be [Appropriate]." Joint App'x at 211.

According to Magellan, the July 2021 Memorandum heightened the standard of review by saying that the FDA would conduct a "fatal flaw" analysis for the absence of an RCT or longitudinal cohort study. However, the July 2021 Memorandum was circulated internally and superseded before Magellan received its MDO. *See Avail Vapor*, 55 F.4th at 424 (reasoning that "internal documents [are] unlikely to create reliance interests" and the July 2021 Memorandum was "rescinded . . . or superseded" by the time the FDA issued its MDO).

Nor does the record support Magellan's contention that the FDA surreptitiously applied the July 2021 Memorandum's "fatal flaw" analysis to Magellan's PMTA notwithstanding that the July 2021 Memorandum was superseded shortly after its internal circulation. Instead, the record shows that the FDA considered Magellan's evidence and found it insufficient. Specifically, the FDA's Technical Project Lead ("TPL"), a document Magellan received with the MDO, identified deficiencies in the evidence Magellan submitted, which led the FDA to conclude that Magellan's evidence was "not adequate" to support an Appropriate finding. Joint App'x at 38. This analysis

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- "[P]ublished literature reviews . . . or reports may be acceptable to support a PMTA, but are considered a less robust form of support . . . ." *Id.* at 246.

would have been unnecessary had the FDA engaged in a fatal flaw review because the FDA could have denied the application solely on the grounds that it lacked an RCT or longitudinal cohort study.

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. We therefore conclude that the FDA did not act arbitrarily or capriciously. *See Prohibition Juice*, 45 F.4th at 20–21; *see also Avail Vapor*, 55 F.4th at 422; *Liquid Labs LLC v. FDA*, 52 F.4th 533, 539–42 (3d Cir. 2022); *Gripum, LLC v. FDA*, 47 F.4th 553, 559–60 (7th Cir. 2022), *cert. denied*, No. 22-708, 2023 WL 3440578, at *1 (U.S. May 15, 2023).

B. Magellan's Challenge to the FDA's Failure to Consider Its Marketing Plan

Even assuming that the FDA's decision not to evaluate Magellan's marketing plan as part of its PMTA review was error, any such error was harmless because it did not affect the outcome of the FDA's review.[5]

As previously stated, agency action is arbitrary and capricious when the agency "entirely failed to consider

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[5] Magellan also argues that the FDA's failure to consider its other evidence—its four studies and literature review—was arbitrary and capricious. But as discussed above, the FDA did consider this evidence and concluded that it was "not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate product switching or cigarette reduction based on flavor type to enable comparisons between tobacco and other flavors." Joint App'x at 38.

an important aspect of the problem," *State Farm*, 463 U.S. at 43, or when the decision did not include "a consideration of the relevant factors," *id.* (quotation marks omitted). In Magellan's TPL, the FDA noted that evidence regarding risk to youth "would . . . be evaluated to determine that the totality of the evidence supports a marketing authorization" and that such an assessment would "include[] evaluating the appropriateness of the proposed marketing plan." Joint App'x at 35. However, in the same document, the FDA stated that "for the sake of efficiency," it had "not evaluated any marketing plan[] submitted with the[] application[]." *Id.* at 35 n.xix. Given that the FDA itself identified the marketing plan as a relevant factor to its determination of whether Magellan's flavored pods would be marketed, it was likely error that the FDA did not review the marketing plan. *See Green Island Power Auth.*, 577 F.3d at 158.

The potential error, however, did not affect the outcome of the FDA's review of Magellan's PMTA because there is no indication that the marketing plan would have made up for the PMTA's other defects. *See Shinseki*, 556 U.S. at 406; *see also Green Island Power Auth.*, 577 F.3d at 165. According to Magellan, the focus of its marketing plan was to "limit[] youth access and exposure" to ENDS products and marketing material principally through the implementation of various age verification provisions. Pet'r's Br. at 37–38. But the FDA had previously stated that similar age verification strategies "would not be sufficient to address youth use of [ENDS] products." Joint App'x at 118. Magellan does not explain how its marketing strategies differ from the similar measures the FDA

had uniformly rejected or why conditions had changed such that the measures would now be effective. Thus, Magellan has not shown that the FDA would have reached a different result had it reviewed Magellan's marketing plan. *See Bechtel v. Admin. Rev. Bd., U.S. Dep't of Lab.*, 710 F.3d 443, 449 (2d Cir. 2013) (finding legal error immaterial where petitioner's failure to establish a needed element was a sufficient reason to rule against his claim); *see also Prohibition Juice*, 45 F.4th at 25 ("Where a petitioner had ample opportunity yet failed to show that an agency error harmed it, vacatur and remand to give the agency an opportunity to fix the error is unwarranted."); *Liquid Labs*, 52 F.4th at 543 ("The FDA's decision to decline to review [petitioner's] marketing plan does not change the result because there is no indication the plan would have made up for the deficiencies the FDA identified in [petitioner's] applications."). Accordingly, any error was harmless.

C. Magellan's Challenges to the FDA's Statutory Authority

The FDA was well within its statutory authority to impose on applicants a comparative efficacy requirement—the requirement that applicants demonstrate their flavored ENDS products are more effective than tobacco-flavored products at promoting cessation or switching from combustible cigarettes to ENDS products.

The TCA expressly contemplates a comparative analysis among tobacco products in the context of evaluating whether the products are Appropriate. The TCA states that PMTAs must include "full reports of

all information . . . concerning investigations which have been made to show the health risks of such tobacco product and *whether such tobacco product presents less risk than other tobacco products*." 21 U.S.C. § 387j(b)(1)(A) (emphasis added). The TCA also requires that the FDA deny PMTAs where "there is a lack of a showing that permitting such tobacco product to be marketed would be [Appropriate]." *Id.* § 387j(c)(2)(A).

Because the TCA instructs the FDA to consider this type of comparative evidence, we conclude that the FDA was well within its authority to require applicants to submit it. *See Prohibition Juice*, 45 F.4th at 19 ("[T]he [TCA] not only allows but expressly instructs the FDA to consider evidence regarding just the comparison that the manufacturers say the FDA lacks statutory authority to make."); *Avail Vapor,* 55 F.4th at 427 ("The TCA explicitly contemplates that FDA must embark on a comparative inquiry before allowing any marketing of a new tobacco product."). Finally, we also reject the argument that the comparative efficacy requirement would lead to irrational results.[6]

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[6] First, Magellan contends that by requiring applicants to demonstrate their flavored ENDS products are more effective than tobacco-flavored products at promoting cessation or switching from combustible cigarettes to ENDS products, the FDA more rigorously regulates flavored ENDS products, and this is irrational. But this is not irrational. The FDA found that flavored ENDS products pose a much greater risk of youth uptake than tobacco and menthol-flavored ENDS products do. Given the greater risk, it is appropriate that flavored ENDS products are subject to higher standards than their tobacco and menthol-flavored counterparts. Second, Magellan argues that the comparative efficacy

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For the foregoing reasons, we **DENY** Magellan's petition for review.[7]

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requirement leads to flavored ENDS products being regulated more rigorously than nicotine replacement therapy drugs and modified risk tobacco products. This is demonstrably false. These more heavily regulated tobacco products are subject to entirely distinct statutory provisions, which renders the evidentiary standards different and Magellan's contrast inapposite. At bottom, we need not consider these arguments at all because the TCA expressly empowers the FDA to perform the comparative analysis with which Magellan takes issue.

[7] In denying Magellan's petition for review, we join the majority of our sister circuits who have considered these issues. *See Avail Vapor*, 55 F.4th at 428; *Liquid Labs*, 52 F.4th at 545; *Gripum,* 47 F.4th at 561; *Prohibition Juice*, 45 F.4th at 26.

APPENDIX B

UNITED STATES COURT OF APPEALS FOR THE SECOND CIRCUIT

Docket No. 21-2426

[Filed June 16, 2023]

At a Stated Term of the United States Court of Appeals for the Second Circuit, held at the Thurgood Marshall United States Courthouse, 40 Foley Square, in the City of New York, on the 16th day of June, two thousand twenty-three,

Before: Dennis Jacobs,
Myrna Pérez,
Sarah A. L. Merriam,
Circuit Judges.

Magellan Technology, Inc.,	)
	)
Petitioner,	)
	)
v.	)
	)
United States Food and Drug Administration,	)
	)
Respondent.	)
	)

JUDGMENT

The petition for review in the above captioned case from a decision of the United States Food and Drug Administration was argued on the agency's record and the parties' briefs. Upon consideration thereof,

IT IS HEREBY ORDERED, ADJUDGED and DECREED that the petition for review is DENIED.

For the Court:

Catherine O'Hagan Wolfe,
Clerk of Court

/s/ Catherine O'Hagan Wolfe

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE
SECOND CIRCUIT

Docket No: 21-2426

[Filed August 25, 2023]

At a stated term of the United States Court of Appeals for the Second Circuit, held at the Thurgood Marshall United States Courthouse, 40 Foley Square, in the City of New York, on the 25th day of August, two thousand twenty-three.

Magellan Technology, Inc.,	)
	)
Petitioner,	)
	)
v.	)
	)
United States Food and Drug Administration,	)
	)
Respondent.	)
	)

ORDER

Petitioner, Magellan Technology, Inc., filed a petition for panel rehearing, or, in the alternative, for rehearing *en banc*. The panel that determined the appeal has considered the request for panel rehearing,

and the active members of the Court have considered the request for rehearing *en banc*.

IT IS HEREBY ORDERED that the petition is denied.

FOR THE COURT:
Catherine O'Hagan Wolfe, Clerk

/s/ Catherine O'Hagan Wolfe

APPENDIX D

MANDATE

UNITED STATES COURT OF APPEALS
FOR THE
SECOND CIRCUIT

Docket No. 21-2426

[Filed June 16, 2023]

At a Stated Term of the United States Court of Appeals for the Second Circuit, held at the Thurgood Marshall United States Courthouse, 40 Foley Square, in the City of New York, on the 16th day of June, two thousand twenty-three,

Before: Dennis Jacobs,
Myrna Pérez,
Sarah A. L. Merriam,
Circuit Judges.

Magellan Technology, Inc.,	)
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Petitioner,	)
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v.	)
	)
United States Food and Drug Administration,	)
	)
Respondent.	)
	)

JUDGMENT

The petition for review in the above captioned case from a decision of the United States Food and Drug Administration was argued on the agency's record and the parties' briefs. Upon consideration thereof,

IT IS HEREBY ORDERED, ADJUDGED and DECREED that the petition for review is DENIED.

For the Court:

Catherine O'Hagan Wolfe,
Clerk of Court

/s/ Catherine O'Hagan Wolfe

A True Copy

Catherine O'Hagan Wolfe, Clerk

United States Court of Appeals, Second Circuit

/s/ Catherine O'Hagan Wolfe

MANDATE ISSUED ON 09/01/2023

APPENDIX E

[Dated September 8, 2021]

FDA | U.S. FOOD & DRUG ADMINISTRATION

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

September 08, 2021

DENIAL

Magellan Technology Inc.
Attention: Dr. Angelico
820 Southlake Boulevard
North Chesterfield, VA 23236

FDA Submission Tracking Number (STN): PM0001594, see Appendix A

Dear Dr. Angelico:

We are denying a marketing granted order for the products identified in Appendix A.

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

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

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 PMTAs 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

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

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 from a probability-based sample examining demographics and usage of current and former smokers including product-specific (i.e., Juno) items, a focus group of perceptions and intentions, a diary study of users of the products focused on usage and attitudes, and a human factors study, this evidence is not sufficient to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate product switching or cigarette reduction resulting from use of these products over time nor evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors evaluate product switching or cigarette reduction based on flavor type to enable comparisons between tobacco and other flavors. Accordingly, this is insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

Without this information, FDA concludes that your applications are 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 these 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:

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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

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 Kenna Randall, Regulatory Health Project Manager, at (301) 796-4164 or Kenna.Randall@fda.hhs.gov.

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2021.09.08 14:48:16 -04'00'
Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

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

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

Appendix A — New Tobacco Products Subject of This Letter

Appendix A

New Tobacco Products Subject to This Letter

[*See Fold-Out Exhibit*]

Appendix A
New Tobacco Products Subject of This Letter

STN	PD Number	Product Name	Category	Subcategory	Package Type	Package Quantity	Characterizing Flavor	Additional Property
PM0001594	PD12	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 48mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD20	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 48mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD16	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 48mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD14	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 18mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD10	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 18mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD13	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 0mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD9	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 0mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD19	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 36mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD15	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 36mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD18	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 18mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD17	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 0mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD11	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 36mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device

MAGELLAN - FDA 1 - 000016

APPENDIX F

[Dated September 8, 2021]

FDA | U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking numbers (STNs)	PM0001594, See Appendix A
Common Attributes	
Submission date	September 8, 2020
Receipt date	September 8, 2020
Applicant	Magellan Technology Inc.
Product manufacturer	Shenzhen JWE Electronics Co., Ltd.
Application type	Standard
Product category	ENDS (VAPES)

[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.

Product subcategory	ENDS Component
Cross-Referenced Submissions	
All STNs	MF0000243, MF0000262, MF0000276, MF0000282, MF0000401, MF0000447
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):

Robin L. Toblin -S
Digitally signed by Robin L. Toblin -S
Date: 2021.09.08 12:30:36 -04'00'

CAPT Robin Toblin, Ph.D., M.P.H.
Associate Director
Division of Population Health Science

Signatory Decision:

Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2021.09.08 14:47:36 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

[****The Table of Contents Has Been Omitted for Printing Purposes****]

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.

[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.

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

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[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

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

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

As a result, the applicant has failed to provide evidence to overcome the risk to youth and show a net population health benefit necessary to

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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.

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 May 3, 2021. FDA issued a Filing letter to the applicant on May 25, 2021.

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

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

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

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

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

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

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

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]

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

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

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 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)

[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.

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

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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.

flavor (internal analysis). Youth current ENDS users were also more likely than adult current ENDS users to use more than one flavor and to use combinations that did not include tobacco flavors.[11]

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

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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.

pod-based flavored ENDS, which were most appealing to youth at the time, we subsequently observed a substantial rise in use of disposable flavored ENDS[xiv]--a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users.[4] This trend illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired flavor options, underscoring the fundamental role of flavor in driving appeal.

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

In addition to the high prevalence of youth ENDS use, the data also suggest this use is leading to increases in nicotine dependence.[10] Indeed, responding to concerns related to youth ENDS dependence, at the end of 2018, 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 $\geq$20 of the past 30 days).[9] By school type, 34.2% (95% CI, 31.2%-37.3%) of high school

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[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.

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

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

Youth and young adult brains are more vulnerable to nicotine's effects than the adult brain due to ongoing neural development.[31,32] Adolescence is a developmental period consisting of major neurobiological and psychosocial changes and is characterized by increased reward-seeking and 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) 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

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

unknown about other potential long-term health risks.

2.3.1.6. Conclusion

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

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 the 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

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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

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

Section 910(c)(5) of the FD&C Act provides that determining whether marketing of a new tobacco product is APPH shall, when appropriate, be based on "well-controlled investigations, which may include one or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product." FDA believes well-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]

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

another well-controlled investigation that could serve as an alternative to conducting 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]

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

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

reach a conclusion that the benefit outweighs the clear risks to youth. For instance, applicants who do not conduct their own behavioral studies must rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. To date, that approach has not been sufficient in our evaluation of flavored ENDS PMTAs because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use 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

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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.

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

[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). 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

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

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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.

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 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,

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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.

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

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. 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.

[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.

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 Kathryn Hartka and Dara Lee on September 8, 2021.

The reviews determined that the PMTAs did not contain evidence from a randomized controlled trial and/or longitudinal cohort study examining the benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes. The PMTAs contained a cross-sectional survey from a probability-based sample examining demograhpics and usage of current and former smokers including product-specific (i.e., Juno)

items, a focus group of perceptions and intentions, a diary study of users of the product focused on usage and attitudes, and a human factors study, but this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate product switching or cigarette reduction based on flavor type to enable comparisons between tobacco and other flavors. Accordingly, this evidence is not adequate and therefore, we did not assess other aspects of the application as part of this scientific review.

4. ENVIRONMENTAL DECISION

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

5. CONCLUSION AND RECOMMENDATION

FDA has reviewed these applications for evidence demonstrating that the new flavored products will provide an added benefit to adult smokers relative to tobacco-flavored products. Based on our 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 from a probability-based sample examining demograhpics and usage of current and former smokers including product-specific (i.e., Juno) items, a focus group of perceptions and intentions, a diary study of users of the product focused on usage and attitudes, and a human factors study, this evidence is not sufficient to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate product switching or cigarette reduction resulting from use of these products over time nor evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors evaluate product switching or cigarette reduction based on flavor type to enable comparisons between tobacco and other flavors. Accordingly, this is insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

Without this information, FDA concludes that your applications are 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

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Appendix A

New Tobacco Products Subject of This Review

[*See Fold-Out Exhibit*]

Appendix A
New Tobacco Products Subject of This Review

STN	PD Number	Product Name	Category	Subcategory	Package Type	Package Quantity	Characterizing Flavor	Additional Property
PM0001594	PD12	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 48mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD20	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 48mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD16	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 48mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD14	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 18mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD10	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 18mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD13	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 0mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD9	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 0mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD19	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 36mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD15	Juno Pods Blue Razz	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Blue Raspberry	Nicotine: 36mg/mL, PG/VG: 70/30, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD18	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 18mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD17	Juno Pods Pretzel Graham	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Pretzel Graham	Nicotine: 0mg/mL, PG/VG: 68/32, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device
PM0001594	PD11	Juno Pods Mango	ENDS(VAPES)	ENDS Component	Pod	1 Pod	Mango	Nicotine: 36mg/mL, PG/VG: 62/38, E-Liquid Volume: 1.6mL, Length: 19.95mm, Diameter: 18.7mm, Coil Resistance: 1.4ohm, Compatible with Juno Device

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APPENDIX G

RELEVANT STATUTORY PROVISIONS

STATUTORY PROVISIONS INVOLVED

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

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

* * *

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

* * *

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

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

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

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

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

(2) Premarket review required.

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

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

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

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

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

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

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

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

C. 21 U.S.C. § 387*l*(b) provides:

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

described in subsection (a) shall be reviewed in accordance with section 706(2)(A) of title 5, United States Code.