No. _____

In the Supreme Court of the United States

LOGIC TECHNOLOGY DEVELOPMENT LLC,
PETITIONER,
v.
U.S. FOOD AND DRUG ADMINISTRATION

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

PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED

1. Whether the Food and Drug Administration's ("FDA") creation of a new, heightened standard for evaluating already-pending premarket tobacco product applications ("PMTAs") for certain electronic nicotine delivery systems ("ENDS") products was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

2. Whether FDA's subsequent, retroactive extension of this heightened evidentiary standard to pending PMTAs for menthol-flavored ENDS was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Id.*

PARTIES TO THE PROCEEDINGS

Petitioner Logic Technology Development LLC was the sole petitioner in the court of appeals.

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

CORPORATE DISCLOSURE STATEMENT

Petitioner's parent company is JTI (US) Holding Inc., a Delaware corporation, and no publicly held company owns 10% or more of its stock.

STATEMENT OF RELATED PROCEEDINGS

The following proceedings are directly related to this case within the meaning of Rule 14.1(b)(iii):

- *Logic Technology Development LLC v. FDA*, No.22-3030 (3d Cir. Oct. 19, 2023).

TABLE OF CONTENTS

TABLE OF APPENDICES

TABLE OF AUTHORITIES

Cases

Statutes And Rules

Regulations

Other Authorities

PETITION FOR WRIT OF CERTIORARI

Electronic nicotine delivery systems ("ENDS"), also known as e-cigarettes, come in different flavors, including tobacco, menthol, candy, fruit, and dessert. Tobacco- and menthol-flavored ENDS are particularly important for adult smokers seeking to switch from combustible cigarettes, as menthol-flavored cigarettes make up roughly 37% of all cigarette sales in the United States, with tobacco-flavored cigarette sales making up the rest. *See* CDC, *Menthol Tobacco Products* (last rev. Aug. 23, 2023).[1] As Former FDA Commissioner Scott Gottlieb explained, menthol-flavored ENDS, in particular, "may be important to adult smokers seeking to transition away from cigarettes," given that "combustible cigarettes are still sold in menthol flavor." *See* Press Release, FDA, Statement from FDA Commissioner Scott Gottlieb, M.D., on Proposed New Steps to Protect Youth (Nov. 15, 2018) (hereinafter "Statement from Commissioner Gottlieb").[2] On the

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[1] Available at https://www.cdc.gov/tobacco/basic_information/menthol/index.html (all websites last visited on Mar. 14, 2024).

[2] Available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-proposed-new-steps-protect-youth-preventing-access.

other hand, candy-, fruit-, and dessert-flavored ENDS have no analogue in lawfully sold cigarettes.

In the present case, Petitioner Logic Technology Development LLC ("Logic") challenges FDA's effort to effectively ban menthol-flavored ENDS. Without notifying regulated parties, FDA's new political leadership overruled its career experts and imposed retroactively on pending menthol-flavored ENDS premarket tobacco product applications ("PMTAs") the same heightened, amorphous, and vague evidentiary standard under which FDA has not "approved a single PMTA for" any "of the more than 1,000,000 flavored e-cigarette products." *See Wages & White Lion Invs., LLC v. FDA*, 90 F.4th 357, 370 (5th Cir. 2024). This heightened standard forces ENDS companies to prove a purposefully impossible proposition: that their ENDS help consumers switch from smoking cigarettes to some unspecified higher degree than tobacco-flavored ENDS. Since FDA never told menthol-flavored ENDS companies that they would need to carry this burden—and, indeed, indicated that its new standard applied only to fruit-, candy-, and dessert-flavored ENDS—the result is that FDA will deny every menthol-flavored ENDS PMTA, effectively outlawing the country's multibillion-dollar menthol-flavored ENDS market.

This Petition thus raises two related but importantly distinct Questions Presented:

(1) whether FDA acted unlawfully in creating and retroactively applying this heightened comparative-efficacy standard, which FDA first imposed on fruit-, candy-, and dessert-flavored ENDS; and (2) whether FDA acted unlawfully in then imposing that standard on pending menthol-flavored ENDS PMTAs.

Currently before this Court are three other petitions for writs of certiorari raising the first of these Questions Presented. As the ENDS company petitioners in *Lotus Vaping Technologies, LLC v. FDA*, No.23-871 (filed Feb. 9, 2024), and *Magellan Technology, Inc. v. FDA*, No.23-799 (filed Jan. 22, 2024), and the Solicitor General in *FDA v. Wages & White Lion Investments, LLC*, No.23-1038 (filed Mar. 19, 2024), have explained, this Court should resolve the first Question Presented. Petitioner here agrees that this Court should take up this Question Presented, which, if resolved in the ENDS companies' favor, would necessarily lead to relief for Logic here. After all, there is no possible argument that FDA acted lawfully in imposing its new evidentiary standard on menthol-flavored ENDS, if it was unlawful for FDA to impose it as to fruit-, candy-, and dessert-flavored ENDS.

This Petition also raises a second Question Presented, which Logic respectfully submits this Court should also answer now: whether FDA's retroactive extension of its heightened evidentiary

standard for fruit-, candy-, and dessert-flavored ENDS to pending PMTAs for menthol-flavored ENDS was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). As the Fifth Circuit and the dissent at the Third Circuit in this case explained, what FDA has done with menthol-flavored ENDS is plainly unlawful. FDA's career experts in the Office of Science recommended granting marketing authorization to Logic's menthol-flavored ENDS, concluding that Logic did everything required under the Family Smoking Prevention and Tobacco Control Act ("Tobacco Control Act") and FDA's extant guidance. Yet, as revealed in two extraordinary internal memoranda, FDA's new political leadership then changed course, concluding in secret that FDA would now treat menthol-flavored ENDS exactly as it treats fruit-, candy-, and dessert-flavored ENDS. That means that a responsible company like Logic—which has never marketed to youth and instead sells menthol-flavored ENDS to adults who want to reduce or stop smoking menthol cigarettes—now needs to carry the same amorphous, purposefully impossible-to-satisfy burden as to adult switching that FDA has imposed on products like "Iced Pineapple Express" and "Suicide Bunny Mother's Milk and Cookies." *See* Pet. for Writ of Cert. at 6, *FDA v. Wages & White Lion Invs., LLC*, No.23-1038 (filed Mar. 19, 2024).

Logic respectfully submits that granting review on only the first Question Presented in one of the three pending petitions, while holding this Petition for resolution of those cases, would leave this Court with an incomplete picture of the nature of FDA's actions. This would allow FDA to avoid answering before this Court for the most indefensible and practically consequential aspect of its new anti-ENDS approach: its effort to outlaw a multibillion-dollar menthol-flavored ENDS industry that is critical to the millions of menthol smokers who want to quit or reduce smoking cigarettes. "If men must turn square corners when they deal with the government, it cannot be too much to expect the government to turn square corners when it deals with them." *Niz-Chavez v. Garland*, 593 U.S. 155, 172 (2021). And if FDA is going to defend its blanket anti-ENDS policy before this Court, it should be required to do so in a case where that policy made the key difference: that is, where the company submitted such robust evidence of its products' benefits and lack of youth appeal that FDA's career experts unanimously recommended granting marketing authorization, before being overruled by FDA's new political leadership.

This Court should grant the Petition on both Questions Presented.

DECISION BELOW

The Third Circuit's decision denying Logic's petition for review is reported at *Logic Technology Development LLC v. FDA*, 84 F.4th 537 (3d Cir. 2023), and is reproduced at Pet.App.1a–59a. The Third Circuit's order denying Logic's petition for rehearing en banc is unreported but is available at Pet. App.228a–229a.

JURISDICTION

FDA entered its Marketing Denial Order ("MDO") on October 26, 2022, Pet.App.60a–70a, and Logic filed a petition for review of that order in the Third Circuit on October 27, 2022. The Third Circuit denied Logic's petition for review on October 19, 2023, Pet.App.1a–59a, and denied Logic's petition for rehearing en banc on December 15, 2023, Pet.App.228a–229a. Justice Alito extended the deadline for petitioning for writ of certiorari to April 15, 2024. This Court has jurisdiction to hear this Petition and review the Third Circuit's decision under 28 U.S.C. § 1254(1).

STATUTORY AND REGULATORY PROVISIONS INVOLVED

The relevant statutory provisions are reproduced in the Appendix. Pet.App.230a–247a.

STATEMENT OF THE CASE

A. Legal And Regulatory Background

Under the Tobacco Control Act, manufacturers seeking to market "new tobacco product[s]" in interstate commerce must first receive authorization from the Secretary of Health and Human Services, 21 U.S.C. § 387j(a)(2)(A), acting through FDA, 21 U.S.C. § 393(d)(2). Applicants must submit PMTAs showing that their product "would be appropriate for the protection of the public health." *Id.* § 387j(c)(2)(A). FDA, in turn, must assess "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." *Id.* § 387j(c)(4). The agency must further consider "the increased or decreased likelihood that existing users of tobacco products will stop using such products," and "the increased or decreased likelihood that those who do not use tobacco products will start using such products." *Id.* § 387j(b)(4)(A)–(B). FDA may premise its decision on "well-controlled investigations," including "clinical investigations," and other "valid scientific evidence." *Id.* § 387j(b)(5).

Although FDA has regulated cigarettes and smokeless tobacco since Congress enacted the Tobacco Control Act in 2009, *see* 21 U.S.C. § 387a(b), the agency did not seek to regulate ENDS until several years later. In 2016, FDA finalized the

"Deeming Rule," which concluded that ENDS meet the statutory definition of a "tobacco product" under the Tobacco Control Act. *See* 81 Fed. Reg. 28,974 (May 10, 2016). Because the United States already had by this time a robust ENDS marketplace, FDA issued guidance in 2017 making clear that ENDS manufacturers could continue to sell products already on the market pending FDA's decision on timely submitted PMTAs. *See Am. Acad. of Pediatrics v. FDA*, 379 F. Supp. 3d 461, 468 (D. Md. 2019). Any other approach would have been unlawful. *See Dep't of Homeland Security v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913 (2020).

The agency initially gave ENDS manufacturers over five years to submit their applications, *see Am. Acad. of Pediatrics*, 379 F. Supp. 3d at 468, 472, but, after litigation with anti-tobacco lobby groups, that deadline was moved up to September 9, 2020, Order, *Am. Acad. of Pediatrics v. FDA*, No.8:18-cv-00883 (D. Md. Apr. 22, 2020), Dkt.182. Logic, the Petitioner here, supported an earlier submission deadline for ENDS manufacturers to submit their PMTAs. *See Vaping in America: E-Cigarette Companies' Impact on Public Health Before the Subcomm. on Oversight and*

Investigations of the H. Comm. on Energy and Com., 116th Cong. 7–8 (2020).[3]

B. Factual And Procedural Background

1. Logic manufactures ENDS products, which serve as a safer alternative to traditional combustible cigarettes. Logic's ENDS feature a rechargeable battery-operated device that delivers nicotine through an aerosolized vapor. *See* JA.1219; JA.1222; JA.1225.[4] Logic has three types of devices: Logic Vapeleaf, Logic Power, and Logic Pro. *See* JA.1298; JA.1315; JA.1332. Logic Power and Logic Pro operate by heating a solution (also known as an "e-liquid") in a disposable cartridge to produce a nicotine-containing aerosol inhaled by the user. JA.1315; JA.1332. Logic Vapeleaf operates by heating an e-liquid in a disposable cartridge to form a vapor that flows through a disposable tobacco capsule containing granulated tobacco. JA.1298. Logic sells the devices

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[3] Available at https://www.congress.gov/116/meeting/house/110462/witnesses/HHRG-116-IF02-Wstate-LoftinJ-20200205.pdf.

[4] Citations of "JA.__" are of the Joint Appendix filed with the court below. 3d Cir. No.22-3030, Dkts.39–45 (Volumes I through VII). Citations of "SA.__" are of the Supplemental Appendix filed with the court below. 3d Cir. No.22-3030, Dkt.65. Citations of "R.__" are of the circuit court's docket. 3d Cir. No.22-3030.

in a matte black finish and in simple packaging designed not to appeal to youth. *See* JA.3026–27.

2. Investing tens of millions of dollars, Logic started preparing PMTAs for its ENDS products in tobacco, menthol, and fruit flavors shortly after FDA finalized the Deeming Rule, and continued this effort until submitting its PMTAs in mid-2019. Throughout this time, FDA never once suggested what would become key to its unlawful anti-menthol ENDS policy: that Logic must submit long-term studies designed to show that menthol-flavored ENDS are more effective, to some unspecified degree, than tobacco-flavored ENDS in helping adults reduce or quit smoking combustibles.

At first, FDA only provided ENDS manufacturers with a May 2016 draft version of FDA's guidance document on PMTAs, *see* FDA, *Premarket Tobacco Product Applications for Electronic Delivery Systems* (May 2016) (hereinafter "2016 Guidance"),[5] which guidance FDA finalized in June 2019, *see* FDA, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems* (June 2019)

[5] Available at https://www.fda.gov/files/tobacco%20products/published/DRAFT-GUIDANCE-Guidance-for-Industry-Premarket-Tobacco-Product-Applications-for-Electronic-Nicotine-Delivery-Systems.pdf.

(hereinafter "2019 Guidance").[6] The 2019 Guidance advised, among other things, that applicants should compare the physiological health risks of their ENDS products as against other ENDS and combustibles. *See id.* This guidance did not suggest that manufacturers should design long-term switching studies to compare the efficacy of their ENDS as against tobacco-flavored ENDS in helping current smokers reduce or quit smoking combustibles.

In 2019, the agency issued a proposed rule on PMTAs for ENDS products, which similarly offered no indication that ENDS manufacturers would need to design long-term studies showing that the submitted ENDS products have some added switching benefit over tobacco-flavored ENDS. *See* 84 Fed. Reg. 50,566 (proposed Sept. 25, 2019). To the contrary, the proposed rule stated that FDA did "not expect that long-term clinical studies (*i.e.*, those lasting approximately 6 months or longer) [would] need to be conducted for each" application. *Id.* at 50,619. The proposed rule further indicated that marketing plans would be "critical to FDA's determination of the likelihood of changes in tobacco product use behavior" and that the agency "will review the marketing plan to evaluate potential youth access to, and youth exposure to, the labeling,

[6] Available at https://www.fda.gov/media/127853/download.

advertising, marketing, or promotion of, a new tobacco product." *Id.* at 50,581.

In 2020, FDA issued another guidance document detailing its enforcement priorities with respect to ENDS products. JA.1106 (the "2020 Guidance"). The 2020 Guidance explicitly distinguished between so-called "flavored" ENDS products—that is, fruit-, candy-, and dessert-flavored ENDS—on the one hand, and tobacco- and menthol-flavored ENDS products, on the other. JA.1109. As FDA explained, it would prioritize enforcement against "flavored, cartridge-based ENDS products (other than tobacco- or menthol-flavored)." JA.1126. "This approach strikes an appropriate balance between restricting youth access to [fruit-, candy- and other dessert-like flavored products], while maintaining availability of potentially less harmful options for current and former adult smokers who have transitioned or wish to transition completely away from combusted tobacco products." *Id.*

After Logic submitted its PMTAs in mid-2019 for several different ENDS products—including the three menthol-flavored products at issue here, as well as three tobacco-flavored ENDS and four fruit-flavored ENDS, *see* JA.1299; JA.1316; JA.1333—on June 26, 2020, FDA sent Logic a deficiency letter outlining additional information that the agency now required to authorize Logic's ENDS products. *See* JA.3010–22.

With respect to Logic's fruit-flavored ENDS, FDA asked Logic for the first time to provide a new category of evidence: "scientific evidence and rationale to demonstrate whether these flavor variants may facilitate adult smokers switching to Logic products at a rate *beyond that of tobacco- or menthol-flavored products, which may have lower youth appeal*." JA.3016 (emphasis added). FDA further indicated that this could include "[d]ata or information from studies demonstrating uptake/switching among adult smokers using *flavored* variants of the products relative to uptake/switching among *tobacco- or menthol-flavored users*," and "[d]ata or information from studies demonstrating *appeal (e.g., preference or intention to use) of flavored variants (fruit and fruit-combination flavored products) compared to tobacco- or menthol-flavored variants* among adult users interested in switching to ENDS." *Id.* (emphases added). Even though this deficiency letter (i) also dealt with Logic's menthol-flavored ENDS PMTAs, *see* JA.3020, and (ii) specifically requested comparative efficacy data for Logic's fruit -flavored ENDS, *see* JA.3016, the letter nowhere suggested that Logic should submit data showing the same comparative switching efficacy as between its menthol- and tobacco-flavored ENDS.

In July 2021, FDA circulated an internal memorandum acknowledging that FDA would now

apply a new "standard for evidence" when evaluating marketing applications for "flavored" ENDS products, a category that FDA then defined to include only fruit-, candy-, and dessert-flavored ENDS, but not menthol- and tobacco-flavored ENDS. *See* Mem. from Anne Radway, Assoc. Dir., Div. of Regul. Project Mgmt., FDA, ENDS Containing Non-Tobacco-Flavored E-Liquid (July 9, 2021).[7] PMTAs with a "fatal flaw"—namely, a lack of long-term studies showing that the applicant's "flavored" ENDS have some undefined added benefit over tobacco-flavored ENDS in helping current smokers reduce or quit smoking combustibles—would "likely" be denied. *Id.* at 2. On August 17, 2021, FDA circulated another internal memorandum reiterating that FDA would deny marketing authorization unless a "flavored" ENDS applicant provided long-term studies showing that the applicant's product was more effective in helping current smokers reduce or quit smoking than an "appropriate comparator" tobacco-flavored ENDS product. *See* Mem. from Benjamin Apelberg, Deputy Dir., Off. of Sci., FDA, PMTA Review: Evidence to Demonstrate Benefit of Flavored ENDS to Adult

[7] Available at https://files.vaporvoice.net/wp-content/uploads/sites/3/2021/11/CTP-OS-Memos-from-Triton-Administrative-Record.pdf.

Smokers (Aug. 17, 2021).[8] FDA purported to rescind this memorandum on August 25, 2021—the day before it issued its first MDOs for flavored ENDS. *See* Mem. from Benjamin Apelberg, Deputy Dir., Off. of Sci., FDA, Rescission of Aug. 17, 2021, Mem. re PMTA Review (Aug. 25, 2021);[9] Press Release, FDA, *FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products* (Aug. 26, 2021).[10]

FDA then proceeded to deny *en masse* PMTAs submitted for fruit-, candy-, and dessert-flavored ENDS, including Logic's fruit-flavored ENDS PMTAs (which products are not at issue in this case). *See* FDA, *Tobacco Products Marketing Orders* (Mar. 7, 2024).[11] As the Fifth Circuit has explained, "months after receiving hundreds of thousands of applications

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[8] Available at https://files.vaporvoice.net/wp-content/uploads/sites/3/2021/11/CTP-OS-Memos-from-Triton-Administrative-Record.pdf.

[9] Available at https://files.vaporvoice.net/wp-content/uploads/sites/3/2021/11/CTP-OS-Memos-from-Triton-Administrative-Record.pdf.

[10] Available at https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-applications-about-55000-flavored-e-cigarette-products-failing-provide-evidence.

[11] Available at https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/tobacco-products-marketing-orders.

predicated on its instructions, FDA turned around, pretended it never gave anyone any instructions about anything, imposed new testing requirements without any notice, and denied all one million flavored e-cigarette applications for failing to predict the agency's *volte face*." *Wages*, 90 F.4th at 362.

3. The agency then went on to perform the same about-face with respect to menthol-flavored ENDS.

Logic invested tens of millions of dollars to prepare its menthol PMTAs, and submitted thousands of pages of documents and evidence supporting those applications. R.8 at 4; *see* JA.1227–50; JA.1251–72; JA.1273–94. As relevant here, that evidence showed both that Logic's menthol-flavored ENDS are beneficial for adult smokers and that they are not used by youth in any appreciable amounts.

With respect to adult benefit, Logic showed that its ENDS products have substantial benefits for current adult smokers. For example, Logic's 60-day studies demonstrated that 76% of study participants who received the Logic Power menthol flavor reduced their cigarettes per day by 80% by the end of the study. SA.087. Current smokers who switched to Logic's ENDS products also had 50–95% lower concentrations of biomarkers of exposure to harmful constituents than when using combusted cigarettes, JA.1988–90; JA.2176–78; JA.2370–72, and were

exposed to significantly less nicotine, JA.1943; JA.2120; JA.2309. Further, study participants who used Logic's menthol products, in particular, for 60 days consistently reported stronger overall impressions of the product's flavor compared to participants who received the tobacco-flavored products, JA.2537; JA.2630; JA.2725, and reported the strongest desire to use the product to reduce and/or quit smoking, JA.2572; JA.2666; JA.2761. Across all three of Logic's products, the study participants assigned the menthol variants had higher compliance with instructions to use the product instead of smoking cigarettes than the participants assigned a tobacco variant. JA.1958; JA.2130–31; *see* JA.2512. The 60-day studies further showed that current menthol cigarette smokers had more positive experiences and perceptions of Logic's ENDS when they received a menthol-flavored product rather than when they received a tobacco-flavored one. JA.2761–62; JA.2666–67; JA.2572.

Logic's PMTAs also demonstrated that youth do not use its ENDS products in any appreciable amounts. Logic submitted data from the National Youth Tobacco Survey ("NYTS"), which showed that youth do not use its ENDS products to any significant degree. The NYTS survey asked high-school and middle-school students across the United States about their tobacco-product use, including their preferred brands of ENDS products. *See* JA.3033.

This data showed that, in 2019, only 0.8% of high school students used Logic products—the lowest reported value in the NYTS at that time—and Logic products were not identified as the usual brand by *any* middle school students. *Id.* Further, in the 2022 NYTS results, 9.4% of youth-survey-respondents identified as ENDS users, and only 0.4% of all youth reported using any Logic products (not just menthol) in the past 30 days. JA.1159. *The 2022 NYTS study, later relied upon by FDA, did not identify any youth who reported Logic as their regular brand*. *Id.* Logic also provided FDA with a marketing plan designed to eliminate youth appeal and access: for example, Logic's products eschew trendy colors, flavors, and vivid imagery, opting instead for a plain, matte black finish and product features designed to avoid concealment during use. *See* JA.3026–28. Logic also terminated its social media accounts in September 2020, JA.3028, and ceased all online sales in early 2021, *see* JA.3168.

3. After Logic's PMTAs were fully submitted and pending, FDA retroactively and in secret imposed upon menthol-flavored PMTAs the same amorphous comparative-efficacy requirement that it had used to deny all fruit-, candy-, and dessert-flavored ENDS PMTAs. The imposition of this secret policy change played out between FDA's career experts and its new political leadership, and did so in the context of Logic's menthol-flavored ENDS PMTAs.

As would later be revealed in two extraordinary internal agency memoranda disclosed for the first time in this litigation, the FDA's Center for Tobacco Products' Office of Science, after reviewing all of Logic's comparative health risk data, unanimously recommended granting Logic's PMTAs for its menthol-flavored ENDS. *See* JA.908. Applying the Tobacco Control Act's risk-benefit analysis, *see* 21 U.S.C. 387j, the Office of Science's non-partisan staff concluded that, "as long as menthol-flavored cigarettes remain on the market, menthol-flavored ENDS could be a direct substitute for them, providing a less harmful alternative for menthol-flavored cigarette smokers, who are less likely to successfully quit smoking than smokers of non-menthol-flavored cigarettes." JA.908. Menthol smokers' "documented preference" for menthol-flavored ENDS, coupled with Logic's "product-specific evidence," outweighed any risk to youth of the menthol products and thus met the "legal standard for authorization." *Id.*

But then the Center's political leadership changed and, in July 2022, that new leadership overruled the Office of Science's evidence-based recommendation. New leadership instead decided to extend the agency's heightened requirements for fruit-, candy-, and dessert-flavored ENDS, now requiring applicants to show that menthol-flavored ENDS are more effective, to some unspecified degree, than tobacco-flavored ENDS in helping current

smokers reduce or quit smoking. JA.904; JA.909; *see* JA.907–08. New leadership stated that, "in light of the substantial risk to youth and the lack of robust evidence of actual differential use to quit or significantly reduce cigarettes per day, the approach to menthol-flavored ENDS should be the same as for other flavored ENDS." JA.909. Put another way, every menthol-flavored ENDS application would be denied unless the applicant provided "robust, product-specific evidence showing that their menthol-flavored products facilitate complete switching or significant reduction in smoking . . . among adults greater than that facilitated by tobacco-flavored ENDS." *Id.* Although new leadership stated that it considered the prospect that its new approach to menthol-flavored ENDS would eliminate all non-tobacco-flavored ENDS products, it offered no answer for this concern. JA.904 & n.3. In internal meetings, Office of Science staff criticized the agency's conduct, including for its lack of "transparency." JA.905.

c. On October 26, 2022, FDA issued the marketing denial order ("MDO") for Logic's three menthol-flavored ENDS, rejecting Logic's PMTAs for these products and ordering Logic to remove them from the market immediately. Pet.App.60a–70a; *see* Pet.App.71a–227a (Technical Project Lead review). Consistent with the new approach to menthol-flavored ENDS articulated in the then-secret memoranda, FDA said that it was unable to ascertain

from Logic's studies or from the peer-reviewed literature "whether or to what extent [Logic's] menthol flavored new products facilitate complete switching [of cigarette smokers to Logic products] or significant cigarette reduction as compared to tobacco flavored ENDS products." Pet.App.64a.

FDA provided no record evidence that would support its decision to extend the same unlawful approach that the agency had previously taken with respect to fruit-, candy-, and dessert-flavored ENDS to menthol-flavored ENDS. Indeed, the agency continued to acknowledge, as it had in the past, that menthol-flavored ENDS are less popular among youth than other ENDS products. *See* Pet.App.158a.

The nature of FDA's reasoning and the evidence before the agency demonstrate that FDA designed its new anti-menthol ENDS policy to be so vague as to allow the agency to deny all menthol-flavored ENDS. Recall that in the PMTAs at issue, Logic submitted the data on its menthol-flavored ENDS and tobacco-flavored ENDS together, so if FDA was actually interested in the comparative efficacy of Logic's products, it could have reviewed that data. *See, e.g.*, JA.1299; JA.1316; JA.1333. For example, that data showed that 76% of study participants who received the Logic Power menthol flavor reduced their cigarettes per day by 80% or more by the end of the 60-day study, whereas 63% of participants who

received the Logic Power tobacco flavor reduced their cigarettes per day by 80% or more by the end of that study. SA.087. FDA did not attempt to explain why this difference did not satisfy its new comparative efficacy standard as to menthol-flavored ENDS, simply declaring that Logic's data was not "acceptably strong" enough to demonstrate "an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking." Pet.App.204a–205a. FDA declined to state what degree of added benefit would, in fact, be sufficient to meet the agency's new, retroactively imposed standard for evaluating menthol-flavored ENDS, instead setting an illusory target for ENDS companies applying for marketing authorization. *See id.*

Thereafter, FDA issued MDOs for several more menthol-flavored ENDS PMTAs submitted by other manufacturers. *See* FDA, *Tobacco Products Marketing Orders*, *supra*. To date, and consistent with its new, effective-ban standard for evaluating menthol products, FDA has not granted marketing authorization to any menthol-flavored ENDS. *See id.* The agency has, moreover, denied these menthol applications in nearly identical fashion, concluding that the applicant's purported failure to provide evidence showing, to some unspecified degree, that their menthol products have an added benefit over

tobacco-flavored ENDS in helping adults reduce or quit smoking was fatal to their application. *See R.J. Reynolds Vapor Co. v. FDA*, 65 F.4th 182, 188 (5th Cir. 2023); Pet.'s Br. at 17–18, *SWT Global, Inc. v. FDA*, No.23-2403 (8th Cir. filed Sept. 14, 2023); *see also* FDA, *FDA Denies Marketing Applications for Flavored blu E-Cigarette Products* (Feb. 5, 2024);[12] FDA, *FDA Denies Marketing of myblu Menthol E-Cigarette Product* (July 10, 2023).[13]

6. On October 27, 2022, Logic filed a petition for review, challenging the MDOs for Logic's menthol-flavored ENDS. R.1. The Third Circuit granted Logic an emergency partial administrative stay as to Logic Pro Menthol e-Liquid Package and Logic Power Menthol e-Liquid Package, the two Logic menthol products currently on the market. R.6. Following briefing, the Third Circuit also granted Logic's motion for a full stay pending its petition for review. R.35.

Logic thereafter submitted its merits briefing. As to the Questions Presented in this case, Third Circuit

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[12] Available at https://www.fda.gov/tobacco-products/ctp-newsroom/fda-denies-marketing-applications-flavored-blu-e-cigarette-products.

[13] Available at https://www.fda.gov/tobacco-products/ctp-newsroom/fda-denies-marketing-myblu-menthol-e-cigarette-product.

precedent foreclosed Logic's ability to argue that FDA's retroactive adoption of its heightened comparative-efficacy standard for fruit-, candy-, and dessert-flavored ENDS was unlawful, *see Liquid Labs LLC v. FDA*, 52 F.4th 533 (3d Cir. 2022), so Logic preserved that argument for further review, including before this Court, R.46 at 41 n.9; R.63 at 16 n.3; R.118 at 11 n.2. After all, if FDA's adoption of that new standard was unlawful as to fruit-, candy-, and dessert-flavored ENDS, it would necessarily be unlawful for FDA to then impose that same standard on menthol-flavored ENDS. As to the second Question Presented, Logic explained how FDA had upset industry reliance interests by retroactively imposing an evidentiary standard designed for fruit-, candy-, and dessert-flavored ENDS on already-pending menthol-flavored ENDS PMTAs without fair notice. *See* R.46 at 34–45. Logic further argued, *inter alia*, that even putting the unlawful retroactivity of imposing this new standard on pending PMTAs aside, there was no evidence that would permit FDA to impose the same burden on all menthol-flavored ENDS as it had imposed on "flavored" ENDS, including such youth-attractive products as, for instance, "OG Island Fusion." *See* R.46 at 46–56.

On October 19, 2023, the Third Circuit, in a divided opinion, denied Logic's petition for review. Pet.App.1a–59a. The panel majority reasoned that FDA did not "change[ ] course with respect to (1) the

types of evidence that would be required for a premarket application to win approval, and (2) the appropriate comparator for menthol-flavored ENDS." Pet.App.30a. The panel majority remarkably blessed as "good government" FDA's 2022 internal memoranda purporting to justify the agency's extension to menthol-flavored ENDS of its heightened, effective-ban approach to fruit-, candy-, and dessert-flavored ENDS. Pet.App.26a–29a. The majority then accepted a similarly implausible interpretation of the 2020 deficiency letter, holding that FDA's failure to request comparative switching evidence as between Logic's menthol- and tobacco-flavored ENDS—despite specifically requesting such evidence for Logic's fruit-flavored ENDS—did not show that the agency later changed its position as to what evidence would be required to support a menthol application. *See* Pet.App.32a–33a. The panel majority further concluded that Logic should have intuited FDA's new comparative-efficacy requirement from the agency's prior guidance, despite the fact that the Office of Science itself was unaware of this new standard when it initially recommended granting marketing authorization for Logic's menthol-flavored ENDS. Pet.App.30a–33a. Finally, the majority accepted FDA's *post hoc* rationale—first articulated by FDA's counsel at oral argument, R.106 at 31:4–7—that Logic's evidence showing that current menthol smokers are more likely to use menthol-flavored

ENDS to reduce or quit smoking was not "statistically significant." *See* Pet.App.32a.

In his dissent, Judge Porter explained that FDA's undisclosed decision to "lump[ ] menthol together with fruit, candy, and dessert flavors" reflected the agency's new, undisclosed policy requiring ENDS manufacturers to include a comparison between menthol- and tobacco-flavored products in PMTAs, which policy upset Logic's substantial reliance interests. Pet.App.41a (Porter, J., dissenting). "No one at the FDA informed Logic of the policy change," or gave "Logic an opportunity to amend the menthol-product PMTAs in response to the new policy." Pet.App.45a. "Nor did the FDA explain why it never requested a comparison between menthol and tobacco products in the deficiency letter despite specifically asking Logic to compare its fruit and fruit-combination flavored ENDS to tobacco-flavored ENDS." Pet.App.52a. Given all of the agency's public guidance to date, "Logic had no reason to compare menthol products to tobacco products." Pet.App.57a. FDA's change of position required FDA to provide Logic "notice of and a reasoned explanation for its policy departure," as well as assess alternatives to denial. Pet.App.59a (citation omitted).

Logic filed a petition for rehearing en banc, which the Third Circuit denied on December 15, 2023. Pet.App.228a–229a. On January 4, 2024, the Third

Circuit granted Logic's motion to stay the mandate pending this Court's decision on the instant Petition. R.126.

REASONS FOR GRANTING THE PETITION

I. This Court Should Grant Review On The First Question Presented Regarding FDA's Creation Of A New, Heightened Evidentiary Standard For Evaluating Pending PMTAs

This Court should grant review on the first Question Presented: whether FDA's retroactive adoption of a heightened evidentiary standard for "flavored" PMTAs—a standard under which FDA has denied every fruit-, candy-, and dessert-flavored ENDS PMTA it has considered—is unlawful. There is a clear circuit split on this Question, detailed in three other petitions for certiorari currently pending before this Court. *See supra* pp.3; Sup. Ct. R. 10(a).

As the Fifth Circuit sitting en banc correctly held in *Wages*, FDA acted arbitrarily and capriciously, *see* 5 U.S.C. § 706(2)(A), when it unfairly surprised ENDS companies by retroactively adopting and applying its heightened evidentiary standard after these companies had already submitted their PMTAs in "good faith reliance" on the agency's prior positions. *Wages*, 90 F.4th at 384–85 (quoting *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156–57

(2012); *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515–16 (2009)). In public guidance, FDA told regulated parties that it would consider a variety of evidence as to whether ENDS products are "appropriate for the protection of the public health." *See Wages*, 90 F.4th at 377–81. But FDA then created a heightened evidentiary standard for "flavored" ENDS (a category that FDA then understood to include only fruit-, candy-, and dessert-flavored ENDS), now requiring that already-submitted PMTAs include long-term studies showing that a "flavored" product has some unspecified degree of added benefit over tobacco-flavored ENDS in helping current adult smokers reduce or quit smoking combustibles. *Supra* pp.14–16; *see Wages*, 90 F.4th at 380–81. FDA "received over one million PMTAs for flavored e-cigarette products" and, of course, "not a single one of them contained the scientific studies that FDA now require[d]." *Wages*, 90 F.4th at 386. FDA provided no "fair notice" for its new evidentiary standard and, indeed, sprung it as an unfair surprise on ENDS manufacturers, which acted in good-faith reliance on FDA's prior guidance. *Id.* at 376–81.

Relatedly, the Fifth Circuit and the Eleventh Circuit have faulted FDA for failing to consider applicants' marketing plans in "flavored" ENDS PMTAs, which the agency had previously identified as "critical" to a successful PMTA. *Id.* at 372–73; *Bidi Vapor LLC v. FDA*, 47 F.4th 1191, 1203 (11th Cir.

2022). "FDA's refusal even to read the once-'critical' marketing plans constitute[s] an arbitrary and capricious failure to consider 'an important aspect of the problem.'" *Wages*, 90 F.4th at 373 (quoting *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)); *Bidi Vapor*, 47 F.4th at 1203. For that reason, too, FDA's treatment of "flavored" ENDS products was unlawful.

Seven other circuits have reached a contrary conclusion to the Fifth and Eleventh Circuits. *See Liquid Labs*, 52 F.4th 533; *Magellan Tech., Inc. v. FDA*, 70 F.4th 622 (2d Cir. 2023); *Avail Vapor, LLC v. FDA*, 55 F.4th 409 (4th Cir. 2022); *Gripum, LLC v. FDA*, 47 F.4th 553 (7th Cir. 2022); *Lotus Vaping Techs., LLC v. FDA*, 73 F.4th 657 (9th Cir. 2023); *Electric Clouds, Inc. v. FDA*, 94 F.4th 950 (10th Cir. 2024); *Prohibition Juice Co. v. FDA*, 45 F.4th 8 (D.C. Cir. 2022). These courts have held that FDA's prior guidance on PMTAs sufficiently put the ENDS industry on notice that FDA would require long-term studies showing that "flavored" ENDS are more effective than tobacco-flavored ENDS in helping adult smokers reduce or quit smoking. *See, e.g.*, *Liquid Labs*, 52 F.4th at 542–43; *Magellan*, 70 F.4th at 629–32; *Avail*, 55 F.4th at 422–25. Further, these courts have determined that FDA's failure to review the applicants' marketing plans was harmless. *See, e.g.*, *Liquid Labs*, 52 F.4th at 543–44; *Magellan*, 70 F.4th at 630–31; *Avail*, 55 F.4th at 425–27. In seeking

certiorari from the Fifth Circuit's decision in *Wages*, the Solicitor General acknowledged the need for this Court to provide uniformity in this area of law. *See* Pet. for Writ of Cert. at 13–14, *Wages*, No.23-1038.

This Petition squarely presents this Question, which Logic has preserved below, given binding Third Circuit precedent foreclosing it. *See* R.46 at 41 n.9; R.63 at 16 n.3; R.118 at 11 n.2; *see also Liquid Labs*, 52 F.4th at 543–44. As explained in Part II, the agency's only justification for imposing its new comparative-efficacy requirement on menthol-flavored ENDS is its claim that menthol-flavored ENDS have substantially the same youth appeal as fruit-, candy-, and dessert-flavored ENDS, and thus need to be supported by the same evidence of adult benefit. *See infra* pp.37–38. While there is no record basis for this equivalence, *see infra* pp.37–38, if FDA's policy with respect to fruit-, candy-, and dessert-flavored ENDS is unlawful, then it follows that imposing that policy on menthol-flavored ENDS on the basis that the menthol flavor is similar to fruit, candy, and dessert flavors in terms of youth appeal is necessarily also unlawful.

II. This Court Should Grant Review On The Second Question Presented Regarding FDA's Retroactive Imposition Of This Heightened Evidentiary Standard On Menthol-Flavored ENDS

This Petition also raises a second Question Presented: whether FDA acted unlawfully when it extended retroactively its heightened evidentiary standard for fruit-, candy-, and dessert-flavored ENDS to pending PMTAs for menthol-flavored ENDS. It is critical that this Court decide this second Question Presented alongside the first so that the Court may consider the most practically significant and legally indefensible aspect of FDA's anti-ENDS campaign, in the context of PMTAs that included such robust evidence that FDA's career experts recommended granting marketing authorization before FDA's political leadership intervened.

A. The Third Circuit's Erroneous Decision Approving FDA's Retroactive Imposition Of A Heightened Evidentiary Burden On Menthol-Flavored ENDS Creates A Split With The Fifth Circuit

Following its retroactive imposition of a heightened evidentiary burden on fruit-, candy-, and dessert-flavored ENDS PMTAs, FDA extended this same unlawful standard to menthol-flavored ENDS.

Prior to issuing the MDO here, FDA told ENDS manufacturers that it distinguished between menthol and tobacco flavors, on the one hand, and fruit, candy, and dessert flavors, on the other. *See, e.g.*, JA.1109, 1126. In its 2020 Guidance, the agency noted that "[m]enthol is unique compared to other available ENDS product flavors as it is the only characterizing flavor available in cigarettes, and it may reduce the irritation and harshness of smoking." JA.1129. "Menthol cigarettes are also used by a substantial portion of the U.S. population, who are addicted to nicotine and may be looking for an alternative product to seek to transition completely away from combusted products." *Id.* FDA's 2020 deficiency letter to Logic reflected that same policy: while the agency was (unlawfully) asking for comparative-efficacy evidence as between Logic's fruit- versus tobacco- and menthol-flavored ENDS, JA.3016, FDA never requested such evidence with respect to Logic's menthol-flavored ENDS, *see* JA.3010–22; Pet.App.57a–58a (Porter, J., dissenting). FDA's Office of Science then examined Logic's menthol applications under the agency's then-controlling policy, and recommended granting marketing authorization. *See* JA.908. Only later did FDA's new leadership impose, in secret, a new policy "lump[ing] menthol together with fruit, candy, and dessert flavors." Pet.App.41a (Porter, J., dissenting). This policy, in turn, operates as a de facto ban on menthol-flavored ENDS. *See R.J. Reynolds*, 65 F.4th at 192–94. That is confirmed by the internal

memoranda that the agency prepared in connection with Logic PMTAs, which offered no response to FDA staff's fear that the new heightened standard would result in an effective ban on the menthol ENDS category. *See* JA.904 n.3.

There is a circuit split as to whether FDA's conduct with respect to menthol-flavored ENDS, in particular, was arbitrary and capricious. Sup. Ct. R. 10(a). The panel majority's decision below was also contrary to this Court's caselaw. *Id.*

1. There is a circuit split as to whether FDA acted unlawfully by imposing a heightened evidentiary burden on pending menthol-flavored ENDS PMTAs.

The Fifth Circuit, on one side of the divide, has held that FDA's retroactive extension of its amorphous, heightened evidentiary standard for fruit-, candy-, and dessert-flavored ENDS to menthol-flavored ENDS was unlawful. In *R.J. Reynolds*, the Fifth Circuit granted a stay of an MDO for the petitioner's menthol-flavored ENDS, holding that FDA violated the principles of fair notice in evaluating menthol-flavored ENDS applications. 65 F.4th at 189–91, 195. The facts of *R.J. Reynolds* mirror those here: prior to issuing the MDO, FDA told the petitioner in a deficiency letter to provide comparative switching evidence as between its fruit- and tobacco-flavored products, but did not request

such evidence with respect to the petitioner's menthol products. *Id.* at 188, 190. Pointing to the 2022 internal memoranda that FDA prepared in connection with Logic's PMTAs, the Fifth Circuit explained that the agency's "inexplicabl[e] switch[of] position on menthol-flavored e-cigarettes" evidenced a "disregard for the principles of fair notice and consideration of reliance interests," and so violated the APA. *Id.* at 190–91 (citing *Regents*, 140 S. Ct. at 1913). The Fifth Circuit further held that FDA's change of course lacked adequate justification. *Id.* at 191 (citing *Regents*, 140 S. Ct. at 1913). While the Fifth Circuit issued *R.J. Reynolds* in a stay posture, that court has since cited to *R.J. Reynolds* repeatedly as circuit precedent in APA cases. *See, e.g.*, *Inhance Techs., LLC v. EPA*, 96 F.4th 888, 895 (5th Cir. 2024); *Chamber of Comm. of U.S. v. SEC*, 85 F.4th 760, 777 n.23 (5th Cir. 2023).

The Third Circuit panel majority expressly admitted that it was "part[ing] ways" with the Fifth Circuit's *R.J. Reynolds* decision, holding that FDA did not "change[ ] course" as to the "types of evidence that would be required for a premarket application to win approval" for menthol-flavored ENDS, or the "appropriate comparator for menthol-flavored ENDS." Pet.App.30a. According to the panel majority, FDA's secret 2022 internal memoranda evidencing the agency's change of policy with respect to menthol-flavored ENDS were merely "good

government." Pet.App.26a–29a. The panel majority further concluded that the agency's 2020 deficiency letter did not evidence any prior agency policy of treating menthol-flavored ENDS differently than fruit-, candy-, and dessert-flavored ENDS. Pet.App.32a–33a. The panel majority similarly blessed FDA's extension of its heightened evidentiary standard for fruit-, candy, and dessert-flavored ENDS to menthol-flavored ENDS, seeing no legal problem with FDA's complete discounting of Logic's product-specific evidence demonstrating that its products do not appeal to youth. *See* Pet.App.34a–38a.

2. The Fifth Circuit's resolution of this Question Presented was correct, and the Third Circuit's decision below was contrary to this Court's caselaw.

a. FDA's retroactive imposition of a heightened evidentiary burden on menthol-flavored ENDS PMTAs violates the APA, under this Court's caselaw. An agency cannot upset a regulated party's good-faith reliance interests without fair notice when the party has reasonably relied on the agency's prior guidance. *SmithKline Beecham Corp.*, 567 U.S. at 156; *Fox Television*, 556 U.S. at 515. Here, FDA impermissibly upset the reasonable expectations of Logic and other menthol-flavored ENDS manufacturers, which have wasted hundreds of millions of dollars aiming for FDA's illusory target. *See* Pet.App.46a–50a (Porter, J., dissenting). First, the agency publicized its policy

of treating menthol differently from other "flavored" ENDS given the agency's desire not to "foreclose[ ] one potential means by which some adult smokers might seek to transition completely away from combusted tobacco products," JA.1125, and issued deficiency letters to Logic and other menthol-flavored ENDS manufacturers indicating that their menthol applications would be reviewed in accordance with this policy, *see supra* pp.12–13; *R.J. Reynolds*, 65 F.4th at 188. Then, the agency pulled the rug out from under these regulated parties, retroactively imposing upon their PMTAs a requirement that the applicant demonstrate that its menthol-flavored ENDS are more effective, by some unspecified degree, than tobacco-flavored ENDS in helping adults reduce or quit smoking. *See* JA.908; *R.J. Reynolds*, 65 F.4th at 189–91. Without "fair warning," FDA then penalized Logic for purportedly failing to satisfy this retroactive standard. *See SmithKline Beecham*, 567 U.S. at 156, 158–159; *R.J. Reynolds*, 65 F.4th at 189–91.

That the agency performed a bait-and-switch with respect to Logic's menthol-flavored ENDS is beyond serious dispute, given that FDA's own Office of Science—applying FDA's prior policy with respect to the menthol flavor—recommended granting marketing authorization for Logic's menthol products, changing course only after FDA's new leadership changed the policy. *See* JA.908–09. As

Judge Porter pointed out below, there was no change in the data before the agency between when the Office of Science recommended granting marketing authorization and when the FDA issued the MDO. *See* Pet.App.51a–54a (Porter, J., dissenting).

FDA's imposition of the same heightened evidentiary standard on all menthol-flavored ENDS that it had previously imposed on fruit-, candy-, and dessert-flavored ENDS is also *substantively* unlawful in multiple respects, even had FDA not imposed it retroactively on already pending PMTAs.

As a threshold matter, FDA pointed to no record support for equating menthol-flavored ENDS with fruit-, candy-, and dessert-flavored ENDS, and it was thus arbitrary and capricious for FDA to place the same evidentiary burden on menthol-flavored ENDS as it had previously imposed on these other flavored products. *See State Farm*, 463 U.S. at 43. The evidence before the agency clearly showed that the menthol flavor is less popular among youth than candy, fruit, and dessert flavors. *See* Pet.App.158a. Specifically, menthol-flavored ENDS were used by 26.6% of middle- and high-school ENDS users, which figure was lower than the use rates for fruit (69.1%) and candy/desserts/other sweets (38.3%). JA.1158–59. This obviously does not support importing the "same," JA.909, approach to menthol-flavored ENDS

as that applicable to fruit-, candy-, and dessert-flavored ENDS.

Further, FDA's lumping of Logic together with all other ENDS companies, without giving any heed to Logic's particularly successful marketing and other strategies to mitigate potential youth usage, violates the Tobacco Control Act. That Act requires the agency to determine whether the marketing of the *particular products* at issue would be "appropriate for the protection of the public health," 21 U.S.C. § 387j(c)(2)(A), in light of "the risks and benefits to the population as a whole," *id.* § 387j(c)(4). In reviewing the evidence before it, FDA must consider "the increased or decreased likelihood that existing users of tobacco products will stop using such products," as well as "the increased or decreased likelihood that those who do not use tobacco products will start using such products." *Id.* § 387j(c)(4)(A)–(B). Logic here submitted overwhelming evidence showing that its products meet this standard. Logic's data demonstrated that youth do not use its products in any appreciable amounts. *Supra* pp.17–18. Further, data from the 2022 NYTS study demonstrated that no youth reported Logic as their regular brand. *Supra* pp.18. Logic's 60-day studies also showed that smokers who were randomly assigned to use the menthol product for 60 days achieved an 80% reduction in their cigarette consumption at substantial rates, complied with the study's directive

to only use the assigned Logic product at higher rates than those assigned other products, and smoked fewer cigarettes per day than those assigned other products. *Supra* pp.16–17. But FDA disregarded or ignored this product-specific evidence, instead denying Logic's PMTAs under its anti-menthol ENDS policy, after lumping Logic's products with all other companies' ENDS.

b. The Third Circuit's contrary decision is wrong.

First, the Third Circuit violated this Court's caselaw when it treated the 2022 internal memoranda as evidence of "good government" and required Logic and other menthol-flavored ENDS manufacturers to somehow intuit FDA's previously undisclosed evidentiary requirements for PMTAs. *See* Pet.App.26a–29a. As explained, the internal memoranda clearly lay out the agency's decision to apply, retroactively and without prior notice, the same unlawful approach to menthol-flavored ENDS that the agency had previously adopted with respect to fruit-, candy-, and dessert-flavored ENDS. *Supra* pp.19–20. The panel majority's effort to deny the import of the 2020 deficiency letter fails: the panel concluded that the deficiency letter's failure to ask for comparative efficacy evidence with respect to Logic's menthol products while, at the same time, asking for such evidence with respect to Logic's fruit products was of no moment, because the agency had already

told ENDS companies to design studies comparing the efficacy of menthol- and tobacco-flavored ENDS in terms of complete switching. Pet.App.32a–33a. But that latter premise is incorrect, for all the reasons explained above and in the Fifth Circuit's *R.J. Reynolds* decision. *See supra* pp.34–38; *R.J. Reynolds*, 65 F.4th at 189–94. Remarkably and most tellingly, the Third Circuit claimed that Logic should have somehow intuited FDA's new standard before submitting its PMTAs, even though FDA's own Office of Science did not know about this new standard when assessing those PMTAs. *See* Pet.App.30a–32a.

Second, the panel majority improperly sanctioned FDA's equation of the menthol flavor with fruit, candy, and dessert flavors in terms of youth appeal without record evidence for this equivalence. As explained, no data before the agency supported such an equivalence. *Supra* pp.37–38. Indeed, even the dissenting judges in the Fifth Circuit's en banc decision in *Wages* recognized that FDA grouped menthol- and tobacco-flavored ENDS together as having less youth appeal than fruit-, candy-, or dessert-flavored ENDS. *See* 90 F.4th at 398–99 (Haynes, J., dissenting).

The panel majority similarly erred in allowing the agency to discount entirely Logic's product-specific evidence showing that its products, in particular, do not appeal to youth, in favor of rank speculation that

youth's use of Logic's products might substantially change in the future as other ENDS products are removed from the market. *See* Pet.App.37a–38a. The agency did not offer any evidence supporting this claim. *See* JA.157a; *State Farm*, 463 U.S. at 43. Nor did the panel majority explain why it was proper for the agency to "prognosticat[e] what will happen to children's menthol use as other flavored ENDS exit the market," while ignoring what will happen to current menthol smokers when they no longer have access to menthol-flavored ENDS. *See* Pet.App.38a.

Finally, the panel majority erred in blessing FDA's hide-the-ball approach to menthol-flavored ENDS PMTAs, which included designing its new evidentiary standard to be so vague as to permit the agency to deny all menthol-flavored ENDS PMTAs, without regard to the weight of the evidence supporting those PMTAs. As explained, while Logic did not design studies to compare its menthol and tobacco products in terms of switching efficacy, data in Logic's PMTAs happened to illustrate just such a comparison, given that Logic submitted its menthol- and tobacco-flavored PMTAs at the same time: 76% of study participants using the Logic Power menthol flavor reduced their cigarettes per day by 80% or more by the end of the 60-day study, whereas only 63% of participants who used the Logic Power tobacco flavor reduced their cigarettes per day by 80% or more by the end of that time period. SA.087. This data

provides clear evidence that Logic Power menthol-flavored ENDS have an added benefit over tobacco-flavored ENDS in helping adults reduce or quit smoking, assuming that is relevant at all. And yet, the Third Circuit accepted FDA's *post hoc* contention that this data was not "statistically significant." Pet.App.32a. That was error, first because FDA advanced this contention for the first time at oral argument, and did not make this point in the administrative record. R.106 at 31:4–7; *see Calcutt v. FDIC*, 598 U.S. 623, 629 (2023) (per curiam) (citing *SEC v. Chenery Corp.*, 332 U.S. 194, 196 (1947)). Additionally, the agency has to date failed to offer any indication to regulated parties of what comparative-efficacy evidence could be "statistically significant" enough to merit marketing authorization, thus enabling FDA to rely on its heightened, vague evidentiary standard to deny marketing authorization in all cases, in violation of the APA.

B. This Court Should Grant This Question Presented Now, Rather Than Holding This Case For *Wages*

Logic anticipates that the Solicitor General will resist a grant on this second Question Presented and, instead, urge this Court to hold the present Petition pending disposition of the *Wages* petition on the merits, which petition raises only the first Question Presented at issue in this case. *See, e.g.*, Pet. for Writ

of Cert. at 27, *Wages*, No.23-1038 (asking this Court to hold the *Magellan* and *Lotus* petitions pending the *Wages* petition). Logic respectfully submits that this Court should not take that approach for several important reasons.

FDA leadership's campaign to impose retroactively a heightened evidentiary standard for already-pending PMTAs is most practically important and legally indefensible in the context of menthol-flavored ENDS. As FDA's prior leadership aptly explained, menthol-flavored ENDS "may be important to adult smokers looking to transition away from cigarettes" given that "combustible cigarettes are still sold in menthol flavor." Statement from Commissioner Gottlieb, *supra*. Menthol-flavored cigarettes account for roughly 37% of all cigarette sales in this country, and are—in contrast to fruit, candy, and other dessert flavors—lawful. *See Menthol Tobacco Products*, *supra*; JA.1129 ("[m]enthol cigarettes are . . . used by a substantial portion of the U.S. population"). Menthol-flavored ENDS are helpful to adults seeking to transition away from combustibles, as FDA's own scientific career experts recognized when they recommended granting Logic's PMTAs before FDA's political leadership forced them to change course. *See* JA.908. FDA leadership's present anti-menthol ENDS policy threatens the very situation that FDA' prior leadership sought to avoid when regulating in this

context, namely, "a situation where . . . combustible products have features that make them more attractive than . . . non-combustible products." *See* Statement from Commissioner Gottlieb, *supra*.

This Court's immediate review is also necessary to provide uniformity to the multibillion-dollar menthol-flavored ENDS industry. *See* Pet. for Writ of Cert. at 25–26, *Wages*, No.23-1038; *see also* R.121 at 5. The Fifth Circuit's *R.J. Reynolds* decision allows certain menthol-flavored ENDS companies—namely, those who have challenged MDOs in the Fifth Circuit—to continue selling their menthol products, while other manufacturers must pull theirs from the market. Further, when FDA eventually denies other companies' menthol PMTAs (as it surely will continue to do, *see supra* pp.28–29), those companies that are powerful enough to get their retail partners in the Fifth Circuit to join with them in a petition for review will be able to obtain relief from their MDOs in that forum, just as R.J. Reynolds did. *See R.J. Reynolds*, 65 F.4th at 188. The Solicitor General in *Wages* highlighted the harmful, nationwide effects of the current division of authority on FDA's treatment of ENDS products, explaining that "out-of-circuit entities have begun flocking to the Fifth Circuit, thus evading unfavorable precedent in the D.C. Circuit or their own circuits." Pet. for Writ of Cert. at 25, *Wages*, No.23-1038. This Petition will allow the Court to address the current division in authority on menthol-

flavored ENDS, and thus is a critical companion case should this Court decide to grant certiorari in one of the pending fruit-, candy-, and dessert-flavored cases.

More generally, FDA should not have the luxury of defending its comparative-efficacy gambit before this Court only in a case like *Wages*, where the applicants—unlike Logic—did not submit robust evidence supporting marketing authorization. *See* Pet. for Writ of Cert. at 6–7, *Wages*, No.23-1038. Rather, FDA should have to defend its actions in the context of the MDO here, where the menthol flavor at issue is unquestionably more important to the goal of reducing use of combustible cigarettes, given the widespread availability of menthol combustible cigarettes, and Logic's evidence of adult benefit and lack of youth appeal was so robust that the Office of Science recommended granting authorization before FDA's political leadership changed course with respect to menthol-flavored ENDS. This Court should, accordingly, hear this case alongside *Wages* or one of the other pending petitions addressing FDA's unlawful treatment of flavored ENDS products, granting review on both Questions Presented.

CONCLUSION

This Court should grant the Petition.

Respectfully submitted,

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April 2024

APPENDIX

TABLE OF APPENDICES

APPENDIX A — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT, FILED OCTOBER 19, 2023

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 22-3030

LOGIC TECHNOLOGY DEVELOPMENT LLC,

Petitioner,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION.

May 9, 2023, Argued;
October 19, 2023, Filed

On Petition from the United States Food & Drug Administration

(FDA-1: PM0000528.PD1, PM0000534.PD1, PM0000539.PD1).

Before: KRAUSE, PORTER, and AMBRO, *Circuit Judges*

Appendix A

OPINION

KRAUSE, *Circuit Judge.*

New information and changes in the marketplace can alter consumers' decisions about the products they buy, and the same is true of the federal agencies that regulate the marketing of those products. Here, starting in early 2020, the Food and Drug Administration (FDA) began taking aggressive action to remove fruit-and dessert-flavored e-cigarettes, also known as electronic nicotine delivery systems (ENDS), from the stream of commerce, leaving aside at that time tobacco-and menthol-flavored ENDS. More recently, based on additional studies and market data, the FDA has denied the applications of importers and manufacturers like Petitioner Logic Technology Development (Logic) to market menthol-flavored ENDS.

Logic now challenges that denial as a violation of the Administrative Procedure Act (APA), claiming it was arbitrary and capricious for the FDA (1) to apply the same regulatory framework to menthol that it used to assess the appropriateness of sweeter flavors, (2) to ultimately reject its applications for its menthol-flavored ENDS to remain on the market, and (3) to do so without granting Logic a transition period following that decision. For the reasons explained below, however, we find those arguments unpersuasive because the FDA applied a regulatory framework consistent with its statutory mandate, provided a reasoned explanation for its denial, and based its decision on scientific judgments that we may not second-guess. We will therefore deny Logic's petition for review.

Appendix A

I. Background

Because our resolution of Logic's petition requires an understanding of the highly reticulated scheme that Congress laid out in the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), we review that framework before assessing its application to the menthol-flavored products at issue here.

A. Statutory framework

The Tobacco Control Act requires any tobacco product not on the market before February 15, 2007 to receive approval from the FDA. *See* 21 U.S.C. § 387j(a)(1)-(2). Only if the FDA concludes that "permitting such tobacco product to be marketed would be appropriate for the protection of the public health" (health-appropriate) can the product be approved.[1] *Id.* § 387j(c)(2). Manufacturers seeking advance permission to market one of these newer products can submit a "premarket tobacco product application" (PMTA or premarket application) to the agency. *See Liquid Labs LLC v. FDA*, 52 F.4th 533, 537 (3d Cir. 2022) (citations omitted).

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1. The FDA first deemed ENDS and their flavor cartridges "new tobacco products" and thus subject to the Tobacco Control Act in 2016. *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, 28,976 (May 10, 2016). The D.C. Circuit upheld this rule in *Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 281-82, 444 U.S. App. D.C. 357 (D.C. Cir. 2019).

When considering such an application, the FDA is statutorily required to conduct a balancing test to determine whether an ENDS is health-appropriate and, thus, whether it can remain on the market. The agency must assess:

> [T]he risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account—
>
> (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
>
> (B) the increased or decreased likelihood that those who do not use tobacco products will start using such tobacco products.

21 U.S.C. § 387j(c)(4)(A)-(B). This mandate in effect creates a sliding scale: the greater the risk of the new tobacco product to non-smokers, especially children, the greater the benefit to smokers that the manufacturer must demonstrate. *See Bidi Vapor LLC v. FDA*, 47 F.4th 1191, 1211 (11th Cir. 2022) (Rosenbaum, J., dissenting).

When applying that test, the FDA is to consult a wide range of evidence. The agency must deny a premarket application "if, upon the basis of the information submitted to the Secretary as part of the application *and any other information* . . . with respect to such tobacco product," it determines that the product is not health-appropriate. 21 U.S.C. § 387j(c)(2)(A) (emphasis added). And it "shall,

when appropriate" make that determination "on the basis of well-controlled investigations, which may include 1 or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product." *Id.* § 387j(c)(5)(A). But if the agency "determines that there exists valid scientific evidence" beyond those studies that "is sufficient to evaluate the tobacco product, the Secretary may authorize that the [health-appropriateness] determination . . . be made on the basis of such evidence. *Id.* § 387j(c)(5)(B).

B. The FDA's previous regulation of vaping

Within the FDA, the Center for Tobacco Products (the Center) manages the premarket application evaluation process.[2] The Center, in turn, contains multiple divisions, including the Director's office, the Office of Science, and the Office of Compliance and Enforcement.[3] A manufacturer's premarket application passes through several discipline-specific reviews, including engineering, chemistry, epidemiology, and social sciences. The Technical Project Lead then synthesizes those teams' findings and ultimately determines whether the product is health-appropriate. Though the FDA has delegated authority to review premarket applications to the Office

2. U.S. Food & Drug Admin., *About the Center for Tobacco Products (CTP)* (July 21, 2023), https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp.

3. *See* U.S. Food & Drug Admin., *Center for Tobacco Products Organization Chart* (Mar. 30, 2023), https://www.fda.gov/about-fda/fda-organization-charts/center-tobacco-products-organization-chart.

of Science, the Director retains supervisory authority over the Center's component offices. Thus, there is room for deliberation among the Center's teams, but the buck stops with the Director.

The Center's experts began to face a new challenge in the late 2010s as youth tobacco product use suddenly skyrocketed. Prior to 2017, high schoolers' e-cigarette use had been dropping. But from 2017 to 2019, "ENDS product use more than doubled among middle school and high school students." JA 1118. From 2017 to 2018, the proportion of twelfth graders who had smoked an e-cigarette in the past thirty days went from 16.6% to 26.7%. For tenth graders, that figure went from 13.1% to 21.7% in the same period. According to the National Youth Tobacco Survey (the Youth Survey), among high schoolers overall, e-cigarette use went from 11.7% to 20.8%. By 2018, the Surgeon General had deemed youth ENDS use an "epidemic." *Prohibition Juice Co. v. FDA*, 45 F.4th 8, 10 (D.C. Cir. 2022).

Flavored e-cigarettes were the driving force behind this epidemic. Youth Survey data showed that in 2014, 65.1% of high schoolers and 55.1% of middle schoolers who were using ENDS said they were using a non-tobacco flavor (including menthol). By 2022, that figure had risen to 85.5% for high schoolers and 81.5% for middle schoolers, meaning approximately 2,110,000 of the 2,550,000 students using ENDS. Manufacturers were marketing ENDS with names and flavors that were more appropriate for a candy store than a smoke shop, such as "Brain Freeze Caramel Cone, Buncha Crunch . . . Crazy Bubble Grape, Giggle

Juice," *id.* at 15, "Peanut Butter Milk Pie, Bad Monkey Giovanni, and Sunshine Vape Dragon Berry Balls," *Gripum LLC v. FDA*, 47 F.4th 553, 556 (7th Cir. 2022) (internal quotation marks omitted). The results were predictable. Flavors that most resembled fruit, candies, or desserts were more popular with kids than those that resembled combustible cigarettes. In a 2019 survey of kids who used JUUL e-cigarettes—then the most popular ENDS brand—the vast majority of respondents listed mango, mint, or fruit as the flavor they used most often. Tobacco and menthol barely registered with respondents.

The FDA had to figure out how it would address this crisis within the bounds of the Tobacco Control Act. The agency promulgated multiple guidance documents for manufacturers, the most relevant here being one published in June 2019 (Premarket Application Guidance),[4] which set out what the FDA was looking for in premarket applications for ENDS, and another, published in April 2020 (Enforcement Priorities),[5] which articulated the agency's priorities for enforcement actions against manufacturers whose products were not considered health-appropriate.

In the Premarket Application Guidance, the FDA said that "the finding of whether permitting the

4. U.S. Food & Drug Admin., Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (June 2019).

5. U.S. Food & Drug Admin., Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry (Apr. 2020).

marketing of a product would be [health-appropriate] will be determined, when appropriate, on the basis of well-controlled investigations." JA 1027. "Nonclinical studies alone," on the other hand, "generally [would] not [be] sufficient to support [such] a determination." *Id.* The FDA also recommended that manufacturers "compare the health risks of its product to both products within the same category and subcategory" that "are most likely to [be] considered interchangeable." JA 1028. As applied to fruit-flavored ENDS, the Premarket Application Guidance meant that the FDA would not approve a product without evidence that it offered benefits "over an appropriate comparator tobacco-flavored ENDS" with randomized controlled trials, longitudinal cohort studies, or other similar evidence "that could potentially demonstrate the [relative health] benefit[s] of . . . flavored ENDS." *Liquid Labs*, 52 F.4th at 538 (citation omitted).

The Enforcement Priorities reflected recent trends in youth ENDS vaping. Highest priority would be given to non-tobacco, non-menthol flavors, along with other ENDS manufacturers with insufficient marketing restrictions or products marketed to kids. To support this approach, the agency cited survey data like that above, showing both middle-and high-school students using fruit flavors more often than mint or menthol. While survey data disaggregating mint from menthol ENDS was spotty at the time, the JUUL study had found that mint was much more popular than menthol. The FDA received, considered, and rejected comments arguing that menthol should be included among the flavors selected for aggressive enforcement. It noted that "[d]ata shows that

tobacco-and menthol-flavored ENDS products are not as appealing to minors as other flavored ENDS products." JA 1145.

ENDS manufacturers attacked the FDA's application of the Premarket Application Guidance and Enforcement Priorities, with mixed results across the circuit courts.[6] We rebuffed that attack and upheld the FDA's approach in *Liquid Labs*. There, the company had received a marketing denial order for eighteen ENDS with non-tobacco, non-menthol "characterizing" flavors like "OG Summer Blue" and "Berry Au Lait." *Liquid Labs*, 54 F.4th at 537. To support its premarket applications, the manufacturer submitted a marketing plan, "an abuse liability study, a cross-sectional perception and intention study, a population modeling analysis, a clinical literature review, and well-controlled non-clinical analyses." *Id.* (internal quotation marks and citation omitted). The FDA found this evidence insufficient because Liquid Labs had

6. The Second, Fourth, Sixth, Seventh, Ninth, and D.C. Circuits all have denied petitions or stays. *Magellan Tech., Inc. v. FDA*, 70 F.4th 622, 625 (2d Cir. 2023); *Avail Vapor, LLC v. FDA*, 55 F.4th 409, 413 (4th Cir. 2022), *cert. denied*, No. 22-1112, 2023 U.S. LEXIS 4118, 2023 WL 6558399 (Mem) (Oct. 10, 2023); *Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 508 (6th Cir. 2021); *Gripum*, 47 F.4th at 553; *Lotus Vaping Techs., LLC v. FDA*, 73 F.4th 657, 2023 WL 4384447, at *2 (9th Cir. 2023); *Prohibition Juice*, 48 F.4th at 8. The Fifth and Eleventh Circuits have granted stays to manufacturers, albeit for different reasons. *R.J. Reynolds Vapor Co. v. FDA*, 65 F.4th 182, 187 (5th Cir. 2023); *Bidi Vapor*, 47 F.4th at 1191. The Fifth Circuit also has heard en banc argument to determine the validity of the FDA's comparative approach in *Wages and White Lion Invs., LLC v. FDA*, Nos. 21-60766, 21-60800 (5th Cir. May 16, 2023).

failed to submit "randomized controlled trial[s] and/or longitudinal stud[ies]" or any other evidence that "reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time." *Id.* at 538 (internal quotation marks and citation omitted). The manufacturer petitioned for review, arguing that the FDA had "pull[ed] a surprise switcheroo" by changing the evidentiary standard for premarket applications. *Id.* at 539 (internal quotation marks and citation omitted).

We sided with the FDA and sustained the marketing denial order. The Premarket Application Guidance, we determined, "nowhere guaranteed that unspecified other forms of evidence would necessarily be sufficient," *id.* at 540 (quoting *Prohibition Juice*, 45 F.4th at 21), and the text of the Tobacco Control Act "necessarily implie[d] a comparative analysis," *id.* at 543 (quoting *Wages and White Lion Invs., LLC v. FDA*, 41 F.4th 427, 434 (5th Cir. 2022), *vacated and reh'g en banc granted*, 58 F.4th 233 (5th Cir. 2023). Thus, we concluded that Liquid Labs had "fair notice of the analysis the agency would perform and the purpose of those comparisons," *id.* (quoting *Prohibition Juice*, 45 F.4th at 24), and the FDA's comparative evidentiary standard for fruit and similar flavors was not arbitrary or capricious.

C. Procedural background

While the courts were determining the legality of the FDA's approach to these flavors, the FDA made good on its comments in the Enforcement Priorities and turned

its attention to menthol. Menthol posed an additional regulatory challenge because it had a legal substitute in menthol-flavored combustible cigarettes. With menthol making up about 37% of the combustible cigarette market, it was thought that ENDS offering a similar characterizing flavor might help millions of smokers ditch tobacco, potentially dramatically altering the health-appropriateness calculation and decreasing the showing that a manufacturer would need to make in terms of menthol's appeal to children. Thus, manufacturers, Logic among them, sought to make the case that the Tobacco Control Act's balancing test should produce a different result in the case of menthol-flavored ENDS.

1. Logic's Premarket Application

In August 2019, Logic submitted premarket applications[7] for over a dozen of its ENDS, including its menthol-and tobacco-flavored products.[8] To support its applications, Logic submitted hundreds of thousands of pages of data, including clinical studies to determine the products' risk of abuse, two sixty-day randomized

7. Manufacturers submit one premarket application per new tobacco product for which they are seeking agency approval. Logic submitted over a dozen premarket applications for ENDS with various characterizing flavors, three of them menthol-flavored. The Marketing Denial Order covers only these products. For ease of reference, we refer to Logic's applications for the at-issue ENDS as its Premarket Application.

8. The history concerning some of Logic's other applications is recounted below, but only the FDA's rejection of its menthol-flavored ENDS is at issue in this appeal.

controlled studies to determine the products' effects on smokers, and a marketing plan explaining how it would limit sales to children. As Logic saw things, this data offered "overwhelming scientific evidence" that its menthol-flavored ENDS were health-appropriate, Opening Br. at 12, because, among other things, the studies showed that its products helped adult menthol cigarette smokers reduce their daily cigarette intake, lowering their exposure to nicotine and helping them quit, and that these smokers preferred its menthol-flavored ENDS to its tobacco-flavored ones.

And on the other side of the health-appropriateness ledger, Logic provided survey data that it contended showed (1) that children do not use its products,[9] and (2) that menthol as a flavor was not nearly as popular among children as fruit or similar sweet flavors. In the same vein, Logic adopted many of the traditional marketing restrictions that other applicants have employed to keep its products out of children's hands, age-gating its website, quitting social media, and avoiding designs, flavors, and advertising campaigns directed at kids. With this combination, Logic believed it had made a strong case for its menthol-flavored ENDS to remain on the market.

2. The Center's deliberations about menthol

Logic's Premarket Application for menthol-flavored ENDS became something of a test case "because . . . it

9. According to the 2019 Youth Survey, just 0.8% of high-school-aged respondents said that they used Logic's products. At the time, most high schoolers used JUUL or did not have a usual e-cigarette brand.

was one of the applications" for such a product "furthest along in review" when the Center began to assess how the same health-appropriateness balance should apply to that flavor. JA 908.

Because it believed there was a "potential benefit" to adults who smoked menthol-flavored cigarettes, the Office of Science's "preliminary" recommendation was to approve Logic's Premarket Application. *Id.* Menthol cigarette smokers' potential switch to a menthol-flavored ENDS like Logic's could alter the health-appropriateness balance by making the benefit to current smokers greater than in fruit-flavored ENDS. At the same time, the risk to non-smoking youth, while higher than for tobacco-flavored ENDS, appeared lower than for fruit-flavored ones.

But the Office of the Center Director was not so sure, and raised questions about the Office of Science's recommendation that "continued over the course of several months into 2022." JA 908. Director Brian King, who arrived at the Center in July 2022, shared this concern and continued to question whether Logic's menthol-flavored ENDS were appropriate for the protection of public health. JA 904, 909. According to a memorandum by Dr. Todd Cecil, then Acting Director of the Office of Science (the Cecil Memo), Dr. King "raised questions about the [Office of Science's] recommendation, including questions about the role and sufficiency of the general scientific literature on adult menthol smokers' differential preference for menthol ENDS in demonstrating likely behavioral change, and underscored [his] concerns about the substantial appeal of menthol to youth." JA 908. The Director ultimately concluded that "the approach

to menthol-flavored ENDS should be the same as with other flavored ENDS with respect to the evidence of adult benefit." JA 904. Under that approach, as with fruit and similar characterizing flavors, the Center could only approve a menthol-flavored ENDS "if the evidence showed that the benefits . . . were greater than tobacco-flavored ENDS." JA 909.

The Director did not arrive at this conclusion in a vacuum. According to his memorandum (the King Memo), he solicited feedback from Office of Science staffers who may have disagreed with him "in a voluntary, confidential, and non-pressured environment" through the Center's Ombuds Team. JA 905. King's team considered several competing approaches to these products, including:

> whether [the Center's] evaluation of ENDS products places too much emphasis on the risks to youth from ENDS use, is not adequately bearing in mind the dangers from conventional smoking, and is pursuing the elimination of youth ENDS use without adequate regard to the impact on potential benefits to adult smokers. [The Center's] review process [took] into account the magnitude and rigor of the data related to youth ENDS use, how [the Center] should consider these data . . ., and the critical need to weigh evidence among both youth and adults in deciding whether to grant or deny marketing authorization.

JA 904. Notably, as part of this process, the Center also considered whether its "approach to evaluating ENDS

applications will result in the removal of all ENDS from the U.S. market except for tobacco-flavored ENDS . . . based on an assumption that no applicant would ever submit evidence sufficient to support authorization." *Id.* n.3.

Having completed that review, Director King concluded that "nationally representative data have not demonstrated that menthol combustible cigarette smokers are more likely to actually use menthol-flavored ENDS over tobacco-flavored ENDS to completely quit combustible cigarettes or significantly reduce their cigarette use." JA 905. On the other hand, "scientific evidence on the role of flavors in youth use of ENDS is significantly more rigorous and robust than the preference data concerning menthol combustible cigarette smokers." *Id.* Drawing on this scientific literature, King concluded that the primary additional benefit that menthol-flavored ENDS could have brought relative to fruit-flavored ones was illusory, and the risks were higher than the Office of Science had thought.

The Office of Science "on its own initiative" ultimately agreed, concluding that "the literature did not demonstrate that menthol-flavored ENDS were differentially effective, relative to tobacco-flavored ENDS, in terms of promoting significant cigarette reduction or complete switching among adult smokers." JA 909.

3. The FDA's review of Logic's Premarket Application

The appropriate framework in hand and in agreement on the risks and benefits of menthol, Center staff

assessed Logic's Premarket Applications, approving those for tobacco-flavored ENDS, but finding those for menthol-flavored ENDS lacking. On the benefits to current smokers, the agency looked for two things: (1) evidence that menthol cigarette smokers did not just prefer menthol-flavored ENDS to other flavors but in fact would switch to using them, and (2) statistically significant evidence that those benefits were greater than the ones that tobacco offered.

The FDA agreed with Logic that its studies showed that menthol cigarette smokers "show a preference for menthol-flavored ENDS, relative to non-menthol-flavored ENDS." JA 914. It cautioned, however, that "evidence of preference is not evidence of behavior change, and these studies showing preference for menthol-flavored ENDS were not designed to directly address the outcomes of complete switching or cigarette reduction. Actual product use is critical in the evaluation of product switching." *Id.* And when it came to evidence of switching, Logic came up short. The types of surveys Logic used were designed to "assess outcomes believed to be precursors to behavior, such as preferences or intentions . . . but [were] not designed to directly assess actual product use behavior." JA 951. This was consistent with the FDA's view of the broader scientific literature, which only showed that menthol smokers "prefer menthol-flavored ENDS," not that they actually promoted "complete switching or cigarette reduction." *Id.* As the FDA explained:

> [T]he ability of a product to promote switching among smokers arises from a combination of its

> product features . . . 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 user. Moreover, uptake and transition to ENDS use is a behavioral pattern that requires assessment at more than one time point.

Id.

Logic's evidence that menthol offered any benefit beyond what tobacco presented was similarly lacking. Its randomized controlled studies did not demonstrate that its menthol-flavored ENDS generated a statistically greater reduction in cigarette smoking than its tobacco-flavored ENDS. This again tracked the more general literature, which did not show "that menthol-flavored ENDS *differentially* facilitate switching or cigarette reduction." JA 944 (emphasis added). Thus, the potential benefit of menthol-flavored ENDS to current cigarette smokers remained just that—potential.

Turning to the flavor's appeal to non-smokers, menthol was not meaningfully less popular than fruit or dessert flavors such that it could escape comparison to tobacco. True, it remained less popular than fruit or sweets, but the gap was shrinking. By 2022, Youth Survey data showed that, among high schoolers who had used e-cigarettes in the previous thirty days, almost 27% had tried menthol, not far behind mint (about 30%) and sweets (about 38%). The National Institutes of Health (NIH) Population Assessment of Tobacco and Health longitudinal study

had tracked long-term trends in youth vaping with stark results: across waves of this study, the vast majority of youth (12-17 year-olds) and young adults (18-24 year-olds) who started vaping did so with a flavor other than tobacco. A staggering 93.2% of youth in the NIH study's 2016-17 cohort said that their first ENDS product was not tobacco-flavored, while a relatively paltry 54.9% of adults twenty-five or older said the same. This was crucial because even a relatively small gap between tobacco and menthol can have important public health consequences for children. Studies have shown that "non-tobacco flavoring . . . make[s] them more palatable for novice users . . . which can lead to initiation, more frequent and repeated use, and eventually established regular use." JA 945. The key takeaway from the data, per the FDA, was not that menthol was less popular than fruit, but that it was more popular than tobacco.

In addition, the FDA had reason to believe that flavor preference data would trend in menthol's favor in the future. As enforcement actions had taken many cartridge-based flavored ENDS devices off the market, high schoolers in one survey increased their use of disposable flavored ENDS over tenfold (2.4% to 26.5%) in just a year. As the FDA saw it, "[t]his trend underscores the fundamental role of flavor in driving appeal . . . . [T]he removal of one flavored product option prompted youth to migrate to another ENDS type that offered flavor options, even though it exhibited lower youth use prevalence historically." JA 935. For the time being, the FDA had turned its attention to fruit and dessert flavors that had especially strong appeal to kids. But as enforcement

actions removed those flavors from the market, the FDA reasoned, other flavors like menthol could become yet more popular as kids turned to the remaining islands of flavor in the e-cigarette market.

Nor could Logic's marketing restrictions bridge the gap. The FDA already had assessed the efficacy of the types of restrictions that Logic had implemented in previous cases and concluded that they were "insufficient to mitigate the substantial risk to youth from flavored ENDS." JA 966. Indeed, evidence had consistently shown that these marketing restrictions were not responsive to children's actual purchasing patterns because "the majority of youth do not purchase e-cigarettes themselves from retail locations, but rather they obtain them from social sources, including from friends or family members, steal them, or use someone else's product." JA 940. While some new technologies, such as biometrics or geo-fencing, seemed promising to the Center, Logic did not offer them.

The FDA thus issued a Marketing Denial Order for Logic's menthol-flavored ENDS on October 26, 2022. Logic successfully obtained a stay of that order and timely filed this petition for review.

II. Jurisdiction and Standard of Review

We have jurisdiction over Logic's petition under 28 U.S.C. § 1331 and 21 U.S.C. § 387l(a)(1)(B). The Tobacco Control Act directs petitioners to file in the D.C. Circuit or in the circuit encompassing their principal place of business. 21 U.S.C. § 387l(a)(1)(B). Logic's principal place

of business is in Teaneck, New Jersey, so we may hear its petition.

The APA governs our review of the FDA's Marketing Denial Order. We must vacate the agency's decision if it was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Sanofi Aventis U.S. LLC v. HHS*, 58 F.4th 696, 702-03 (3d Cir. 2023) (quoting 5 U.S.C. § 706(2)(A)).

III. Discussion

Logic raises four principal challenges to the Marketing Denial Order. First, it contends that the FDA changed course and rejected its Premarket Application "pursuant to an undisclosed, illegal policy against all menthol ENDS." Opening Br. at 36. Second, and relatedly, it characterizes the Technical Project Lead Review as the product of a new evidentiary standard that unfairly surprised the company. Next, it characterizes the Marketing Denial Order as the product of the FDA's failure to examine important aspects of the regulatory problem and inconsistent with the evidence in its Premarket Application. Finally, it attacks as allegedly inconsistent with agency practice the FDA's decision to require the immediate withdrawal of its menthol-flavored ENDS from the market rather than allow a transition period. In each instance, Logic's arguments are unavailing, so we will deny its petition for review.

Appendix A

A. Arbitrary and capricious review

When an agency acts, it "must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43, 103 S. Ct. 2856, 77 L. Ed. 2d 443 (1983) (citation omitted) (*State Farm*); *see Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 221, 136 S. Ct. 2117, 195 L. Ed. 2d 382 (2016). If it does not, the agency has failed to "engage in reasoned decisionmaking," and the APA requires the agency action be set aside. *Michigan v. EPA*, 576 U.S. 743, 750, 135 S. Ct. 2699, 192 L. Ed. 2d 674 (2015) (internal quotation marks and citation omitted).

In addition, while the APA requires no "more detailed justification than what would suffice for a new policy created on a blank slate," when an agency revises or updates existing policies, it must at least "display awareness that it *is* changing position" and explain "that [it] *believes* [the new action] to be better." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515, 129 S. Ct. 1800, 173 L. Ed. 2d 738 (2009). And when the new approach "rests upon factual findings that contradict those which underlay its prior policy; or when its policy has engendered serious reliance interests that must be taken to account," that extra explanation is necessary. *Id.; see also Encino Motorcars*, 579 U.S. at 222. Relatedly, an agency cannot say that it is going to approach a regulatory or licensing issue using one framework only to pull a "surprise switcheroo" on private parties and

use a different framework instead. *Prohibition Juice*, 45 F.4th at 20; *see also Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156, 132 S. Ct. 2156, 183 L. Ed. 2d 153 (2012) (citation omitted) (noting that "agencies should provide regulated parties 'fair warning of the conduct [a regulation] prohibits or requires'").

We also are not free to sustain agency action based only on any *post hoc* reasoning that the parties offer up in litigation. Instead, we are limited to the justifications that were available to and relied upon by the agency at the time. *See DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1907, 207 L. Ed. 2d 353 (2020) (citation omitted); *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 419, 91 S. Ct. 814, 28 L. Ed. 2d 136 (1971) (citation omitted); *SEC v. Chenery Corp.*, 318 U.S. 80, 94, 63 S. Ct. 454, 87 L. Ed. 626 (1943).

That said, arbitrary and capricious review is not meant to be an exacting standard. Because "a court is not to substitute its judgment for that of the agency," *Fox Television*, 556 U.S. at 513 (quoting *State Farm*, 463 U.S. at 43), we will uphold agency action even if its reasoning is "of less than ideal clarity" as long as "the agency's path may reasonably be discerned," *Garland v. Ming Dai*, 141 S. Ct. 1669, 1679, 210 L. Ed. 2d 11 (2021) (quotation omitted). This is especially true in highly technical areas like public health, as "[w]e are 'particularly reluctant to second-guess agency choices involving scientific disputes that are in the agency's province of expertise.'" *N.J. Env't Fedn v. U.S. Nuclear Regul. Comm'n*, 645 F.3d 220, 230 (3d Cir. 2011) (quotation omitted); *see also Fertilizer Inst.*

v. Browner, 163 F.3d 774, 777 (3d Cir. 1998) ("[T]he court should not substitute its own judgment for the scientific expertise possessed by the agency.").

B. The alleged blanket anti-menthol policy

Logic paints the debate memorialized in the King and Cecil Memos as proof that Director King effectively imposed a blanket anti-menthol policy and overrode the Office of Science's determination that Logic's menthol-flavored ENDS were health-appropriate, violating both the APA and the Tobacco Control Act. Absent a more explicit explanation of why the agency viewed menthol as less dangerous to public health in the Enforcement Priorities and then considered the flavor to be essentially indistinguishable from fruit and sweets in the Technical Project Lead Review, Logic contends that the FDA's change in course was necessarily arbitrary and capricious.

Logic's view aligns in this respect with that recently articulated by the Fifth Circuit in *R.J. Reynolds Vapor*. There, the panel granted a stay to a much larger menthol ENDS manufacturer that had received a marketing denial order, reasoning that these memoranda showed that Director King "told" the Office of Science what the framework for menthol premarket applications would be and "are strong evidence that [the Center] developed and internally circulated new criteria for evaluating [premarket applications] for menthol-flavored ENDS." 65 F.4th at 192. As the Fifth Circuit saw it, the FDA's marketing denial order "rest[ed] upon factual findings that contradict those which underlay its prior policy," so the

FDA was required to offer "a more detailed justification" of its decision. *Id.* (quoting *Fox Television*, 556 U.S. at 515).

We do not share the Fifth Circuit's view of what happened within the Center or its legal impact. First, the pat story about Director King overriding the Office of Science's recommendation both oversimplifies and obscures. True, at first, the Office of Science thought that the health-appropriateness balance might favor menthol and was therefore preliminarily inclined to recommend approval of Logic's Premarket Application. But at this early juncture, the Office of Science only considered the benefit of Logic's menthol-flavored ENDS to menthol cigarette smokers "potential," JA 908, and "did not find that the current literature support[ed] that use of menthol-flavored ENDS by adult smokers [was] associated with greater likelihood of complete switching or significant cigarette reduction relative to tobacco-flavored ENDS,"[10] JA 907-08. So even before any discussions with Director King, the Office of Science was at most lukewarm about treating menthol differently from other non-tobacco characterizing flavors.

And crucially, after discussions with Director King, the Office of Science "*on its own initiative*" went back to the evidence and "decided it was reasonable and consistent to treat menthol-flavored ENDS [premarket applications] in the same way as other non-tobacco-flavored ENDS [premarket applications]." JA 909 (emphasis added). It

10. Of course, the agency eventually adopted this same view in Logic's Technical Project Lead review.

did so, moreover, after multiple opportunities for rigorous discussions about menthol with both the Director and the Center's Ombuds Team. Thus, the record does not support Logic's rendition of a political appointee parachuting in and dictating a new framework for the Office of Science to adopt.[11] *R.J. Reynolds Vapor*, 65 F.4th at 192. Nor does it evince a blanket policy against menthol promulgated from on high. Instead, it reflects that the Office of Science's tenuous preliminary support for Logic's Premarket Application withered in the face of its own evolving understanding of the scientific evidence.

Second, and more fundamentally, the internal debates that the memoranda describe do not reflect a pre-existing agency policy or final agency action. The APA limits our jurisdiction to (1) "[a]gency action made reviewable by statute," and (2) "*final* agency action for which there is no other adequate remedy in a court." 5 U.S.C. § 704 (emphasis added). Agency action counts as "final" only if (1) it "mark[s] the 'consummation' of the agency's decisionmaking process," and (2) it is "one by which 'rights or obligations have been determined' or from which 'legal consequences will flow.'" *Bennett v. Spear*, 520 U.S. 154,

11. Even if the Director were bringing political considerations to bear, that would not render the agency's action here arbitrary or capricious. As the Supreme Court has made clear, "a court may not set aside an agency's policymaking decision solely because it might have been influenced by political considerations or prompted by an Administration's priorities . . . . Such decisions are routinely informed by unstated considerations of politics, the legislative process, public relations, interest group relations, foreign relations, and national security concerns (among others)." *Dep't of Com. v. New York*, 139 S. Ct. 2551, 2573, 2575, 204 L. Ed. 2d 978 (2019).

177-78, 117 S. Ct. 1154, 137 L. Ed. 2d 281 (1997) (citations omitted); *see also* 5 U.S.C. § 551(13) (defining "agency action" for purposes of the APA). The consummation of the process here was the FDA's issuance of the Marketing Denial Order.[12]

In contrast to the Marketing Denial Order, however, the King and Cecil Memos are not—and therefore cannot be reviewed as—"final agency action" because they flunk the first finality requirement.[13] They show only that, to the extent that one component of the Center had developed a view of menthol at all by the second half of 2021, parts of it had arrived at a "preliminary recommendation" to approve Logic's Premarket Application. JA 908. This was nowhere close to a final decision—that would not come for almost a year while it determined what the right framework would

12. The Marketing Denial Order is reviewable pursuant to 21 U.S.C. § 387l(a)(1)(B).

13. We may, of course, consider agency memos and other documents in the administrative record in determining whether an agency's change in existing policy was arbitrary and capricious, and whether its "sole stated reason" for its action is pretextual. *Dep't of Com.*, 139 S. Ct. at 2575 (considering agency documents in determining that the Secretary of Commerce's stated rationale for reversing prior policy and reinstating a citizenship question on the 2020 census questionnaire was "contrived"). Here, the King Memo and the Deficiency Letter do not reflect any prior agency policy, but merely its evolving understanding of the scientific evidence and the exchange of views among its different components. And the FDA's explanation for its final agency action in the Marketing Denial Order is entirely consistent with that evidence and exchange of views, i.e., "with what the record reveals about the agency's priorities and decisionmaking process." *Id.*

be for menthol-flavored ENDS. As it internalized new information about menthol, the Center's understanding of the characterizing flavor crystallized into something more formal.[14] This is not the sort of "change[d] course" that can trigger a heightened burden for the FDA, *Regents*, 140 S. Ct. at 1913, nor does it expose some "secret" and nefarious anti-menthol policy, as Logic contends.[15] Crediting that

14. Our dissenting colleague characterizes the FDA's preliminary discussions differently, insisting that the FDA's statements suggesting that menthol-flavored ENDS could be less harmful to public health reflected a "policy position," Dissent at 12, and that the FDA then "changed the agency's menthol policy 'out of Logic's sight,'" *id.* at 8. But the very portions of the record that the dissent has quoted contradict this characterization. *See id.* at 10 (citing agency's language in the Deficiency Letter indicating that menthol products "may have lower youth appeal"); *id.* at 11 (citing an internal FDA memo explaining that menthol-flavored ENDS offered a "potential means by which some adult smokers might seek to transition completely away from combusted tobacco products to potentially less harmful tobacco products"). These portions of the record underscore the tentative and preliminary nature of the agency's inconclusive inclinations before it issued the Marketing Denial Order.

15. To be clear, Logic's advocacy is the lone source for the dissent's assertion that the FDA rejected Logic's applications as "a matter of policy, not science." Dissent at 6. The dissent cites a report outside the record for that proposition. *See id.* (citing Lauren Silvis et al., Reagan-Udall Found., Operational Evaluation of Certain Components of FDA's Tobacco Program ("Reagan-Udall Report") 15 (2022), https://perma.cc/NP3A-3QNJ). But that report does not concern Logic's application. *See* Lauren Silvis et al., Reagan-Udall Found., Operational Evaluation of Certain Components of FDA's Tobacco Program ("Reagan-Udall Report") 15 (2022), https://perma.cc/NP3A-3QNJ. Instead, the report generally acknowledges that weighing an ENDS application's public health benefits to adult

argument would penalize the Center for engaging in the "ongoing dialogue" and deliberation that is supposed to be the hallmark of reasoned agency decision-making.[16] *See Avail Vapor*, 55 F.4th at 424.

It is also notable that these debates took place within the FDA, out of Logic's sight, and therefore could not have "engendered serious reliance interests that must be taken into account." *Regents*, 140 S. Ct. at 1913 (quoting *Encino Motorcars*, 579 U.S. at 222). The Fourth Circuit ably explained why deliberations like these cannot fall within the APA's reach in *Avail Vapor*, another case denying an ENDS manufacturer's petition. There, the petitioner raised concerns about internal FDA memoranda discussing the weight that the agency was going to accord certain evidence in premarket applications. *See Avail Vapor*, 55 F.4th at 423-24. Judge Wilkinson forcefully rejected the petitioner's assertions that these memoranda

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smokers (who may use the product to quit combustible tobacco products) against the risks to youth non-smokers (whom the product may appeal to) implicates policy questions as well as scientific ones. But that assertion is clearly irrelevant here, where the FDA determined, as a scientific matter, both that Logic's menthol-flavored ENDS posed a risk to youth non-smokers *and* that there was insufficient evidence of any benefits to adult smokers. JA 914, 945, 951. The FDA therefore did not need to engage in the weighing analysis that the Reagan-Udall Report characterizes as a policy decision.

16. Nor was there anything untoward about the Center considering the possibility that the standard it was adopting amounted to a per se anti-flavoring rule. The Center is to be commended, not disparaged, for considering this possibility and taking pains to rule it out.

exposed a turnabout in FDA policy: "What Avail fails to recognize . . . is that these internal documents were just that: internal," and agencies merit "latitude in their internal discussions and debates" that "needs to be broad in the case of a statutory charge as general as this one, where internal discussions involve complex predictions within the [FDA's] area of special expertise." *Id.* at 424 (internal quotation marks and citations omitted); *see also Regents*, 140 S. Ct. at 1913-15. A contrary rule, he observed, would lead to "gridlock, an agency decisional process robbed of the value of ongoing dialogue." *Avail Vapor*, 55 F.4th at 424.

Echoing the Fourth Circuit, we will not "locate a point where agency deliberations become frozen in time." *Id.* We also will not acquiesce in binding the FDA to what were, by their own terms, the preliminary recommendations of one section of one of its divisions or require it to offer an additional explanation under *Regents* and *Fox Television* as a penalty for engaging in an iterative, deliberative discussion. *Id.; cf. Fertilizer Inst.*, 163 F.3d at 778 (holding that the EPA did not need to justify updating its definition of "chronic health effects" from the one it had put in an unpromulgated draft guideline); *but see R.J. Reynolds Vapor*, 65 F.4th at 192. Reasoned disagreement among civil servants is the stuff of good government, not APA violations.

C. Change in evidentiary standard for menthol

Stripped of the hyperbole that the FDA laid down a blanket anti-menthol policy, the record reflects nothing

more than the application to menthol-flavored ENDS of the same regulatory framework and evidentiary standard that the agency had applied previously to other non-tobacco flavored ENDS and that we upheld in *Liquid Labs*. *See* 52 F.4th at 542-43. Analyzing new information under the same framework is no change at all as far as the APA is concerned.[17]

Here, too, we part ways with the Fifth Circuit, which accepted the argument that the FDA had changed course with respect to (1) the types of evidence that would be required for a premarket application to win approval, and (2) the appropriate comparator for menthol-flavored ENDS. *R.J. Reynolds Vapor*, 65 F.4th at 190. We already tread this ground in *Liquid Labs*, where we held that the FDA's evidentiary requirements did not constitute a "surprise switcheroo." 52 F.4th at 540. Even if *Liquid Labs* had not paved the way, however, we would reach the same conclusion here about the FDA's guidance for menthol premarket applications specifically.

To review, the Premarket Application Guidance advised ENDS manufacturers in 2019 that "well-

17. The record does not support the proposition, espoused by the dissent, that the framework the FDA applied to Logic's application was "previously reserved for non-menthol flavored ENDS." Dissent at 1. What it does reflect is that the agency established a framework that it determined was appropriate to assess whether the marketing of ENDS was health-appropriate, and it proceeded to apply that framework to ENDS products in descending order of enforcement priority, starting with fruit-flavored ENDS and eventually turning to menthol-and mint-flavored ENDS.

controlled investigations" would be necessary for their products to remain on the market, and that "[n]onclinical studies alone" probably would not be enough to win approval. JA 1027. The FDA made clear what it was looking for, recommending that applicants "compare the health risks of its product to . . . products within the same category and subcategory" that "are most likely to [be] considered interchangeable." JA 1028. For Logic's products, that meant menthol combustible cigarettes and tobacco-flavored ENDS.

Those expectations were not lost on Logic. Our dissenting colleague asserts that "Logic had no reason to compare menthol products to tobacco products." Dissent at 16. But the Premarket Application speaks for itself, as Logic made a point of providing those comparisons in the application. They included randomized controlled studies that juxtaposed the observed change in cigarette consumption for subjects who received Logic's menthol-flavored ENDS with the same effect for subjects who received Logic's tobacco-flavored ENDS. And at argument, Logic sought to persuade us that this comparison should have resulted in a favorable decision because its studies allegedly proved the decreases were attributable to the ENDS' menthol flavor alone.[18]

18. Indeed, counsel argued that the FDA "overlooked" the aspects of Logic's submission that "do exactly what they claim to want to do, which is the comparison between the actual efficacy of switching between the menthol flavored ends and the tobacco flavored ends." Oral Arg. Tr. 18:10-14. According to counsel, the comparison between menthol-flavored ENDS and tobacco-flavored ENDS "was there in plain black and white in the submission." *Id.* at 20:19-20.

But that is not quite right. Logic included a comparison, but not one that was statistically significant. As the Technical Project Lead Review pointed out, these studies "were not designed to address direct comparisons between Logic's menthol-flavored ENDS and tobacco-flavored ENDS (or any other flavor combinations)." JA 949. So the problem was not that Logic had no reason to compare menthol products to tobacco products, but that it failed its statutory responsibility to present "well-controlled investigations." 21 U.S.C. § 387j(c)(5)(A).

No matter, Logic retorts, because the APA violation here was the FDA's "egregious" "bait-and-switch" in telling Logic in a Deficiency Letter that Logic should compare its menthol-flavored ENDS to other flavored ENDS, and then insisting that it compare those products to tobacco-flavored products instead. Opening Br. at 40. This argument might have traction if the FDA indeed had tacked on "an additional, previously undisclosed evidentiary requirement" for the approval of Logic's menthol-flavored ENDS, *id.* at 40-41, and failed to communicate it to the company. *See SmithKline Beecham*, 567 U.S. at 156-57. But that is not what happened here.

The part of the Deficiency Letter to which Logic refers concerned only its Premarket Applications for certain fruit flavors, not the menthol-flavored ENDS at issue in this case. *Cf. Fontem US, LLC v. FDA*, ___ F.4th ___, 2023 U.S. App. LEXIS 22716, 2023 WL 5536194, at *9 (D.C. Cir. Aug. 29, 2023) (determining that the FDA "pull[ed] a surprise switcheroo" by representing in a deficiency letter that the information being requested "would be

sufficient for the agency to approve Fontem's products" but later denying Fontem's application because Fontem failed to provide additional information). The FDA had made clear already both the appropriate comparators, including tobacco, and the types of data that would show their relative efficacy. *See Liquid Labs*, 52 F.4th at 539-40. Nothing in the Deficiency Letter changed those standards.[19]

In sum, because the FDA's Marketing Denial Order applied the same standard it had been applying since 2019 to other non-tobacco flavors, Logic cannot rest its APA claim on any unfair surprise.

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19. The Enforcement Priorities do not compel a different conclusion. That document did not modify the FDA's guidance about the evidentiary standards to which the agency would subject premarket applications for menthol-flavored ENDS. It only set the order in which the FDA would launch enforcement actions against "certain deemed tobacco products that do not have premarket authorization." JA 1108. Our dissenting colleague characterizes the Enforcement Priorities differently, suggesting that statements in that document are probative of a prior agency policy. But this characterization contradicts the FDA's own description of the document, which explained that it merely delineated the agency's enforcement priorities and was "not binding on FDA or the public." JA 1108. The dissent may disagree with the agency's description of its document or, like Logic, may disagree with the agency's scientific determination. But agree or disagree, on matters of science we may not "substitute [our] judgment for that of the agency." *See Sierra Club v. U.S. Env't Prot. Agency*, 972 F.3d 290, 298 (3d Cir. 2020) (quoting *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43, 103 S. Ct. 2856, 77 L. Ed. 2d 443 (1983)).

D. Conformity with the evidence before the agency

Logic next asserts that the Marketing Denial Order and Technical Project Lead Review "fall[] short of the 'reasoned decisionmaking' standard mandated by the APA," Opening Br. at 50 (quoting *Michigan*, 576 U.S. at 750), because the FDA incorrectly weighed the evidence it submitted, and improperly discounted its "product-specific" evidence, relying instead on "general claims concerning other menthol-and candy and fruit flavored ENDS products," *id.* at 49. The record tells a different story.

1. Benefits to adults

Logic challenges the FDA's conclusion that the potential benefit of menthol-flavored ENDS—their ability to serve as a substitute for menthol cigarette smokers—was largely illusory. Its menthol-flavored ENDS, it maintains, "are both preferred to and likely more effective than its tobacco-flavored ENDS in helping adult smokers reduce their combustible cigarette use or quit smoking altogether." Opening Br. at 48.

The Tobacco Control Act, however, requires the agency to assess whether "existing *users* of tobacco products will stop *using* such products." 21 U.S.C. § 387j(c)(4) (emphasis added). The lodestar is not what products smokers may prefer, but what products they actually use. Yet Logic's data proved the former, not the latter. As the FDA explained at length in the Technical Project Lead

Review, its Premarket Application "assess[ed] precursors to . . . product use behavior" like quitting, JA 951, and did not show a differential benefit for the menthol-flavored ENDS over and above its tobacco-flavored ones. While Logic may quarrel with the appropriateness of that standard, we already crossed that bridge in *Liquid Labs.* 52 F.4th at 542-43. That precedent controls.

So does the FDA's scientific judgment about the validity of Logic's studies. As Article III judges, "[w]e are 'particularly reluctant to second-guess agency choices involving scientific disputes that are in the agency's province of expertise.'" *N.J. Env't Fed'n*, 645 F.3d at 230 (quotation omitted); *Fertilizer Inst.*, 163 F.3d at 777. When asked to determine whether agency action was arbitrary or capricious, our job is only to (1) assess the sufficiency of the agency's review of the record, (2) ensure the agency offered a reasoned explanation for its decision, and (3) confirm the explanation accords with that record. *See State Farm*, 463 U.S. at 43. We overstep when we purport to substitute our judgment for the agency's as to the statistical validity or ultimate findings of clinical studies. *N.J. Env't Fed'n*, 645 F.3d at 230.

Yet that is precisely what Logic asks us to do. And Logic does not argue that the FDA ignored the evidence. Instead, it contends that the FDA did not weigh the evidence to Logic's liking. It objects that, after looking at the evidence that Logic's menthol-flavored ENDS would get smokers to stop smoking, the FDA found that evidence lacking and discounted the company's studies accordingly. So this is not a situation where the FDA failed to "address

the potential benefits of [the applicant's] products for the public at large" or to "consider the possibility that existing users of combustible tobacco products such as cigarettes would reap health benefits by transitioning to [Logic's] products." *Fontem US, LLC*, 2023 U.S. App. LEXIS 22716, 2023 WL 5536194, at *7. This is instead a scientific debate, so the "fundamental principle of judicial restraint" dictates that we avoid it. *Washington State Grange v. Washington State Republican Party*, 552 U.S. 442, 450, 128 S. Ct. 1184, 170 L. Ed. 2d 151 (2008).

It is enough for our purposes that the FDA's decision to deny Logic's Premarket Application was not "without substantial basis in fact" and was "within [the FDA's] area of competence." *N.J. Env't Fed'n*, 645 F.3d at 230 (quotation omitted).

2. Risks to children

Logic's arguments on the other side of the health-appropriateness scale fail for similar reasons. Logic contends it was arbitrary and capricious to issue a Marketing Denial Order to a company whose products were so unpopular with kids, taking particular exception to the FDA's reliance on "general statistics [that] do not account for Logic's particular products." Opening Br. at 51, 53. In Logic's view, the only way the agency could reject its Premarket Application was by "resort[ing] to improper speculation . . . further demonstrating that the FDA did not care at all about the evidence concerning Logic's particular product." *Id.* at 53.

Under the Tobacco Control Act, however, the FDA was well within its rights to rely on both Logic's product-specific evidence and broader scientific literature about the appeal of menthol. The Act permits the agency to look at "any . . . information before the Secretary with respect to such tobacco product," 21 U.S.C. § 387j(c)(2)(A), including, "when appropriate, . . . well-controlled investigations, which may include . . . clinical investigations by experts," *id.* § 387j(c)(5)(A), or other "valid scientific evidence" that "is sufficient to evaluate the tobacco product," *id.* § 387j(c)(5)(B). Taken together, Congress set limitations on the quality of the evidence consulted by the agency—*i.e.*, whether the studies are "well-controlled," or whether the other evidence is "valid"—but not on the subject matter or scope of that evidence—*i.e.*, whether it only analyzed a specific applicant's ENDS. Of course, scientific evidence may be more persuasive when it evaluates the particular ENDS at issue, but that does not render otherwise "valid" general evidence irrelevant or incompetent.

Nor was the Center's conclusion about menthol's appeal to children improperly "speculative." Opening Br. at 49. The agency was acting pursuant to Congress's express directive in the Tobacco Control Act. When making the health-appropriateness determination, the FDA must look at "the risks and benefits to the population as a whole." 21 U.S.C. § 387j(c)(4). "Risk" encompasses far more than facts currently known to an agency beyond a reasonable doubt—assessing risk requires looking to the future, *i.e.*, examining "the chance of injury, damage, or loss[, especially] the existence and extent of the possibility of harm." *Risk*, Black's Law Dictionary (11th ed. 2019).

There is nothing improper under the APA about the Center prognosticating what will happen to children's menthol use as other flavored ENDS exit the market. It made reasoned projections based on market responses to previous enforcement actions, and it did so pursuant to a statute that not only permits it to forecast, but requires it to do so. *See Avail Vapor*, 55 F.4th at 424. The conclusions the FDA reached as a result thus comport with its statutory mandate.

Logic seeks to change the calculus, touting its efforts to avoid marketing to children, but the FDA's skepticism on this score also had a reasoned basis. In *Liquid Labs*, we upheld the FDA's marketing denial order even though the agency had ignored the manufacturer's marketing plan because "there [was] no indication the plan would have made up for the deficiencies the FDA identified in Liquid Labs' applications." 52 F.4th at 543 (citations omitted). Here, the FDA did analyze Logic's marketing plan and found it lacking, clearing the low bar we set in *Liquid Labs*. The statute is not preoccupied with whether children are deterred from *buying* Logic's products; it focuses instead on the much broader question of whether they are deterred from *using* them. *See* 21 U.S.C. § 387j(c)(4). And the evidence has shown for years that marketing restrictions like Logic's do not cut down on youth use sufficiently to change the health-appropriateness balance.

E. Transition period

Finally, Logic complains that, in its treatment of its menthol-flavored ENDS, the FDA modified its purported

"policy when removing marketing authorization for drugs, tobacco, or other products already on the market to give manufacturers a reasonable transition period before requiring that they remove their products completely from the market." Opening Br. at 57. But the products it identifies that received transition periods share little in common with Logic's menthol-flavored ENDS.[20] *See, e.g.*, 85 Fed. Reg. 13,312, 13,349 (Mar. 6, 2020) (electrical stimulation devices "for self-injurious or aggressive behavior"); 83 Fed. Reg. 50,490, 50,502 (Oct. 9, 2018) (styrene for food flavoring); 81 Fed. Reg. 91,722, 91,728 (Dec. 19, 2016) (powdered surgeon's gloves). Nor do the few instances in which the FDA has issued ENDS manufacturers an administrative stay add up to an established agency policy. *See Bennett*, 520 U.S. at 177-78. And with approximately 2,110,000 students using flavored ends in 2022 and youth continuing to migrate to menthol-flavored ENDS in the absence of fruit-flavored ENDS, the FDA could reasonably conclude that immediate removal of these products from the marketplace was "appropriate for the protection of the public health." 21 U.S.C. § 387j(c)(2)(A).

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20. In its Reply Brief, Logic suggests that the dearth of tobacco-related transition periods supports its argument because the "FDA is admitting that it has treated tobacco products, including even some ENDS products, worse than non-tobacco products," which "itself violates the APA" because the FDA "provides no reasoned explanation as to why ENDS products should be treated more harshly than other types of products." Reply Br. at 27. Because this argument was not pressed in Logic's Opening Brief, it is forfeited. *See Barna v. Bd. of Sch. Dirs. of Panther Valley Sch. Dist.*, 877 F.3d 136, 146 (3d Cir. 2017) (citing *In re Grand Jury*, 635 F.3d 101, 105 n.4 (3d Cir. 2011)).

IV. Conclusion

The FDA here fulfilled its statutory mandate in all respects. It saw a public health crisis—youth vaping—unfolding at the sweet spot of its expertise and the core of the jurisdiction it was given in the Tobacco Control Act. It reasonably prioritized among the products at issue, and when it reached menthol-flavored ENDS and Logic's Premarket Application, the scientific studies and market changes in the interim led it to conclude the marketing of that product was not "appropriate for the protection of the public health." 21 U.S.C. § 387j(c)(2)(A). That was a reasoned decision, with substantial basis in fact, and thus did not run afoul of the APA or the Tobacco Control Act.

For the foregoing reasons, we will deny Logic's petition for review.

PORTER, *Circuit Judge*, dissenting.

The majority concludes that the FDA's secret, unexplained policy decision to treat menthol electronic delivery systems (ENDS) like fruit-and-dessert-flavored ENDS was not arbitrary and capricious but an example of "good government." Maj. Op. at 29. Logic Tech (Logic) was therefore foolish to rely on the agency's previous representations that (1) menthol and tobacco ENDS were different than flavored ENDS and (2) Logic needn't demonstrate that its menthol products are more likely to promote cigarette reduction compared to tobacco-flavored products. The majority says Logic has no ground to complain that the agency disregarded its own scientific conclusions and denied Logic's menthol ENDS applications using an evidentiary standard previously reserved for non-menthol flavored ENDS.

I view the FDA's actions differently. Before July 2022, it treated menthol ENDS like tobacco ENDS and told Logic that was its policy. According to the agency, menthol offered benefits to smokers wanting to transition from combustible cigarettes and posed less risk to youth, who prefer sweet and fruity flavors. But that month, unbeknownst to Logic, the agency abruptly changed its policy and lumped menthol together with fruit, candy, and dessert flavors. The FDA never informed Logic of the policy shift until after it denied Logic's menthol-product applications. Because the agency failed to give a reasoned analysis or detailed justification for the policy change, I respectfully dissent.

Appendix A

I

In July and August 2019, Logic submitted Premarket Tobacco Product Applications (PMTA) for fifteen ENDS. Three of the PMTAs were for menthol products.

While the applications were pending, the FDA twice communicated to Logic that it viewed menthol ENDS more like tobacco ENDS and not like flavored ENDS. In April 2020, the agency published guidance describing its ENDS enforcement priorities: It would target unlawfully marketed "flavored, cartridge-based ENDS products (other than tobacco-and menthol-flavored)." J.A. 1109. By targeting fruit and other flavored products but not tobacco or menthol products, the FDA said it sought to "strike[] an appropriate balance between restricting youth access to [fruit and mint products], while maintaining availability of potentially less harmful options for current and former adult smokers who have transitioned or wish to transition completely away from combusted tobacco products." J.A. 1126.

In June 2020, the FDA issued a deficiency notice to Logic requesting additional information that was "needed for a marketing granted order determination." J.A. 3010. The FDA requested, among other things, additional data comparing the use of "products with fruit-or fruit-combination flavors," which "pose particular risks for youth initiation and progression to regular ENDS use," to "tobacco-or menthol-flavored products, which may have lower youth appeal." J.A. 3016. Pointedly, the notice did not request such data comparing menthol to tobacco

products. This was the final correspondence that Logic received from the FDA until the MDO was issued.

By March 2022, every discipline within the Office of Science (OS) concluded that Logic's menthol products should be approved for marketing. At a PMTA Preliminary Assessment Meeting in May 2021, the Engineering, Chemistry, Microbiology, Behavioral and Clinical Pharmacology, and Medical Disciplines and the Office of Compliance and Enforcement identified no deficiencies with *any* Logic PMTA. The Toxicology and Environmental Science Disciplines joined their cohorts after a second review of Logic's PMTAs in March 2022. And that same month, the Social Science and Epidemiology Disciplines advised that Logic's menthol and tobacco products be approved for marketing but recommended that Logic's fruit and fruit-combination applications be denied. Social Science noted that the "menthol flavored new products . . . have lower youth appeal," J.A. 3097, and "may offer menthol cigarette smokers an appealing option to transition away from combusted cigarette smoking, an option particularly important given some menthol smokers' lower rates of combusted cigarette cessation," J.A. 3101. Epidemiology, similarly, distinguished menthol from other flavored ENDS by expressing its "concerns regarding the lack of evidence on the new products' with non-tobacco/non-menthol characterizing flavors ability to facilitate switching or cigarette reduction among adult combusted cigarette smokers." J.A. 3067.

Given these recommendations, the OS decided that Logic's menthol products merited approval. It found that

that the "potential benefit" of adult menthol smokers switching from combustible cigarettes to menthol ENDS "amounted to a likelihood of greater cessation or significant reduction in smoking that would outweigh the known risks to youth from the marketing of the products, sufficient to meet the legal standard for authorization." J.A. 908 (Cecil Memo). On March 24, 2022, FDA approved PMTAs for Logic's e-cigarette devices and tobacco-flavored products and denied the applications for fruit- and fruit-combination-flavored products, but it did not announce a decision on Logic's menthol products.

In July 2022, after each of the OS disciplines had cleared Logic's menthol applications, Brian King was appointed Office of the Center Director (OCD) of the Center for Tobacco Products (CTP). King immediately changed the FDA's approach to menthol ENDS, communicating to the OS, through his Senior Science Advisor, that for the first time, "the approach to menthol-flavored ENDS should be the same as for" fruit, candy, and dessert flavored ENDS. J.A. 909 (Cecil Memo).

Chastened by the new directive, OS leadership acquiesced to King's policy decision "to treat menthol-flavored ENDS PMTAs in the same way as other non-tobacco-flavored ENDS PMTAs regarding the evidence needed to show a potential benefit to adult smokers." J.A. 909.

King explained the agency's new menthol policy in an internal memo dated October 25, 2022. Without citing any scientific studies or published articles, he asserted

that "scientific evidence on the role of flavors in youth use of ENDS is significantly more rigorous and robust than the preference data concerning menthol combustible cigarette smokers." J.A. 905 (King Memo). Therefore, "robust evidence of benefit is required to overcome the risk to youth and show that authorizing the marketing of a menthol-flavored ENDS would be appropriate for the protection of the public health." *Id.*

The majority insists that this decision was made, not "in a vacuum," but with "feedback from Office of Science staffers." Maj. Op. at 14. I read the Cecil and King memoranda very differently.

The decision to change the agency's menthol policy was made unilaterally by the new OCD after the OS divisions approved Logic's menthol applications and before consultation with OS. After the policy change was a *fait accompli*, OS leadership complied based on its "new awareness and understanding of the OCD position," as Cecil delicately wrote in his after-the-fact memo. J.A. 909. Still later, OS staff who had undertaken the menthol-flavored ENDS reviews—and whose scientific conclusions were overridden by the new policy—were given the opportunity to speak with the CTP Ombuds regarding the new approach. J.A. 905.

No one at the FDA informed Logic of the policy change. Nor did the agency give Logic an opportunity to amend the menthol-product PMTAs in response to the new policy. The agency simply relied on the new policy to deny Logic's applications on October 26, 2022—one day after King wrote his internal memo justifying the shift.

Appendix A

In the Marketing Denial Order (MDO), the FDA explained for the first time that under the new policy it required "a randomized controlled trial, longitudinal cohort study, or other evidence demonstrating the benefit of the new products to adult smokers relative to tobacco-flavored ENDS products." J.A. 2. Logic's PMTAs were deemed insufficient because—of course—they lacked the now-required evidence.

II

As the majority properly observes, "[w]e are particularly reluctant to second-guess agency choices involving scientific disputes that are in the agency's province of expertise." Maj. Op. at 22 (quoting *N.J. Env't Fed'n v. NRC*, 645 F.3d 220, 230 (3d Cir. 2011) (quotation marks omitted)). But the FDA's choice was a matter of policy, not science. *See* Lauren Silvis et al., *Operational Evaluation of Certain Components of FDA's Tobacco Program*, Reagan-Udall Found. 15 (2022), https://perma.cc/NP3A-3QNJ. [1] Indeed, OCD's policy change *overrode* the unanimous OS divisions' careful scientific analyses. *Id.* at 15 (observing that "a lack of clarity about the distinction between, and the intersection between, policy and science has created controversy within CTP and may lead to a perception that the Center's scientific integrity is being challenged *when, in fact, policy decisions that*

1. The Reagan-Udall Foundation is an independent organization created by Congress to support the FDA. Silvis et al., *supra*, at 5. In 2022, the Foundation performed an independent evaluation of the CTP and PMTA review process upon the request of FDA Commissioner Robert Califf. *Id.*

transcended the science are being made") (emphasis added).

Because the FDA's decision to treat menthol ENDS like other flavored ENDS rather than tobacco was a policy change, the FDA was required to "supply a reasoned analysis."[2] *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 57, 103 S. Ct. 2856, 77 L. Ed. 2d 443 (1983) (quoting *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852, 143 U.S. App. D.C. 383 (D.C. Cir. 1970)); *see also CBS Corp. v. FCC*, 663 F.3d 122, 138 (3d Cir. 2011) ("[An agency] cannot change a well-established course of action without supplying notice of and a reasoned explanation for its policy departure."). Although an agency "is not precluded from announcing new principles in an adjudicative proceeding," *NLRB v. Bell Aerospace Co.*, 416 U.S. 267, 294, 94 S. Ct. 1757, 40 L. Ed. 2d 134 (1974), it "acts arbitrarily if it departs from its established precedents without 'announcing a principled reason' for the departure," *Johnson v. Ashcroft*, 286 F.3d 696, 700 (3d Cir. 2002) (quoting *Fertilizer Inst. v. Browner*, 163 F.3d 774, 778 (3d Cir. 1998).

At a minimum, the agency must "display awareness that it *is* changing position." *FCC v. Fox TV Stations, Inc.*,

2. The majority emphasizes that the policy change was wholly internal. *See* Maj. Op. at 28 ("It is also notable that these debates took place within the FDA, out of Logic's sight."). But that's precisely the problem. As far as Logic knew, the FDA's previously communicated policy was that menthol ENDS offered benefits to menthol smokers and were less appealing to youth, so menthol, like tobacco, would be treated differently than other flavors.

556 U.S. 502, 515, 129 S. Ct. 1800, 173 L. Ed. 2d 738 (2009). It cannot "depart from a prior policy *sub silentio*[.]" *Id.* An agency "fail[ing] to acknowledge that it has changed its policy . . . is unable to comply with the requirement under *State Farm* that an agency supply a reasoned explanation for its departure from prior policy." *CBS Corp.*, 663 F.3d at 151-52.

When a "new policy rests upon factual findings that contradict those which underlay its prior policy; or when its prior policy has engendered serious reliance interests that must be taken into account," the agency must "provide a more detailed justification than what would suffice for a new policy created on a blank slate." *Fox TV Stations, Inc.*, 556 U.S. at 515. As part of that "more detailed justification" the agency "must consider the alternatives that are within the ambit of the existing policy" and the reliance interests at stake, their significance, and their weight against competing policy concerns. *DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913, 1915, 207 L. Ed. 2d 353 (2020) (quotation marks, citation, and brackets omitted); *see also Prohibition Juice Co. v. FDA*, 45 F.4th 8, 20 (D.C. Cir. 2022) ("Agencies must explain changes in position, particularly once a prior position has engendered regulated parties' reliance.").

To survive the arbitrary and capricious standard of review, the FDA must first have acknowledged that it changed its menthol policy and then provided a reasoned analysis for the change that addressed Logic's reliance interests and considered available alternatives. It did not do so. Instead, King overruled the OS divisions, changed

the agency's menthol policy "out of Logic's sight," and then the agency denied Logic's menthol PMTAs because they failed to meet an undisclosed evidentiary standard. That is not "good government." Maj. Op. at 29.

The majority asserts that these "internal" debates do not reflect a policy change because, "fundamentally," they do not constitute "final agency action" under the APA. Maj. Op. at 25 (quoting 5 U.S.C. § 704). That is, the majority argues that the debates reflected in documents like the King Memo do not "trigger a heightened burden for the FDA" under *Regents* because they were "nowhere close to a final decision." Maj. Op. at 26, 27. Thus, it concludes that these portions of the record "cannot fall within the APA's reach" and should not control our arbitrary-and-capricious review. Maj. Op. at 29.

I disagree with the majority's description of judicial review under the APA. It's true that our review is limited to a "final" agency action—the FDA's denial of Logic's PMTAs. We must determine whether that denial was "reasonable and reasonably explained." *Dep't of Com. v. New York*, 139 S. Ct. 2551, 2571, 204 L. Ed. 2d 978 (2019). But under the APA and the Tobacco Control Act, our review is not limited to the FDA's proffered explanations for the denial, located in the MDO and the Technical Project Lead Review (TPL Review). We are required to "review the whole [administrative] record" in determining whether the FDA's denial was reasonably explained. 5 U.S.C. § 706. The FDA submitted the administrative record, as defined for PMTA proceedings in 21 U.S.C. § 387l(a)(2)(C), on December 6, 2022. *See* Opening Br. at

28. And the Cecil and King Memoranda were included in this submission. *See* Oral Arg. Tr. at 12:8-10 (noting that the "Cecil and King memos . . . were part of the administrative record").

Because these documents are a part of "the whole record," we must review them in determining whether the FDA's denial was reasonably explained. And because they show that the FDA "change[d] course," we must determine whether the FDA's explanation satisfied the requirements outlined in *Regents*. 140 S. Ct. at 1913. Neither the APA nor the Tobacco Control Act requires that these documents reflect any final agency actions to serve this purpose.

The Supreme Court's decision in *Dep't of Com. v. New York* supports this understanding of judicial review under the APA. There, the Court found that the Secretary of Commerce's decision to include a citizenship question on the decennial census failed the "reasoned explanation requirement of administrative law" under § 706. 139 S. Ct. at 2575. In reaching this conclusion, the Court did not limit its review to the Secretary's proffered "explanation for agency action." *Id.* It broadly considered "what the record reveal[ed] about the agency's priorities and decisionmaking process." *Id.* This included several communications that were not "final" agency actions under § 704, including letters that the Secretary exchanged with the Department of Justice. *Id.* Accordingly, we may—indeed, we *should*—consider documents like the King Memo in determining whether the FDA's denial was reasonably explained. And because those documents reveal a policy change, the FDA's explanation must satisfy *Regents*' special requirements.

III

"Deciding whether agency action was adequately explained requires, first, knowing where to look for the agency's explanation." *Regents of the Univ. of Cal.*, 140 S. Ct. at 1907. For that we have the MDO and the TPL Review, which provides in-depth explanation of the FDA's reasons for denial. *See Liquid Labs LLC v. FDA*, 52 F.4th 533, 537-38 (3d Cir. 2022) (relying on the same).

The FDA did not provide a principled reason for the policy change in the MDO. The agency wrote, "There is substantial evidence that the use of menthol flavors in tobacco products, like the menthol flavors in the new products, has significant appeal to youth and is associated with youth initiation of such products." J.A. 2. But it did not explain why it adopted this position despite telling Logic in the deficiency notice that menthol products "may have lower youth appeal," J.A. 3016, or what had changed in the weeks following the Social Science discipline's March 18 conclusion that the "menthol flavored new products . . . have lower youth appeal," J.A. 3097.

The FDA also reported that it was "unable to determine whether or to what extent [Logic's] menthol-flavored new products facilitate complete switching or significant cigarette reduction as compared to tobacco-flavored ENDS products." J.A. 2-3. Again, the FDA did not explain why it abandoned its earlier position that menthol ENDS offered a "potential means by which some adult smokers might seek to transition completely away from combusted tobacco products to potentially less harmful tobacco products." J.A. 1125.

Nor did the FDA explain why it never requested a comparison between menthol and tobacco products in the deficiency letter despite specifically asking Logic to compare its fruit and fruit-combination flavored ENDS to tobacco-flavored ENDS.

So we must look for a principled reason for the policy change in the TPL Review. The FDA acknowledged that it was applying a novel approach to menthol ENDS. J.A. 3174 ("The clear evidence of substantial use of menthol-flavored ENDS products among youth also reflects evidence beyond what was available at the time that FDA issued [the 2019 enforcement] guidance."), 3179 ("This grouping of tobacco and menthol together . . . reflected the perspective, at that time, that the menthol ENDS products might not necessitate the same strength of product-specific evidence of benefit that other flavored ENDS require relative to tobacco flavored ENDS."). But it failed to provide sufficient reasons for the departure.

The project leader wrote in the TPL Review, "I disagree with the social science reviewer's conclusion" that menthol ENDS are less appealing to youth than other flavors. J.A. 3180. An unsubstantiated personal opinion is an insufficient reason for a departure from agency policy.

The FDA cited several studies purporting to show that the use of flavored ENDS, including menthol, was rising among student populations as cause to abandon its previous conclusion that menthol was less appealing to youth. These studies are unavailing for several reasons.

First, the studies predated the earlier policy position. *See* J.A. 3157 (studies from 2015 to 2020); 3171-72 (studies from 2004 to 2022). OS was still adhering to that policy as late as March 2022. *See* J.A. 3052-3156 (March 2022 OS Review of PMTAs, treating flavored ENDS differently than menthol and tobacco ENDS). So the July 2022 policy change was not based on fresh scientific data that OS hadn't already considered.

The National Youth Tobacco Surveys (NYTS), which the majority cites as evidence that "[f]lavored e-cigarettes were the driving force behind [the youth ENDS] epidemic," Maj. Op. at 7, show that ENDS use was relatively unchanged between 2014 and 2022. In 2014, NYTS published that "65.1% of high schoolers and 55.1% of middle schoolers who were using ENDS said they were using non-tobacco flavor (including menthol)." *Id.* In total, the NYTS estimated that 1,580,000 students used flavored ENDS in 2014. Corey et al., *Flavored Tobacco Use Among Middle and High School Students — United States, 2014*, Morbidity and Mortality Weekly Report (Oct. 2, 2015), https://perma.cc/99KK-MHUN. Because 63.3% of ENDS users reported flavored use, this means that roughly 2,496,000 students used ENDS of any kind in 2014. *See id.*

By 2022, the number of flavored ENDS users "had risen to 85.5% for high schoolers and 81.5% for middle schoolers" who were using ENDS of any kind. Maj. Op. at 7. But the data showed only that the number of flavored ENDS users increased, not the total number of ENDS users. NYTS estimated that 2,110,000 students

used flavored ENDS and that 2,550,000 students used ENDS of any kind in 2022. J.A. 1159. Compared with the 2,496,000 student ENDS users in 2014, there were only fifty thousand more in 2022.

These fifty thousand individuals may have been students who would not have used any tobacco products but for the availability of flavored ENDS. Or they may have been individuals who would have otherwise consumed a different tobacco product if not for the option of using ENDS—the NYTS estimated that, in 2014, 2,950,000 students used a tobacco product other than ENDS. Corey et al., *supra*. Because the 2022 NYTS only surveyed ENDS use, the majority doesn't know how the use of other tobacco products might have changed. *See* 21 U.S.C. § 387j(c)(4) (instructing the FDA to consider "the increased or decreased likelihood that existing users of tobacco products will stop using such products").

And because neither the NYTS nor any other survey independently assessed menthol ENDS use until 2022, the majority's confident assertion that the "gap [between menthol and flavored ENDS use] was shrinking" is baseless. Maj. Op. at 18. The 2014 NYTS grouped all flavors together and the 2019 NYTS grouped menthol and mint together. J.A. 3174; Corey et al., *supra*. Without any data comparing menthol use to other flavors, the majority cannot possibly know whether "the gap was shrinking." Maj. Op. at 18.

The majority seeks to bolster its assertion by reference to the TPL Review, dated October 26, 2022 (the same day

that FDA sent Logic the MDO). *Id.* In particular, the majority focuses on the TPL Review's treatment of 2022 NYTS data. But the majority's discussion is misleading because it indulges the *post hoc ergo propter hoc* fallacy. The 2022 NYTS results first appeared in the CDC's Morbidity and Mortality Weekly Report dated October 7, 2022. J.A. 1158. There is no evidence that King had or relied on them when he changed the policy three months earlier, but the majority inexplicably assumes that the October data informed the July decision.

In this and other instances, the majority omits too many inconvenient facts in its comforting narrative of apolitical, science-driven "good government," so I must demur. My skepticism is shared by a unanimous Fifth Circuit panel that considered a different manufacturer's challenge to FDA's rejection of its menthol-product PMTAs. *See R.J. Reynolds Vapor Co. v. FDA*, 65 F.4th 182, 189 (5th Cir. 2023).

Oddly, the majority says the *R.J. Reynolds* decision rejects "Logic's rendition of a political appointee parachuting in and dictating a new framework for the Office of Science to adopt." Maj. Op. at 24 (citing *R.J. Reynolds*, 65 F.4th at 192). But that is precisely what the Fifth Circuit *did* find. Like me, our sister circuit perceives that shortly after OS recommended that the menthol-flavored PMTAs be granted "a new CTP director appeared on the scene and told OS that 'the approach to menthol-flavored ENDS should be the same as for other flavored ENDS . . . .' OS then changed its position." *Id.* at 192. The *R.J. Reynolds* court characterized this as "strong

evidence that CTP developed and internally circulated new criteria for evaluating PMTAs for menthol-flavored ENDS in Summer 2022 . . . ." *Id.* The Fifth Circuit's analysis in *R.J. Reynolds* is clear-eyed and correct, but the majority barely engages it. [3]

Importantly, the majority fails to consider what the FDA did *not* say: The agency never discussed Logic's reliance interests or "the alternatives that are within the ambit of the existing policy." *See Regents of the Univ. of Cal.*, 140 S. Ct at 1913, 1915.

Neither the FDA nor the majority consider how Logic may have reasonably relied on the previous policy of

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3. The majority brusquely dismisses the Fifth Circuit's decision, asserting that "we already tread this ground in *Liquid Labs*, where we held that the FDA's evidentiary requirements did not constitute a 'surprise switcheroo.'" Maj. Op. at 30. That is plainly wrong. Unlike this case and *R.J. Reynolds*, our decision in *Liquid Labs* addressed only fruit-and-dessert flavored ENDS and not menthol-flavored or tobacco-flavored ENDS. *Liquid Labs*, 65 F.4th at 537. The manufacturer's "surprise switcheroo" argument in *Liquid Labs* was different from Logic's argument here. In *Liquid Labs*, the petitioner challenged the FDA's requirement that it perform randomized control trials or longitudinal cohort studies after the agency had said in an industry guidance document that such studies would not be necessary. *Id.* at 540. Here, Logic is challenging the FDA's decision to treat menthol products like fruit, dessert, and candy flavored ENDS despite previously treating menthol like tobacco given its lower youth appeal and benefit as a combustible cigarette alternative for adult smokers. The analogous Fifth Circuit decision to *Liquid Labs* is not *R.J. Reynolds* but *Wages & White Lion Invs., LLC v. FDA*, 41 F.4th 427 (5th Cir. 2022), *reh'g granted*, 58 F.4th 233 (5th Cir. 2023), which the majority does not cite.

grouping menthol and tobacco ENDS together. "Dealing with administrative agencies is all too often a complicated and expensive game, and players like [Logic] are entitled to know the rules." *R.J. Reynolds v. FDA*, 65 F.4th at 189 (citation and quotation marks omitted). "To keep things fair, agencies must give notice of conduct the agency 'prohibits or requires' and cannot 'surprise' a party by penalizing it for 'good-faith reliance' on the agency's prior positions." *Id.* (citing *Christopher v. Smithkline Beecham Corp.*, 567 U.S. 142, 156-57, 132 S. Ct. 2156, 183 L. Ed. 2d 153 (2012)).

The FDA dismissed Logic's randomized clinical trials as insufficient evidence that menthol encouraged switching from combustible cigarettes. But, as Logic explained, the goal of these studies was not to explore the benefits of menthol but "to assess biomarkers of tobacco exposure and effect during a 60-day controlled switch to [a Logic ENDS] compared with the continued use of combustible cigarettes or tobacco cessation." J.A. 1946, 2312. Logic had no reason to compare menthol products to tobacco products because FDA never said it required such information. The agency specifically instructed Logic to compare its fruit and fruit-combination flavored ENDS to tobacco ENDS in the deficiency notice, but "never told [Logic] that similar evidence would be required for its menthol . . . PMTA[s]." *R.J. Reynolds*, 65 F.4th at 190.

The FDA also failed to indicate that it considered alternatives to denying Logic's applications. *See Regents of the Univ. of Cal.*, 140 S. Ct at 1913. For one, the agency could have issued another deficiency notice asking Logic

for data comparing menthol products to tobacco products. In the TPL Review, the FDA explained,

> One approach to evaluate whether the menthol-flavored varieties are more effective than tobacco-flavored varieties at increasing complete switching or significant reductions in [cigarettes per day], would have been to conduct a study that randomized smokers of menthol cigarettes to receive either the menthol-or tobacco-flavored variety.

J.A. 3177. But this was the first time that FDA made that recommendation to Logic, and it only came by way of explaining why the PMTAs were denied. FDA could have issued a second deficiency notice asking for more information regarding the benefits of menthol in light of its new menthol policy.[4] *See, e.g., R.J. Reynolds*, 65 F.4th at 191 (noting that the FDA accepted thirteen amendments to R.J. Reynolds' non-menthol and non-tobacco PMTAs). That's not to say that the FDA had to issue a second deficiency notice, but it was at least required to take Logic's reliance interest into account.

4. The FDA is required to act on an application in 180 days. 21 U.S.C. § 387j(c)(1)(A). But that deadline had long since elapsed. Logic's PMTAs had been pending for three years. There would have been no harm in delaying a decision to permit Logic to perform a "long-term (i.e. six months or longer)" study on the benefits of menthol. J.A. 3175 n.15.

IV

The FDA "cannot change a well-established course of action without supplying notice of and a reasoned explanation for its policy departure." *CBS Corp.*, 663 F.3d at 138. That is exactly what happened here. Without such explanation, the agency's action was arbitrary and capricious, so I respectfully dissent.

APPENDIX B — FDA MARKETING DENIAL ORDER

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

October 26, 2022

DENIAL

Logic Technology Development LLC
Attention: Emil H. Weiss, Regulatory Affairs Manager
300 Frank West Burr Boulevard, Suite 70
Teaneck, NJ 07666

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

Dear Emil Weiss,

We completed substantive scientific review of your PMTAs[1] and are denying issuance of marketing granted orders for the tobacco products identified in Appendix A. Refer to Appendix B for a list of amendments received in support of your applications.

The statute places the burden on the applicant to make the required showing by providing that FDA

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

"shall deny an application" for a product to receive a PMTA marketing authorization if, "upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product," FDA finds that "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health" (APPH). Section 910(c)(2)(A). Based on our review of your PMTAs, we determined that the applications for the new tobacco products, as described in your applications and specified in Appendix A, lack sufficient evidence to demonstrate that permitting the marketing of the products subject to these applications is APPH. 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.

You may submit new applications or resubmissions for the products that are subject to this marketing denial order. Resubmissions to address the deficiency set out below would be appropriate and facilitate an efficient review. Note that resubmissions are subject to all the requirements set forth in § 1114.17 of the "Premarket Tobacco Product Applications and Recordkeeping Requirements" rule. If you choose to submit resubmissions for these products, you should clearly identify the PMTA type as resubmissions and you must fulfill all requirements set forth in section 910(b) of the FD&C Act and 21 CFR Part 1114. To do so, you may cross reference information submitted in:

- The new tobacco product applications, PM0000528. PD1, PM0000534.PD1 and PM0000539.PD1. subject to this Denial (see 21 CFR 1114.17)

- A Tobacco Product Master File submission (see 21 CFR 1114.7(b)(2) or 1114.17(c)(2); and guidelines at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/tobacco-product-master-files)

Whether new submissions or resubmissions, your PMTAs should include all information necessary to respond to the deficiency identified in this letter (see 21 CFR 1114.17(d)). Please note, however, that the deficiency identified in this letter is not necessarily the sole deficiency in your applications. We found that the deficiency identified below is dispositive of your applications because it precludes a finding that permitting the marketing of your new tobacco products is APPH. Accordingly, although FDA has reviewed your application from a toxicology perspective, FDA has not reached final conclusions about the overall toxicological profile of the new products.

We provide the following basis for our determination:

1. Your PMTAs lack sufficient evidence demonstrating that the new products have a potential to benefit adult smokers in terms of complete switching or significant cigarette use reduction, that would outweigh the risk to youth.

Appendix B

There is substantial evidence that the use of menthol flavors in tobacco products, like the menthol flavors in the new products, has significant appeal to youth and is associated with youth initiation of such products. The marketing restrictions and other mitigation measures that you proposed cannot mitigate these risks to youth sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH. In light of the known risks to youth of marketing flavored ENDS (including menthol flavor), 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, longitudinal cohort study, or other evidence demonstrating the benefit of the new products to adult smokers relative to tobacco flavored ENDS products. Such evidence should include an appropriate comparator tobacco flavored ENDS. Reliable and robust data are needed to evaluate the impact of the new products as compared to tobacco flavored products on adult smokers' complete switching or significant reduction in cigarette use over time because tobacco flavored products have not been shown to present the same risks to youth as tobacco products with other characterizing flavors. Whether other products give adult smokers comparable options for complete switching or significant cigarette reduction bears on the extent of the public health benefit that the new products arguably provide to that population. Finally, although this evidence is necessary to demonstrate that the subject ENDS provide benefits for adult smokers, it may not be sufficient to demonstrate that

the marketing of the subject ENDS is appropriate for the protection of the public health: having established the benefit to adults, applications containing this evidence would still be evaluated to determine that the totality of the evidence supports a marketing authorization.

Although your PMTAs include use behavior information from randomized clinical trial studies LP004 and LP005, those studies did not demonstrate that your menthol flavored new products are more likely to promote complete switching or significant cigarette reduction compared to tobacco flavored products. In addition, the published literature on the role of menthol flavored ENDS and smoking cessation or reduction is limited and does not demonstrate that menthol flavored ENDS are more effective in promoting complete switching or significant cigarette reduction relative to tobacco flavored ENDS.

Thus, based on your applicant sponsored studies and the peer reviewed studies in the literature, FDA is unable to determine whether or to what extent your menthol flavored new products facilitate complete switching or significant cigarette reduction as compared to tobacco flavored ENDS products. Given the known risks to youth of marketing flavored ENDS, FDA would have needed this information to demonstrate that your menthol flavored new products (PM0000528.PD1, PM0000534.PD1, and PM0000539.PD1) would provide a benefit to adult smokers sufficient to outweigh their risk to youth.

Because you have not met your burden of "showing" that permitting the marketing of the new products would be APPH as required by section 910(c)(2)(A), we must deny authorization for your application.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal[2,3] using eSubmitter.[4] Alternatively, submissions may be mailed to:

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

The CTP Portal and FDA's Electronic Submission Gateway (ESG) are generally available 24 hours a day, seven days a week; submissions are considered received by DCC on the day of successful upload. Submissions delivered to DCC by courier or physical mail will be considered timely if received during delivery hours on or before the due date[5];

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

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

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

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

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 Carlos Suarez, MPH, Regulatory Health Project Manager, at (301) 796-5453 or Carlos.Suarez@fda.hhs.gov.

Sincerely
Todd Cecil, Ph.D.
Acting Director
Office of Science
Center for Tobacco Products

Enclosures:

Appendix A – New Tobacco Products Subject of This Letter
Appendix B – Amendments Received for These Applications

Appendix B

Appendix A[6],[7]
New Tobacco Products Subject of This Letter

Common Attributes of PMTAs	
Submission date	August 19, 2019
Receipt date	August 19, 2019
Applicant	Logic Technology Development LLC
Product manufacturer	Logic Technology Development LLC
Product category	ENDS (VAPES)
Attributes	**New Tobacco Product**
STN	PM0000528.PD1[8]
Product name	Logic Vapeleaf Menthol Green Cartridge/Capsule Package
Product subcategory	ENDS Other
Package type	Blister Pack
Package quantity	5 Capsules
Characterizing flavor	Menthol
Nicotine source	Tobacco
Additional properties	Mass of flavored tobacco granules per capsule: 310 mg, Nicotine Content: < 48.4 mg-dry base/g

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

7. Effective April 14, 2022, FDA's authority to regulate tobacco products was extended to include tobacco products containing nicotine from any source. As such, nicotine source is considered a required property for unique identification. https://www.congress.gov/bill/117th-congress/house-bill/2471

8. PD numbers were not used in previously issued letters.

Appendix B

STN	**PM0000534.PD1**
Product name	Logic Pro Menthol e-Liquid Package
Product subcategory	Closed E-Liquid
Package type	Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Menthol
Nicotine concentration	20.0 mg/mL
E-liquid volume	1.5 mL
PG/VG ratio	70/25
Nicotine source	Tobacco
STN	**PM0000539.PD1**
Product name	Logic Power Menthol e-Liquid Package
Product subcategory	Closed E-Liquid
Package type	Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Menthol
Nicotine concentration	27.0 mg/mL
E-liquid volume	1.2 mL
PG/VG ratio	69/25
Nicotine source	Tobacco

Appendix B
Amendments Received for These Applications

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
September 25, 2019	September 25, 2019	All	Yes	Response to FDA's September 18, 2019, information request
October 22, 2019	October 22, 2019	All	Yes	Response to FDA's October 15, 2019, information request
November 1, 2019	November 1, 2019	All	Yes	Response to FDA's October 24, 2019, information request
November 18, 2019	November 18, 2019	All	Yes	Final Site Inspection Agenda
December 20, 2019	December 20, 2019	All	Yes	Final Site Inspection Logistics

Appendix B

February 27, 2020	February 27, 2020	PM0000534. PD1 and PM0000539. PD1	Yes	New product label information
July 9, 2020	July 9, 2020	All	Yes	Request for extension to June 26, 2020, Deficiency letter
December 17, 2020	December 17, 2020	All	Yes	Response to June 26, 2020, Deficiency letter

APPENDIX C — TECHNICAL PROJECT LEAD (TPL) REVIEW

FDA
U.S. FOOD & DRUG ADMINISTRATION
Technical Project Lead (TPL) Review of PMTA's

New Products Subject to this Review[1]

Submission tracking numbers (STNs)	PM0000528.PD1, PM0000534.PD1, PM0000539.PD1

Common Attributes

Submission date	August 19, 2019
Receipt date	August 19, 2019
Applicant	Logic Technology Development LLC
Product Manufacturer	Logic Technology Development LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	Closed E-Liquid, ENDS Component

Cross-Referenced Submissions

All STNs	MF0000068, MF0000320, MF0000243, MF0000338,

1. Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application(s).

Appendix C

Supporting FDA Memoranda Relied Upon in this Review

PM0000527-PM0000541	Medical Consultation Memorandum finalized on 6/28/2021 Tobacco Product Surveillance Team Consultation finalized on 5/24/2021 and 2/2/2022 OHCE Consultation finalized on 11/22/2021

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

Technical Project Lead (TPL):

Digitally signed by Megan J. Schroeder -S
Date: 2022.10.26 07:51:09 -04'00'

Megan J. Schroeder, Ph.D.
Supervisory Pharmacologist
Division of Individual Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Todd L. Cecil -S
Digitally signed by Todd L. Cecil -S
Date: 2022.10.26 08:19:40 -04'00'

Todd Cecil, Ph.D.
Acting Director
Office of Science

Appendix C

[Tables intentionally omitted]

Appendix C

1. EXECUTIVE SUMMARY

Based on the information provided in the application and other scientific data, as described in this Technical Project Lead review, I find that the applicant has not demonstrated that permitting the marketing of the three new products listed above ("new products"; Logic Vapeleaf Menthol Green Cartridge/Capsule Package, Logic Pro Menthol e-Liquid Package, Logic Power Menthol e-Liquid Package) is appropriate for the protection of the public health (APPH). Accordingly, I recommend that marketing denial orders (MDO) be issued for the new products.

1.1. APPH STANDARD

Section 910 of the FD&C Act requires that, for a product to receive a premarket tobacco product application (PMTA) marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute places the burden on the applicant to make the required showing by providing that FDA "shall deny an application" for a product to receive a PMTA marketing authorization if, "upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product," FDA finds that "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." Section 910(c)(2)(A).

The statute specifies that, in assessing whether permitting marketing of a new product would be APPH,

FDA must 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. Section 910(c)(4). The APPH standard requires a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. As the statutory text makes clear, it is the applicant's burden to make a "showing"—with sufficient supporting information—that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole. In determining whether permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching).

In making the APPH assessment for a non-combustible tobacco product such as an electronic nicotine delivery system (ENDS), FDA weighs, among other things, the negative public health impact stemming from youth initiation and use of the product against the potential positive public health impact stemming from adult cigarette smokers transitioning completely from combustible cigarettes (CC) to the ENDS product or

significantly reducing smoking. In order to show that marketing of an ENDS is APPH, an applicant must show that the benefits, including those to adult smokers, outweigh the risks, including those to youth, resulting in a net benefit to the public health. As the known risks of the product increase or decrease, the burden of demonstrating a substantial enough benefit may increase or decrease. For non-tobacco-flavored, non-menthol-flavored ENDS, FDA has previously concluded there is a known and substantial risk of youth initiation and use; accordingly, an applicant has a higher burden to establish that the likely benefits to adult CC smokers outweigh that risk. In particular, an applicant would need to provide robust evidence demonstrating that the product provides an added benefit relative to that of tobacco-flavored ENDS in facilitating adult smokers completely switching or significantly reducing their smoking. For tobacco-flavored ENDS the risk to youth is lower; accordingly, a lesser showing of benefit may suffice.

In making the APPH assessment for non-tobacco-flavored, non-menthol-flavored ENDS, FDA has determined that it is appropriate to compare such ENDS with tobacco-flavored ENDS. Tobacco-flavored ENDS may offer the same type of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Whether other products, such as tobacco-flavored ENDS, give adult smokers comparable options for complete switching or significant cigarette reduction bears on the extent of the public health benefit that the subject ENDS arguably provide to that

population. Therefore, in making the APPH determination for non-tobacco-flavored, non-menthol-flavored ENDS, FDA considers whether the applicant has provided acceptably strong evidence of an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers in completely switching from or significantly reducing their smoking.

Beginning in August 2021, FDA has issued marketing denial orders for PMTAs for numerous non-tobacco-flavored, non-menthol-flavored ENDS after implementing the approach described above with respect to the individual applications. At that time and in the year that followed, FDA excluded menthol products from application decisions to allow more time to consider whether there were any factors unique to menthol that would affect the APPH assessment. Among other things, FDA considered the significance of the fact that menthol-flavored CC currently remain on the market unlike other non-tobacco characterizing flavors that are prohibited in CC and whether menthol-flavored ENDS could be a direct substitute for them, providing a less harmful alternative for menthol-flavored CC smokers. FDA conducted a thorough examination of the peer-reviewed scientific literature and considered whether it established that menthol-flavored ENDS provide a sufficient benefit for adult smokers relative to that of tobacco-flavored ENDS.

As discussed further below in Section 3.4.2, the scientific literature suggests that smokers of menthol-flavored CC (referred to as menthol smokers) show a preference for menthol-flavored ENDS, relative to non-

menthol-flavored ENDS. Based on this literature, FDA explored whether that preference for menthol-flavored ENDS among menthol smokers would be sufficient to demonstrate a benefit to adult smokers that outweighs the increased youth risks relative to tobacco-flavored ENDS, such that FDA could authorize the marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS products. However, evidence of preference is not evidence of behavior change, and these studies showing preference for menthol-flavored ENDS were not designed to directly address the outcomes of complete switching or cigarette reduction. Actual product use is critical in the evaluation of product switching because the ability of a product to promote switching among smokers arises from a combination of its product features, including the sensory and subjective experience of use (e.g., taste, throat hit, nicotine delivery) and how the device itself looks and feels to the user. Complete switching to ENDS or significant reduction in smoking are the behavioral changes that provide potential benefit to users, and evidence based on assessing actual ENDS product use at more than one point in time is the most robust and reliable way to demonstrate that benefit. Robust demonstration of benefit is particularly critical because, as described in more detail in Section 3.4.2, menthol-flavored ENDS, pose substantial risk of youth appeal and use similar to that posed by candy/dessert/sweets and mint flavors. Ultimately, FDA has concluded that the existing scientific literature does not demonstrate a benefit to adult smokers that outweighs the increased youth risks relative to tobacco-flavored ENDS, such that FDA could authorize marketing of menthol-

flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS. Thus, the approach to the APPH analysis for menthol-flavored ENDS is the same as for other non-tobacco-flavored ENDS[2] where an applicant has failed to demonstrate that the risk to youth is sufficiently mitigated through marketing restrictions and other mitigation measures (see below). That is, to overcome the risk to youth, an applicant must provide evidence demonstrating that its menthol-flavored ENDS products provide an added benefit for adult smokers relative to tobacco-flavored ENDS.

Before determining that permitting the marketing of a new tobacco product would be APPH, FDA also considers the potential impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and tobacco use. Marketing restrictions include advertising and promotion restrictions intended to limit youth exposure to and appeal of tobacco product marketing (e.g., measures such as limiting advertising to platforms that are predominantly used by adults and using advertising content and methods that are not known to resonate with youth, or even eliminating advertising in certain media channels altogether) and sales access restrictions intended to restrict youth access to tobacco products (e.g., measures such as selling products only in face-to-face interactions, in adult-only facilities, or via

2. Hereinafter, unless otherwise noted, the term "flavored ENDS" in this review refers to an ENDS product with a characterizing flavor other than tobacco, including menthol. For the purposes of this review, it is synonymous with "non-tobacco-flavored ENDS."

websites that require robust age- and identity-verification). In recent years, there have been efforts to develop novel and potentially more effective types of risk mitigation measures aimed at reducing youth initiation risks, such as device access restrictions (e.g., technologies that require adult user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product). FDA evaluates these measures in the context of the overall public health evaluation of the product, weighing the known risks to youth against the benefit to adults. In the case of flavored ENDS, the risk of youth initiation and use is well documented and substantial. Thus far, FDA's experience shows that advertising and promotion restrictions and sales access restrictions cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH.[3] Rather, for flavored ENDS, including menthol flavor, only the most stringent mitigation measures have such mitigation potential; to date, the only such measures identified with the potential for that kind of impact have been device access restrictions. In contrast, the risk of youth initiation and use with tobacco-flavored ENDS is lower. Restrictions on advertising and promotion and sales access for tobacco-flavored ENDS could mitigate that more limited risk and impact the overall net benefit

3. *See* FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry* 44 (Apr. 2020) ("The reality is that youth have continued access to ENDS products in the face of legal prohibitions and even after voluntary actions by some manufacturers."); *see also id.* at 45 (noting "data that many youth obtain their ENDS products from friends or sources in their social networks").

assessment. In addition, restrictions on advertising and promotion and sales access are important to include in marketing granted orders (MGOs) because they can help ensure that the marketing of a new tobacco product remains APPH after authorization. FDA has included such restrictions in MGOs issued to date.

Finally, before determining that permitting the marketing of a tobacco product would be APPH, FDA also takes into account whether the applicant has provided sufficient information regarding product design, chemistry, stability, manufacturing controls including process controls and quality assurance procedures, toxicology, abuse liability, and other factors that can impact the product's risks and benefits to individual users, including relative to those of other tobacco products on the market.

1.2. SUBJECT APPLICATIONS

FDA's evaluation of these PMTAs determined that the applicant failed to demonstrate that the new products have a potential benefit to adult smokers who switch completely or significantly reduce their CC use that would outweigh the products' risk to youth. For flavored ENDS, including menthol flavor, existing evidence demonstrates that the known and substantial risk to youth in particular is high. As discussed below, flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth. There is also a known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use.

The PMTAs provide insufficient evidence to diminish or dispel those risks in connection with the new products. The applicant did not propose any novel or materially different marketing restrictions or other mitigation measures from those that FDA has previously considered and found insufficient to mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to show APPH. Thus, the new products could be appropriate for the protection of the public health only if the PMTAs present reliable and robust evidence of a potential benefit to adult smokers switching from or reducing cigarettes that could outweigh that risk to youth. To effectively demonstrate this benefit in terms of product use behavior, the PMTAs would likely need to provide product-specific evidence from a randomized controlled trial (RCT)[4] or longitudinal cohort study,[5] although FDA evaluates other types of evidence

4. A randomized controlled trial is a clinical investigation or a clinical study in which human subjects 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.

5. 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 non-tobacco-flavored ENDS compared with users of tobacco-flavored ENDS).

on a case-by-case basis to determine if it is sufficiently reliable and robust to make the necessary showing. Moreover, tobacco flavored ENDS may offer the same type of public health benefit claimed by flavored ENDS, i.e., increased complete switching and/or significant reduction in smoking, without posing the same degree of risk of youth uptake. Therefore, to evaluate the potential benefit to current users, FDA reviewed the PMTAs for any acceptably strong evidence that the flavored new products have an added benefit relative to that of tobacco-flavored ENDS in facilitating adult smokers completely switching away from or significantly reducing their smoking.

Although the PMTAs contained evidence from two RCTs that evaluated the impact of the new products on switching and cigarette consumption, the results of these studies did not demonstrate that the menthol-flavored new products were more likely to promote switching or cigarette reduction compared to tobacco-flavored products. The other evidence provided in the PMTAs regarding the potential benefit to adult users likewise is not adequate to make the required showing (see Section 3.4. for details).

Based on the information provided in the PMTAs and the available evidence, the PMTAs lack sufficient evidence to show that the new products have the potential to benefit adult smokers who switch completely or significantly reduce their CC use that would outweigh the risk to youth.

Appendix C

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the three new products listed on the cover page and with more detail in the Appendix, sold under the brand names Logic Vapeleaf, Logic Pro, and Logic Power. Two of the new products are ENDS with disposable, closed pre-filled e-liquid cartridges/capsules. One new product is a tobacco capsule. The applicant described the "Menthol Green" flavor as menthol flavor[6] and discussed the commercial decision to develop the flavor to "reflect an apparent preference, among conventional cigarette smokers, for menthol flavor." Additionally, the applicant described sensory assessments which included testing for the menthol taste among adult CC smokers in Japan.[7] After evaluating the information submitted by the applicant, we determined

6. The applicant states that "The menthol-green (menthol) flavor blend used in the Logic Vapeleaf™ tobacco vapor system was developed by Japan Tobacco Inc (JT) in 2014-2015 for the Japanese market, which was the first market for this new product introduction (known as Ploom TECH™ in Japan)." (p.1; section 2.; document "h-1-4-5-3-flavor-e-liquid-develop-report-gre-lf").

7. Three flavor blend candidates for the menthol flavor blend were evaluated by a sample of 80 respondents in Japan. While there was no testing conducted in the U.S., the applicant states that "…however, the validity of menthol taste is confirmed by the continued prevalence of menthol in the conventional cigarette category. The final menthol blend was chosen based on achieving a significantly higher score than other flavor blend candidates within the sample." (p.4; section 3.4.; document "h-1-4-5-3-flavor-e-liquid-develop-report-gre-lf").

the "Menthol Green" products are menthol flavored. As such, we find the following products to include menthol as a characterizing flavor: the Logic Vapeleaf Menthol Green Cartridge/Capsule Package (PM0000528.PD1), the Logic Pro Menthol e-Liquid Package (PM0000534.PD1), and the Logic Power Menthol e-Liquid Package (PM0000539.PD1).

2.2. REGULATORY ACTIVITY

On August 19, 2019, FDA received three PMTAs (PM0000528.PD1, PM0000534.PD1, PM0000539.PD1) from Logic Technology Development LLC (Logic) within three product sub-brands: Logic Vapeleaf, Logic Pro and Logic Power products. On September 18, 2019, FDA issued an Acceptance letter. On October 7, 2019, FDA issued a Samples Request letter. On October 18, 2019, FDA issued a Filing letter. On October 24, 2019, FDA issued an Inspection Request letter and conducted three site inspections at manufacturing facilities between January 6, 2020 and January 16, 2020. On June 26, 2020, FDA issued a Deficiency letter. On August 13, 2020, FDA issued a correction letter rescinding Deficiency 8, described in the Deficiency letter dated June 26, 2020.

Refer to the Appendix, Table 4 for a complete list of amendments received by FDA.

2.3. SCOPE OF REVIEW

This review captures all compliance and scientific reviews for the new products subject to this review.

Appendix C

The applicant-submitted amendment (PM0004435) in response to the Deficiency letter was reviewed by engineering, chemistry, toxicology, social science, epidemiology, and environmental science disciplines. Medical and Behavioral and Clinical Pharmacology (BCP) disciplines did not identify deficiencies in the 1st review cycle and, therefore, did not review PM0004435. The microbiology discipline did not identify deficiencies in the 1st review cycle but reviewed new stability data received in PM0004435 during the 2nd review cycle.

Two cross-referenced TPMFs (MF0000068 and MF0000338) were reviewed by the chemistry and toxicology disciplines to support these new products. Because the chemistry discipline identified deficiencies in the 1st review cycle for MF0000338, the amendments submitted by the TPMF owners were reviewed by the chemistry discipline in the 2nd review cycle.

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	**Review Date**	**Reviewer(s)**	**Review Date**
Engineering	Rashele Moore and Morgan Lee	6/24/2020	Mohammad Ali	3/21/2022
Chemistry	Margaret Schmierer	6/24/2020	Margaret Schmierer	3/17/2022
Microbiology	Almaris Alonso Claudio	6/24/2020	Prashanthi Mulinti	3/17/2022
Toxicology	Guy Lagaud	6/24/2020	Kimberly Stratford	3/22/2022
Behavioral and Clinical Pharmacology	Carolina Ramoa	6/24/2020	Colin Cunningham	3/17/2022
Medical	Omoye Imoisili	6/24/2020	Dara Lee	3/17/2022
Epidemiology	Michael Sawdey	6/23/2020	Ibrahim Zaganjor	3/17/2022

Social science	Izabella Zandberg	6/24/2020	Stephanie Pitts	3/18/2022
Environmental Science	Shannon Hanna	6/23/2020	Bria Martin	3/18/2022
OCE – BIMO[8]	Julian Moore	6/23/2020	N/A	N/A
OCE – manufacturing/lab[3]	Abraham Agyapong	6/24/2020	N/A	N/A

8. Second cycle review was not necessary as there was no additional data that required review by this discipline.

Table 2. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer(s)	**Review Date**	**Reviewer(s)**	**Review Date**
Statistics	N/A	N/A	N/A	N/A
OCE – DPAL	Melissa View	1/16/2020	N/A	N/A
OHCE	None	N/A	Emily Talbert	11/22/2021
Tobacco Product Surveillance Team	Susan Rudy	N/A	Susan Rudy	5/24/2021 and 2/2/2022

Appendix C

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

Per the chemistry review:

- Several products were included as possible comparison products: Pall Mall Red Kings (combusted cigarette [CC]), VUSE Vibe ("tank style" ENDS) Original flavor, blu PLUS (ENDS used with disposable cartridge) Classic Tobacco flavor.

- Justification for ENDS comparison products was that they were similar style ENDS to the new products. The applicant did not specify which comparison product was meant to be similar to which new product, so all new product data was compared to all comparison product data submitted. Further descriptive information about the comparison products (e.g., ingredient listings, device power, nicotine source) was not provided. However, the information provided was adequate for review from a chemistry perspective because the product characteristics of the submitted ENDS comparison products are similar to the product characteristics of the assembled new products

(e.g., VUSE Vibe is from the same product category as the assembled Logic Pro product; blu PLUS is from the same product category as the assembled Logic Power product) and thus, the assembled Logic Pro and Logic Power products are expected to have comparable aerosol emissions with the submitted ENDS comparison products. Based on product design characteristics (presence of tobacco capsule), the aerosol emissions from the assembled Logic Vapeleaf product are more appropriate to be compared with the submitted CC comparison product.

Per the toxicology review:

- The applicant provided comparisons between the new products and CC (Pall Mall Red Kings) as well as reference cigarette 3R4F for in vitro mutagenicity, cytotoxicity and genotoxicity studies. The applicant conducted a separate in vivo 90-day inhalation study for the comparison products and provided in vitro mutagenicity, cytotoxicity and genotoxicity studies. All new products were compared to other ENDS (VUSE Vibe Original and blu PLUS Classic Tobacco). The applicant's rationale for this comparison is based on the premise that adverse health outcomes are reduced when CC smokers switch completely to new products. Therefore, from a toxicological perspective, the applicant's rationale for using CC as a comparator is appropriate.

Appendix C

Per the BCP review:

- The applicant compared all of the new products to usual brand (UB) CC in applicant-submitted clinical studies that provided data on abuse liability, use behaviors, and BOE (LP001-LP005). From a BCP perspective, CC are an appropriate comparison product, as the applicant's stated intended user population for the new products is current smokers interested in switching to ENDS.

- The applicant also provided comparisons of some of the new products with other ENDS (PM0000528.PD1 compared to blu PLUS Classic Tobacco, 2.4% nicotine, LP001; PM0000539.PD1 compared to VUSE Vibe Original with an unknown nicotine content, LP003), nicotine gum (PM0000534.PD1 compared to Nicorette White Ice Mint, 2 mg nicotine, LP001 and LP002), or nicotine inhaler (PM0000539.PD1 compared to NICOTROL, 4 mg nicotine delivered per 10 mg nicotine cartridge, LP004) in the clinical studies to provide context for how abuse liability, use behaviors, and BOE associated with use of the new products might compare to other nicotine-containing products. Furthermore, ad libitum use of all new products was compared to continued use of UB CC; Logic Vapeleaf Menthol Green (PM0000528.PD1) and Logic Power Menthol (PM0000539.PD1) product use was also compared to tobacco cessation (no tobacco product use). Thus, while CC are the most appropriate comparison products from the

BCP perspective, these representative ENDS and nicotine replacement therapy (NRT) products provide context for where the new products may fit within tobacco products' abuse liability continuum.

Per the medical review:

- The applicant compared UB CC to the new products in all clinical studies that provided data on adverse experiences (AEs), health effects, and biomarkers of potential harm (BOPH). In nicotine pharmacokinetic/pharmacodynamic single center randomized cross-over studies (LP001-LP003), there were also additional comparisons of:
    - o Logic Vapeleaf Menthol Green product (PM0000528.PD1) to nicotine gum
    - o Logic Pro Menthol product (PM0000534.PD1) to a closed ENDS and nicotine inhaler
    - o Logic Power Menthol product (PM0000539. PD1) to a closed ENDS and nicotine gum
- The selection of these comparison and representative products is appropriate.
- The applicant provided a literature review of studies that typically used either CC or closed ENDS for evaluating effects on BOPH and health effects.

Appendix C

Per the epidemiology review:

- The new products are closed ENDS. Since adult CC smokers are a likely user population, comparisons between the new products and CC are appropriate.

Per the social science review:

- The information provided by the applicant suggests that adult CC users are likely users of the new products. Therefore, from the social science perspective, comparisons between the new products and CC are appropriate.

3.1.2. Synthesis

The aerosol data from all new products were primarily compared to data provided for CC comparison products, the Pall Mall Red Kings. These data were also compared to two representative ENDS: VUSE Vibe Original and blu PLUS Classic Tobacco. In the applicant-submitted clinical studies (LP001-LP005), the new products were compared to UB CC. Some new products were compared to the representative ENDS as well as nicotine replacement therapy (NRT) products.

CC are the primary comparison products, in part because the applicant stated that the new products are intended for CC smokers.[9] Evidence from the applicant-

9. Note that although the applicant stated that the new products are intended for CC smokers, FDA's evaluation assesses

submitted clinical and Consumer Perception Studies, as well as the peer-reviewed ENDS literature, suggest that CC smokers will likely use the new products with the intention of decreasing CPD and dual using, but not complete smoking cessation (see Section 3.4.1.2.). Therefore, the totality of evidence suggests that CC are appropriate comparison products. The applicant submitted harmful and potentially harmful constituent (HPHC) comparison data to one CC with significant U.S. market share, Pall Mall Red Kings. As TPL, I find this approach to be reasonable and appropriate, and agree with the relevant scientific discipline reviews on this issue.

Representative products, including the in-class ENDS and NRT, are helpful to define where the new products fit within the continuum of risk among nicotine-containing products. The comparison of actual use behaviors associated with Logic Vapeleaf Menthol Green (PM0000528.PD1) and Logic Power Menthol (PM0000539.PD1) products to tobacco cessation (NRT was available upon request) is helpful to determine the risks associated with use of the new products compared to tobacco cessation.

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the potential for product use across a range of different types of tobacco product users and non-users based on all available evidence.

Appendix C

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.2.1.1 Product design and composition

Per the engineering review:

- For all new products, the applicant provided an adequate product description and sufficient information for all necessary design parameters.

- The applicant provided appropriate information regarding the tobacco filler and filter plug for PM0000528.PD1.

- The applicant submitted results from child-resistance packaging test for Logic Pro and Power e-liquids (PM0000534.PD1, PM0000539.PD1) to demonstrate that these e-liquids have appropriate child-resistant packaging.

- Assessment of the Tobacco Product Surveillance Team (TPST) Adverse Event reports did not raise any issues for Engineering associated with the new products. As such, the TPST Adverse Event report does not modify any conclusions in the engineering review.

Appendix C

Per the chemistry review:

- Logic Vapeleaf Menthol Green (PM0000528.PD1) product:
    - PM0000528.PD1 is a tobacco capsule through which heated e-liquid flows, where it extracts compounds (including menthol flavor) and then produces an aerosol.
    - PM0000528.PD1 contains 310 mg total tobacco, flavorings, and casings. The tobacco blend is a mixture of Burley and Oriental tobaccos and was fully identified. Menthol Green flavorings, two partial casings, capsule, and capsule end piece ingredients were provided in a TPMF. This information was found sufficient to characterize the new product from the chemistry perspective.
- Logic Pro Menthol (PM0000534.PD1) product:
    - PM0000534.PD1 is a menthol flavored e-liquid capsule, which contains a mixture of PG, VG, nicotine, and flavorings. PG, VG, and nicotine are sufficiently identified in the PMTA and flavoring ingredients were submitted in a TPMF. The PMTA and the TPMF information were sufficient to characterize the new product from a chemistry perspective.

- During inspection of the Shenzhen Smoore manufacturing site, the applicant provided documentation indicating they received reports about leakage of the Logic Pro e-liquid cartridge (PM0000534.PD1) and completed a corrective and preventative action (CAPA) report to investigate and fix the leakage issue.

- Logic Power Menthol (PM0000539.PD1) product:

  - PM0000539.PD1 is a menthol flavored e-liquid cartridge, which contains a mixture of PG, VG, nicotine, and flavorings. PG, VG, and nicotine are sufficiently identified in the PMTA and flavoring ingredients were submitted in a TPMF. The TPMF information was sufficient to characterize the new products from a chemistry perspective.

Per the microbiology review:

- PM0000534.PD1 and PM0000539.PD1 contain humectants (PG, VG, and/or water), which may impact microbial activity during the applicant-determined product shelf life. The applicant adequately addressed this concern by providing microbial counts data which showed total aerobic microbial count (TAMC) and total yeast and mold count (TYMC) values below the method limit of detection (<100 colony forming units [cfu]/mL) for all new products over the complete shelf life.

- PM0000528.PD1 includes a tobacco capsule component which includes air-cured burley and sun-cured oriental tobaccos that are not fermented. Fermentation can impact microbial activity and potentially promote tobacco-specific nitrosamine (TSNA) formation, thereby negatively affecting stability of the finished product during shelf life. Therefore, use of non-fermented tobacco improves stability from a microbiology perspective.

3.2.1.2 Manufacturing

Per the engineering review:

- For all new products, the applicant provides summaries of the manufacturing steps, including the source of all assemblies, facilities used, external vendor oversight strategies, and all associated quality control measures that are in place. The applicant provides evidence demonstrating that the new products are manufactured in a consistent manner to minimize variability in product quality. The available inspection documents also support product consistency.

- A product risk assessment was submitted for all products and their consumables using a failure mode and effects analysis (FMEA). The applicant stated that all the new products were designed to prevent consumers from adjusting or altering performance parameters without significant effort. PM0000534.PD1 and PM0000539.PD1 are

closed e-liquid cartridges to reduce the likelihood of product tampering and were designed to have unique connections between them and their associated battery units (not subject to this PMTA review) to mitigate misuse and promote intended product usage. Further, several features (e.g., puff duration limits, product shut-off to avoid potential overcurrent discharge) are incorporated into Logic devices' (not subject of this PMTA review) design to mitigate misuse and promote intended product usage. The applicant submitted adequate risk analysis information for all new products. Furthermore, the applicant provided adequate instructions about how the new products should be used and warnings against misuse in the leaflets.

- The shelf-life/stability information provided for e-liquid relative density, aerosol generation, visual inspection, and capsule/cartridge resistance is sufficient and appropriate to characterize the new products.

- The aerosol particle size delivered by all new products remains consistent over time.

Per the chemistry review:

- The applicant provided complete and detailed descriptions of manufacturing processes and standard operating procedures for the new products and components.

- Each incoming raw material and manufactured new product is controlled through the Japan Tobacco Inc. Quality Management System, raw material testing, in-process testing, and finished product testing.

- Quality and manufacturing of all new products and components is well controlled at all stages, and the applicant provided sufficient information to show all new products are consistently manufactured.

- Three manufacturing site inspections were performed: JT Tokai, Shenzhen First Union, and Shenzhen Smoore. Final Logic EIRs were completed with exhibits collected during each inspection. Findings from each manufacturing site inspection did not raise new issues, and therefore are adequate to suggest complete and appropriate manufacturing practices from a chemistry perspective.

Per the microbiology review:

- The applicant provided adequate descriptions of the manufacturing processes and standard operating procedures for all new products.

- Manufacturing was assessed via inspection in January 2020. The manufacturing of all new products is well controlled at all stages and the manufacturing controls demonstrate adequate environmental controls and storage conditions

to ensure product quality. The findings of the inspection did not raise new issues, and therefore are adequate to suggest appropriate manufacturing practices from a microbiology perspective.

3.2.1.3 Product stability

Per the chemistry review:

- Complete method information was submitted for all stability studies. One stability method (photostability for PM0000534.PD1) was provided in a TPMF.

- The applicant provided complete shelf life data sets for all finished new products and the intermediate bulk e-liquids for PM0000534.PD1 and PM0000539.PD1 under long-term (25°C, 60% relative humidity; 24 months for bulk e-liquids, 18 months for finished products) and accelerated conditions (40°C, 75% relative humidity, 6 months for all bulk and finished products).

- The applicant also submitted leachable and extractable data for all structural components, e-liquid, tobacco, and aerosol HPHC stability data under long-term and accelerated conditions, particle size stability data, and microbial stability data. Leachable and extractable data were adequate to suggest the container closure systems for the new products are stable for the intended shelf life of each product

- HPHC stability data and shelf life stability studies submitted were sufficient from a chemistry perspective to support proposed finished product shelf lives.

- The studies showed that the new products are stable for up to 12 (for all bulk e-liquids and PM0000528.PD1) or 15 (PM0000534.PD1 and PM0000539.PD1) months.

Per the microbiology review:

- The microbial stability data are necessary for the proposed shelf life of the new products as bacterial communities change as a function of storage time (Chopyk et al., 2017; Djordjevic, Fan, Bush, Brunnemann, & Hoffann, 1993). Increased microbial growth over time can impact stability of the product and may result in an increased risk to public health as the new products sit in storage.

- The applicant provided stability data over shelf life of all new products. pH and moisture data were provided over the complete shelf life of PM0000528.PD1, PM0000534.PD1, and PM0000539.PD1. pH values of the new products were within the pH values observed in published literature for marketed e-liquids. Moisture content of the new products increased (62-116%) during storage, which could potentially affect microbial growth and TSNA levels in the finished products. The applicant adequately addressed this concern

by providing complete microbial (TAMC, TYMC) and TSNA (N-Nitrosonornicotine [NNN] and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) stability data for all new products.

- PM0000534.PD1 and PM0000539.PD1 showed TAMC and TYMC values below method limit of detection (<100 colony forming units [cfu]/mL) at all time points tested over shelf life, which are acceptable from a microbiology perspective. Additionally, the NNN and NNK levels for all these products were below detection limits (≤ 0.985 ng/g and ≤ 1.51 ng/g, respectively) over shelf life.

- PM0000528.PD1 showed high microbial counts (TAMC:590,000-1,200,000 cfu/mL and TYMC: 3,500-9,500 cfu/mL) over shelf life, which was a potential microbiological concern. However, these higher counts are not of concern due to the submitted TSNA data.

- The quantities of NNN (514-656 ng/g) and NNK (186-218 ng/g) in PM0000528.PD1 are lower than the quantities found in tobacco filler of marketed CC products available in the U.S. (median [range] for NNN and NNK in tobacco filler is 1945 ng/g [306–2970 ng/g] and 494 ng/g [194–1093 ng/g], respectively).

- From a microbiology perspective, the applicant provided adequate stability data to demonstrate a

shelf life of 12 months for PM0000528.PD1 and 15 months for PM0000534.PD1 and PM0000539.PD1.

3.2.1.4 Product test data

Per the engineering review:

- The applicant provides test data needed to fully characterize and evaluate the new products. The applicant provides test data for coil diameter, e-liquid viscosity, e-liquid boiling point, amount of wicking material, wicking rate, total coil length (uncoiled), coil surface area, coil temperature, coil temperature cut-off, current cut-off, and inhaled aerosol temperature for all new products. The product performance testing results adequately demonstrate all new product consistency.

- Adequate manufacturing processes and controls were used to ensure that all new products meet manufacturer's specifications, and they will operate consistently throughout the life of the assembled product.

Per the chemistry review:

- The applicant provided e-liquid, tobacco (PM0000528.PD1[10]), and aerosol HPHC data

10. For all instances where a complete ENDS is required, all components and parts are implied with the inclusion of the Logic sub-brand e-liquids' STN.

for the new products. Aerosol HPHC data were generated under CORESTA recommended method (CRM) 81 for all new products and a product-specific developed intense puff regimen for Logic Pro Menthol (PM0000534.PD1) and Logic Power Menthol (PM0000539.PD1) products. Additional aerosol data was not provided for the Logic Vapeleaf Menthol Green (PM0000528.PD1) product under this product-specific developed intense puff regimen because the data generated under CRM81 already represented data generated under an intense regimen. The maximum puff duration for the Logic Vapeleaf products is 2.4 seconds, which is lower than the puff duration of CRM81 (3 seconds), so all data generated under the CRM81 is generated under more extreme conditions than the product would typically be used under.

- New product aerosol data generated under two puff regimens (CRM 81 and a product-specific developed intense puff regimen) was compared to the Pall Mall Red Kings CC smoke yields. Generally, all aerosol yields for the new products were lower than the CC smoke yields. Most new product aerosol HPHC yields were lower than, or analytically equivalent to, the representative ENDS aerosol yields.

- Under the product-specific intense puff regimens, some formaldehyde yields were slightly higher than the corresponding CC smoke yield; however,

this may have been the result of overestimating intense new product use and underestimating intense CC use. Additionally, the intense puff regimen conditions were based on the upper 2.5% of results of clinical data from LP004 and LP005 for different puff parameters and represent conditions likely to be used only by the most intense users of all characterizing flavors of Logic Pro and Power products (PM0000532.PD1-PM0000535.PD1 and PM0000538.PD1-PM0000540.PD1, some not subject to this PMTA review). The data submitted is sufficient to characterize the new products from a chemistry perspective.

- Complete descriptions of analytical methods were provided in a TPMF and found sufficient to support the analytical testing from a chemistry perspective. In addition, the applicant provided complete information regarding the testing laboratory (Enthalpy) and accreditation, sample storage, manufacture and test dates, and details of puff generation for each puff protocol. All of this information was found sufficient to support the analytical testing from a chemistry perspective.

- FDA verification testing was completed for NNN and NNK quantities in PM0000528.PD1. FDA testing verified the accuracy of the test results provided by the applicant.

Appendix C

3.2.2. Synthesis

As TPL, I agree with the engineering, chemistry, and microbiology conclusions that these PMTAs contain sufficient information to characterize the ingredients and product design; the applicant submitted adequate processes and controls to ensure that the new products meet the manufacturer's specifications for consistent manufacturing. Furthermore, the NNN and NNK content within the tobacco capsule in PM0000528.PD1 were lower than median levels for quantities found in tobacco filler of marketed CC in the U.S. and the levels within the new products' aerosol were below the detection limit.

The applicant-submitted data are sufficient to demonstrate satisfactory microbial and chemical stability and engineering functionality/safety over the new products' (evaluated for bulk-e-liquids, aerosol, and finished products) shelf-lives:

- PM0000528.PD1: 12 months
- PM0000534.PD1, PM0000539.PD1: 15 months

The applicant conducted HPHC analyses in all new products' aerosols under two puff regimens for comparison with the comparison CC: CRM 81 and an intense puffing regimen that reflected the upper 2.5% of topography variables collected in LP004 and LP005 (for PM0000534.PD1, PM0000539.PD1). As TPL, I agree with the chemistry review conclusions: most HPHCs and other constituents were lower in aerosol yields from the new

products compared to CC smoke yields. Importantly, the chemistry review noted that the constituent yields that slightly surpassed that of the CC (e.g., formaldehyde) are likely due to over-estimations of intense ENDS use. The toxicology review also evaluated these HPHC data from the toxicology perspective (see Section 3.5.1.1.). These HPHC yield data are supported by the lower BOE (compared to continued CC smoking) evident for all new products in the LP004 and LP005 clinical studies (see Section 3.5.1.3.) – indeed, exposure to non-nicotine HPHCs did not increase upon actual use of the new products (see Section 3.5.1.3.).

Data from an applicant-submitted child-resistant-packaging study demonstrate adequate evidence to suggest Logic Pro and Power e-liquids (PM0000534.PD1 and PM0000539.PD1) have appropriate child-resistant packaging. PM0000528.PD1 has appropriate tamper-evident packaging.

To better ensure proper usage and safety, the new products were designed to prevent consumers from adjusting or altering performance parameters. PM0000534.PD1 andPM0000539.PD1 are closed e-liquid cartridges to prevent product tampering and were designed to have unique connections between them and their associated battery units (not subject to this PMTA review) to mitigate misuse and promote intended product usage. Product leakage was evident under a long-term and accelerated study in PM0000534.PD1 and the applicant has received some complaints about leakage from this new product. The Logic Pro product leaflets contain a warning

about possible leakage. I believe these steps appropriately respond to the low level of risk associated with leakage.

3.3. ABUSE LIABILITY

The BCP review considered the five applicant-sponsored clinical studies in adult smokers. Three studies investigated the abuse liability of Logic Power Menthol (PM0000539.PD1; LP001), Logic Vapeleaf Menthol Green (PM0000528; LP002), and Logic Pro Menthol (PM0000534.PD1; LP003) products under controlled laboratory conditions, compared to UB CC smoking, representative ENDS, and nicotine gum or inhaler. Nicotine exposure and exposure to non-nicotine BOE, as well as subjective effects, were evaluated in forced-switch, 60-day ad libitum use studies (PM0000528.PD1, PM0000539.PD1; LP004 and PM0000534.PD1; LP005); BOE were compared to continued CC smoking and, in one study, complete tobacco cessation (although NRT was provided, if requested).

3.3.1. Discipline key findings

The following discussion is based on key findings provided in the BCP review.

3.3.1.1 Current tobacco users

- 'Abuse liability' refers to the ability of the product to promote continued use, and the development of addiction and dependence. This can be relevant to determining the likelihood that addicted users of one nicotine product would switch to another. For

example, if a new tobacco product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using. Low abuse liability also makes it less likely that new users will become addicted.

- Results of applicant-sponsored clinical laboratory studies (LP001, LP002, and LP003) show nicotine exposure is significantly and substantially lower following use of all new products relative to UB CC under controlled conditions among adult ENDS naïve CC smokers. The new products' relatively lower abuse liability compared to CC suggests two potential benefits: 1) a relatively low likelihood that new ENDS users will progress to regular use of the new products, and 2) reduced nicotine exposure may lead to lower nicotine dependence which may improve cessation outcomes in CC smokers who are motivated to quit.

- Data from all of the applicant-sponsored clinical studies show subjective effects (e.g., liking, satisfaction) were lower for PM0000539.PD1 and PM0000528.PD1 relative to UB CC, and subjective effects were similar or lower for PM0000534.PD1 relative to UB CC.

- The abuse liability of the Logic Vapeleaf Menthol Green product (PM0000528.PD1) is substantially lower than UB CC and lower than nicotine gum in adult CC smokers.

- The abuse liability of the Logic Pro Menthol product (PM0000534.PD1) is substantially lower than UB CC, similar to or greater than nicotine inhaler, and similar to or slightly higher than VUSE Vibe Original (a representative ENDS) in adult CC smokers.

- The abuse liability of the Logic Power Menthol product (PM0000539.PD1) is substantially lower than UB CC, similar to or greater than nicotine gum, and similar to or slightly higher than blu PLUS Classic Tobacco (a representative ENDS) in adult CC smokers.

- The abuse liability of the new products for regular ENDS users, former smokers, other tobacco product users, or never-users was not assessed.

- Applicant-submitted evidence suggests Logic Vapeleaf Menthol Green (PM0000528.PD1) was more preferred than Logic Vapeleaf tobacco-flavored products (not subject to this PMTA review), and the Logic Pro Menthol product (PM0000534.PD1) may be more preferred than the Logic Pro tobacco-flavored product (not subject to this PMTA review). The Logic Pro Menthol (PM0000534.PD1) cohort reported similar satisfaction as CC, whereas the Logic Vapeleaf Menthol Green (PM0000528.PD1) product cohort had lower subjective effects as CC.

- The abuse liability of the new products was slightly greater than, or comparable to, the abuse liability

of 2mg nicotine gum and 4mg nicotine inhaler, which may increase the likelihood of use of and adherences to the new products compared to NRT in adult CC smokers interested in quitting all tobacco products.

- There were no differences in nicotine pharmacokinetics and exposure among different characterizing flavors within each Logic product line (including comparisons between menthol-flavored products [PM0000528.PD1, PM0000534.PD1, and PM0000539.PD1] and tobacco-flavored products [not subject to this PMTA review]) in the applicant-sponsored clinical studies.

- The new products' menthol characterizing flavors do not appear to have a significant impact on abuse liability as compared to the other flavored (including tobacco-flavored) varieties of Logic products tested. PK and subjective effects data suggest a similar profile among the new products. However, no direct statistical comparisons were made between menthol and other flavored new products.

- Although abuse liability of the new products may be expected to be higher in individuals with a history of ENDS use, results from the applicant-sponsored 60-day clinical studies showed that abuse liability of the new products was still lower than UB CC in adult smokers who were more familiar with the new products and who had used them regularly for several weeks.

Appendix C

3.3.2. Synthesis

As TPL, I agree with the BCP review conclusions that the nicotine pharmacokinetic profiles and lower positive subjective effects ratings for the new products indicate a lower abuse liability than UB CC, the comparison product. Furthermore, the abuse liability of the new products appears to be similar to representative ENDS with similar design features and e-liquid nicotine concentrations. However, it should be noted that the applicant-submitted clinical studies were conducted in CC smokers with little to no ENDS experience; among experienced ENDS users, the new products may have somewhat higher abuse liability, although it would not be expected to surpass the abuse liability of CC. Indeed, the new products maintained their relatively lower abuse liability in participants who used the new products during the 60-day clinical studies (LP004 and LP005) and became more experienced ENDS users throughout the process. These studies (although they do not represent real-world use behaviors) also suggest that nicotine exposure, upon dual use of the new products and UB CC, is unlikely to exceed that of the comparison product, UB CC.

The applicant-submitted studies were not designed (i.e., statistically powered) to evaluate differences between the new products' characterizing flavors (e.g., statistically significant differences in nicotine pharmacokinetics between Logic Pro Menthol and Tobacco [not subject to this PMTA review] products); the applicant-submitted data suggest few differences in outcomes that comprise abuse liability, including nicotine pharmacokinetics and subjective effects, among the characterizing flavors in

current, adult smokers. Trends in subjective effects of "liking" and "satisfaction", suggest that the Logic Pro Menthol product may have been more preferred than Logic Pro Tobacco product (not subject to this PMTA review) by adult CC smokers; however, as discussed in Section 3.4.1.2. below, data from the 60-day clinical studies did not show that these preference trends resulted in the increased likelihood that adult CC smokers using these new products had an increase in complete switching or significant reduction in CPD as compared to the those using the tobacco-flavored ENDS (not subject to this PMTA review). All new products had relatively lower abuse liability than CC in adult smokers but, with experience, ENDS users may achieve higher nicotine levels to satisfy the withdrawal and craving symptoms. These characteristics may be potentially beneficial for adult CC smokers trying to completely switch to ENDS or significantly reduce smoking, as the new products are more likely to have satisfactory results and reduce the likelihood that former CC smokers will resume smoking. In addition, the slightly greater abuse liability of these new products compared to NRT may increase the likelihood of use of these new products compared to NRT among adult smokers interested in quitting. The nicotine levels may pose an addiction risk for non-tobacco users, including youth, despite the relatively low abuse liability of the new products as compared to CC, as non-tobacco flavors can increase nicotine exposure and influence the rewarding and reinforcing effects of e-liquids.

The abuse liability of the Logic Vapeleaf Menthol Green (PM0000528.PD1) product is likely below that of 2mg nicotine gum. The BCP review notes that

many CC smokers may be unlikely to use this product because it does not deliver nicotine beyond that of NRT, has low subjective appeal, and is associated with little reinforcement. However, despite its relatively low abuse liability profile as compared to CC, use of the Logic Vapeleaf Menthol Green product did decrease CPD by greater than 80% and showed significantly lower BOE upon use (see Sections 3.4.1.2. and 3.5.1.2.). These data suggest that the Logic Vapeleaf Menthol Green product might offer a means towards CC cessation among adults. However, there was insufficient evidence to suggest that the Logic Vapeleaf Menthol Green product facilitated complete switching from CC or significant reduction in CPD beyond that of a tobacco-flavored ENDS.

Despite their relatively lower abuse liability profile than CC, the new products were successfully used in LP004 and LP005 to decrease nicotine exposure and significantly decrease CC smoking (see Section 3.4.1.2.) in adult CC smokers. Decreased nicotine exposure and CPD may help to facilitate CC cessation in CC smokers who are motivated to quit. Thus, CC smokers who choose to use the new menthol products may experience the benefits of significantly reducing their nicotine exposure, reducing their exposure to BOE (see Section 3.5.1.2.), reducing their nicotine dependence, and facilitating smoking quit attempts and success.

Regarding impact on youth, nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason (Ambrose et al., 2015; Tsai et al., 2018).

Among U.S. Population Assessment of Tobacco and Health Study (PATH) (2016-2017) youth current (past 30 day) ENDS users, 71% reported using ENDS because of flavors (B. L. Rostron, Cheng, Gardner, & Ambrose, 2020). 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 non-tobacco-flavored ENDS are rated as more satisfying than tobacco-flavored ENDS among adults. Participants will work harder for and take more puffs of non-tobacco-flavored ENDS compared to tobacco-flavored ENDS, and flavors can increase nicotine exposure by potentially influencing the rewarding and reinforcing effects of e-liquids (Kim et al., 2016; St Helen, Dempsey, Havel, Jacob, & Benowitz, 2017; St Helen, Shahid, Chu, & Benowitz, 2018; Voos et al., 2020).

3.4. USER POPULATIONS

The BCP review considered the five applicant-submitted clinical studies (LP001-LP005).

The social science review considered the following studies: Focus Groups (LOGIC-CMA-CPS-001), Cognitive interviews (LOGIC-CMA-CPS-002), Consumer Perception Studies (LOGIC-CMA-CPS-003; LOGIC-CMA-CPS-004; LOGIC-CMA-CPS-005), and Exit Interviews conducted with participants at the conclusion of two 60-day clinical studies (LOGIC-CMA-EI-001, participants from clinical studies LP004 and LP005).

Appendix C

The epidemiology review considered data from the Exit Interviews conducted with participants at the conclusion of two 60-day clinical studies (LOGIC-CMA-EI-001, participants from clinical studies LP004 and LP005).

3.4.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.4.1.1 Intended user population(s) (target population)

Per the BCP, epidemiology, and social science reviews:

- The applicant stated that the intended population for the new products is adult CC smokers.

Per the BCP review:

- The applicant submitted five clinical studies that were conducted in current CC smokers, which provide sufficient evidence to inform use behavior in those populations.

Per the social science review:

- The information provided suggests that the likely users of the new products include current CC smokers and current ENDS users.

Appendix C

3.4.1.2 Current tobacco users

Per the BCP review:

- The abuse liability of all new products in adult smokers is lower than CC; therefore, complete switching is unlikely, and dual use of the new products with CC is the most likely use behavior. Some CC smokers (including menthol CC smokers) may temporarily adopt the new products before switching back to CC. These smokers may switch back to CC because the latter are rated higher in terms of liking and satisfaction compared with the new products. Menthol CC smokers with the intent to quit smoking may use these new products as a means to transition away from menthol CC smoking (reduce CPD or experience CC cessation).

- It is unclear how many participants completely switched (i.e., completely quit CC use) to the new products in the applicant-submitted 60-day clinical studies (LP004, LP005).

- Most participants in all new product (including new products not subject to this PMTA review) cohorts (LP004, LP005) substantially decreased CPD from an average of 13-16 CPD at screening to 1-2 CPD by Day 59 (greater than 80% reduction). CC consumption decreased to 1-2 CPD in all new product cohorts (regardless of Logic sub-brand); however, the studies were not designed to evaluate differences among the characterizing flavors.

Dual use occurred despite free access to the new products and study instructions to solely use the new products.

- Study compliance was reported as the percentage of participants who completed the protocol within the PPS (per protocol set) in LP004 and LP005, which includes product switching as a component. However, the studies were not designed or powered to detect complete switching and, in themselves, do not constitute evidence of added benefit. More detailed studies and/or analyses, (i.e., specifically designed and powered for this endpoint), would be needed to assess whether these results reflect or are indicative of differences in actual benefit in the form of complete switching or significant reduction in cigarettes.

Per the epidemiology review:

- The applicant did not provide studies or information from the peer-reviewed literature that contained prevalence of use estimates for the new products among adults. They relied on e-commerce sales data as a proxy for data on prevalence of use of their new products; however, e-commerce sales data is limited in its ability to characterize actual patterns of tobacco use, and thus may not be an adequate proxy for describing prevalence of use. Evidence from the peer-reviewed literature suggests that adult use of closed ENDS, like the new products, is likely to be non-daily and concurrent with CC.

- The applicant emphasized results from the Exit Interviews, conducted among LP004 and LP005 clinical study participants who were smokers at baseline, which suggested that dual use was common (with nearly two-thirds reporting smoking a CC during one of the clinical studies). The applicant did not provide studies from the peer-reviewed literature that contained prevalence estimates of dual-use or poly-use of the new products with other tobacco products. The peer-reviewed literature indicates that, in general, ENDS use among CC smoking adults is common and that dual use is particularly common among young adults.

    - In the applicant-submitted 60-day clinical studies (LP004 and LP005), a large majority of participants in the full analysis set decreased self-reported CPD by 80%:

        - Logic Vapeleaf Menthol Green (PM0000528): 75%-80%

        - Logic Pro Menthol (PM0000534): 83%-93%

        - Logic Power Menthol (PM0000539): 76%-81%

  However, the extent to which participants maintained their reduced CPD outside of the clinical study setting or completely switched from CC in these studies (i.e., CC cessation) was not described

based on the study design. Of the LP004 and LP005 clinical study participants who participated in the Exit Interviews, 52-63% of participants reported dual using one of the new products and CC while participating in the 60-day clinical studies.

Per the social science review:

- Results from the Consumer Perception Studies and Exit Interviews are limited in generalizability to describe the likelihood of actual use of the new products in the U.S. population due to methodological limitations, particularly among youth. These limitations were considered in the synthesis of this data.

    - The Consumer Perception Studies included current, former and never tobacco using adults (21+) who were assessed for product appeal and intent to use after viewing pictures of the new products. They did not use the products.

    - The Exit Interviews were conducted for study participants at the end of the longer clinical studies. The study participants were adult current CC smokers who were randomly assigned to use one of the new products during the study.

- Respondents within all tobacco-use status groups (dual users [those who dually use ENDS and at least one other tobacco product], current users [those who currently use tobacco products other

than ENDS, such as combusted cigarettes, cigars, or smokeless tobacco], former users, and never users) in the Consumer Perception Studies rated the perceived health risks and addiction risks of all new products below CC, at a similar level or slightly above NRT, and above cessation. Current tobacco users and dual users rated all new products on health risks and addiction risks as "Moderate Risk."

- In the Consumer Perception Studies, for all new products, dual users reported the greatest interest in purchase, trial, and use of the new products, followed by current tobacco users and then former and never users, suggesting the highest likelihood of uptake by current dual users of ENDS and other tobacco products. For all new products, between 31% to 64% of dual users responded "Likely" or "Definitely Likely" for the intentions items for the new products after viewing an image of the new products. In comparison, between 7.4% to 35% of current CC users responded "Likely" or "Definitely Likely" to the items assessing intentions to purchase, try, and use the new products. When presented with reasons why respondents would use the new products, more dual users endorsed intentions to use the new products to reduce current use of tobacco products than to use it to quit all forms of tobacco.

- The Consumer Perception Studies, which assess product appeal and consumer intent to use based

on a picture of the new products rather than actual product use, indicate that across the Logic sub-brands, current tobacco users were least likely to indicate intent to use the product if offered by a friend when it was a menthol flavor (23.3% for PM0000528.PD1, 22.7% for PM0000534.PD1, and 24.7% for PM0000539.PD1). As discussed below, the Exit Interviews, which assessed participants who actually used the new products, suggest that the menthol-flavored new products may be associated with greater appeal ratings (among users of the new products) than other Logic products, including tobacco-flavored and non-tobacco-flavored Logic products (not subject to this PMTA review).

- Data obtained from the Consumer Perception Studies with adult dual users (those who dually use ENDS and other tobacco products) differed slightly in intent to use patterns from current users (those who currently use tobacco products). Intent to use menthol-flavored products (PM0000528. PD1, PM0000534.PD1, and PM0000539.PD1) varied from 53.6% to 63.4%. 56% of dual users were interested in trying the Logic Vapeleaf Menthol Green product whereas interest in trying Logic Vapeleaf products with tobacco or non-tobacco/ non-menthol flavors (not subject to this PMTA review) was 48-63%. Interest in trying the Logic Power Menthol product was 53.6%, whereas interest in trying the tobacco or non-tobacco/non-menthol flavors (not subject to this review) was

56-62%. Interest in trying the Logic Pro Menthol product was 63.4% and interest in the tobacco or non-tobacco/non-menthol-flavored products was 60-67.7%. However, the Consumer Perception Studies are limited in generalizability due to methodological limitations.

- Data from the applicant's clinical studies' Exit Interviews (following product use in the 60-day studies) suggest that the menthol-flavored new products may be associated with somewhat higher appeal ratings and may be associated with greater intention to use among Logic Power products (after reducing CPD), compared to other Logic products (not subject to this PMTA review) among adult tobacco users; however, no statistical testing was performed to substantiate such an association. The applicant also provided literature which supports that adult smokers find non-tobacco flavors, including menthol, appealing.

- The peer-reviewed literature supports that menthol CC users indicate more enjoyment, satisfaction, and intent to use menthol-flavored ENDS compared to tobacco-flavored ENDS after ENDS trial (DeVito et al., 2020; Goldenson, Buchhalter, Augustson, Rubinstein, & Henningfield, 2020; Rosbrook & Green, 2016; Voos et al., 2020). Behavioral economics experiments that evaluate the ability for one product to serve as substitute for another show that menthol CC users will most commonly substitute menthol CC with menthol

ENDS—in scenarios where menthol ENDS are available—compared to other tobacco products, including tobacco-flavored ENDS (Denlinger-Apte et al., 2021; Shang et al., 2020). Indeed, a nationally representative survey documented that 52.2% of dual users of menthol CC and ENDS use menthol/mint-flavored ENDS (13.1% indicate exclusive menthol/mint ENDS use) and 41.4% of menthol CC users who switched completely from CC to ENDS used menthol/mint-flavored ENDS (21.3% report exclusive menthol/mint-flavored ENDS use) (Brian L Rostron, Chang, Chang, Jackson, & Ambrose, 2021). The potential for a comparatively better means to facilitate menthol CC cessation is relevant to FDA's analysis, given some menthol smokers' markedly lower rates of CC cessation than non-menthol CC smokers (e.g., Smith et al., 2020; Villanti, Collins, Niaura, Gagosian, & Abrams, 2017).

3.4.1.3 Tobacco nonusers (including youth)

Per the BCP review:

- The applicant submitted five clinical studies (LP001-LP005) indicating lower abuse liability for the new products relative to CC. Although tobacco nonusers including youth were not included in the applicant-submitted clinical studies, the comparably low abuse liability of the new products relative to CC suggests progression to and

sustained use of the new products among tobacco nonusers is likely to be lower than progression to and sustained use of tobacco products with greater abuse liability (e.g., CC).

- However, findings from the published literature indicate that non-tobacco flavors can influence the rewarding and reinforcing effects of e-liquids (Kim et al. 2016), thereby facilitating ENDS use and increasing abuse liability. Research also shows that ENDS flavors can increase nicotine exposure by potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use (St Helen et al., 2017; Voos et al., 2020). This evidence suggests flavored ENDS may pose greater addiction risk to tobacco nonusers relative to tobacco flavored ENDS, which increases concerns of addiction in youth.

Per the social science review:

- Results from the Consumer Perception Studies and Exit Interviews were conducted in adults only and are limited in their ability to describe the likelihood of actual use of the new products in the U.S. population due to methodological limitations, particularly among youth. These limitations were considered in the synthesis of this data.

- The Consumer Perception Studies provided data on intent to use the new products for adult never users by product: 5.9% were interested

in trying the Logic Vapeleaf Menthol Green (PM0000528.PD1) product; 6% were interested in trying the Logic Power Menthol (PM0000539.PD1) product; 4% were interested in trying the Logic Pro Menthol (PM0000534.PD1) product if recommended by a friend. However, the Consumer Perception Studies are limited in generalizability, due to methodological limitations including lack of a representative sample due to only a small percentage of the invited participants completing the studies.

- Taking into consideration the existing low prevalence of ENDS use by older adult (aged 25 + years) never tobacco users, and the findings from the Consumer Perception Studies, the likelihood of initiation of tobacco use with the new products by adult nonusers is low.

- In the Consumer Perception Studies, former tobacco users, on average, rated the new products as "Moderate Risk" to "High Risk," while never users rated the new products as "High Risk."

- The applicant did not submit any data from individuals under age 21 and did not discuss the submitted data's applicability to youth. The lack of applicant-submitted youth data and sufficient bridging information, coupled with no information in the literature regarding use of the new products by youth, limited the social science review to make conclusions about whether young people

will initiate ENDS use with the new products. However, other data relevant to youth use of Logic products has become available, as noted below.

- In 2021, Logic products were not among the top five brands reported for use among youth despite being one of the options available for selection in NYTS 2021 (Park-Lee et al., 2021). However, use of the new products by youth ENDS users might substantially change, depending on the availability of other products on the market.

- Preference for ENDS device types is not static and is affected by the marketplace, particularly the options, especially flavors, that are available for consumers to choose from. After FDA implemented the 2020 Enforcement Priorities Guidance1 to prioritize cartridge-based flavored ENDS, which were most appealing to youth at the time, a substantial rise in use of disposable flavored ENDS was observed, with a ten-fold increase (from 2.4% to 26.5%) among high school current ENDS users during 2019 - 2020 (Wang et al., 2020). This trend underscores the fundamental role of flavor in driving appeal. Specifically, it illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered flavor options, even though it exhibited lower youth use prevalence historically.

- Furthermore, NYTS 2021 and Monitoring the Future 2020 data support that youth have

higher use prevalence of menthol flavored ENDS compared to tobacco-flavored ENDS (Miech, Patrick, O'Malley, & Johnston, 2017; Park-Lee et al., 2021). While the literature suggests that youth appeal and interest in menthol/mint/wintergreen-flavored ENDS are lower compared to fruit-flavored ENDS (Groom et al., 2020), they remain higher than for tobacco-flavored ENDS.

- NYTS 2021 data show that the most common ENDS flavors used by middle- and high-school past 30-day flavored ENDS users are fruit (71.6% of youth past 30-day flavored ENDS users, 95% CI [67.8–75.1]), followed by candy, desserts, or other sweets (34.1%, 95% CI [30.3–38.2]), mint (30.2%, 95% CI [26.9–33.7]), and menthol (28.8%, 95% CI [23.6–34.8]) (Park-Lee et al., 2021). These data represent flavor preference from the 84.7% (95% CI [81.4–87.5]) of youth past 30-day ENDS users who indicated they use flavored ENDS (tobacco flavor not included) (Park-Lee et al., 2021). These data indicate that fruit is the most common flavor of ENDS used by youth and that youth use of candy-, mint-, and menthol-flavored ENDS does not differ significantly.

- In 2021, 11.3% of high school students and 2.8% of middle school students reported current ENDS use (Park-Lee et al., 2021). It is possible that the number of youth who were current ENDS users was higher than reported in 2021; approximately half of students took the survey at home, which

may have resulted in an under-reporting of tobacco use behaviors (Biglan, Gilpin, Rohrbach, & Pierce, 2004; U.S. Department of Health and Human Services, 2012). Longitudinal research using 2013-2015 U.S. Population Assessment of Tobacco and Health Study (PATH) data indicated that 42.2% of past 30-day youth ENDS users remained past 30-day ENDS users one year later (Stanton et al., 2019).

- Youth are more likely to initiate with non-tobacco-flavored ENDS and subsequently progress to regular use than with tobacco-flavored ENDS. For instance, between Wave 1 and Wave 2 of the PATH Study from 2013-2015, over 81% of youth aged 12-17, 71% of young adults 18-24, and 53% of adults 25 and older reported that the first ENDS that they used was non-tobacco-flavored (Villanti et al., 2019). In another PATH study, more youth, young adults and adults who initiated ENDS use between Wave 1 and Wave 2 reported use of a non-tobacco-flavored product than a tobacco-flavored product (Rose et al., 2020). 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 non-tobacco-flavored compared to 54.9% among adult ever users 25 and older (Rostron, Cheng, et al., 2020). Additionally, existing literature on non-tobacco-flavored product use suggests that non-tobacco flavors not only facilitate initiation, but also promote established regular ENDS use.

For example, regional studies have found that the use of non-tobacco-flavored ENDS was associated with a greater frequency of ENDS used per day among a sample of adolescents in Connecticut in 2014 (Morean et al., 2018). Data from a regional survey in Philadelphia, PA found initial use of a non-tobacco-flavored vs. 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 (Audrain-McGovern, Rodriguez, Pianin, & Alexander, 2019). Finally, similar effects have been found in the PATH study among young adults (18-24 years), where "ever use" of non-tobacco-flavored ENDS at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2 (Villanti et al., 2019). Collectively, these findings indicate that while all ENDS pose risks to youth, youth are less likely to initiate tobacco-flavored ENDS, and to subsequently progress to regular use of such products, than with non-tobacco-flavored ENDS.

- Research has also shown that youth find flavored ENDS, including menthol-flavored ENDS, particularly appealing. Nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason (Ambrose et al., 2015; Tsai et al., 2018). Among Wave 4 youth current ENDS users, 71% reported using ENDS because of flavors (B. L. Rostron, Cheng, et al.,

2020). Among youth ever-ENDS users, more than 40% endorsed "good flavors" as a reason for trying ENDS (Bold, Kong, Cavallo, Camenga, & Krishnan-Sarin, 2016). In a systematic review, six studies found an association between flavors and ENDS use intentions among youth (Meernik, Baker, Kowitt, Ranney, & Goldstein, 2019). Three additional studies found that youth were more likely to try non-tobacco flavored ENDS compared to tobacco-flavored ENDS. Additional findings from these studies suggest that youth nonusers of CC who had used non-tobacco-flavored ENDS were more likely to be susceptible to initiating CC. The NYTS data showed that rates of ENDS use fell from 2019 to 2020 among high school (27.5% to 19.6%) and middle school (10.5% to 4.7%) students (Gentzke et al., 2020). Despite this decrease, fruit-flavored disposable ENDS were the most common flavor and device combination, used by 85.8% of middle and high school students who exclusively used ENDS in the past 30 days (Wang et al., 2021). Together, these data demonstrate that flavored ENDS continue to play an important role in youth ENDS use.

- According to NYTS 2021 data, 28.7% of middle and high school users reported prefilled or refillable pods or cartridges as the ENDS device types they used most often (Park-Lee et al., 2021). Sleek design, ability to use products discreetly, and user-friendly nature make pod-based (rechargeable cartridge-based ENDS) products appealing

among youth (Fadus, Smith, & Squeglia, 2019). The new products are sleek and small in design, user friendly, cartridge-based, and easily rechargeable. Thus, there is some risk that the design may appeal to youth and the menthol flavor may increase that risk.

Per the epidemiology review:

- The applicant presented information on intentions and perceptions from their Consumer Perception Studies in an attempt to discuss the likelihood of initiation of the new products; however, the applicant did not present actual use or initiation estimates. The applicant did not provide studies from the peer-reviewed literature containing information on the likelihood that adult or young adult nonusers of tobacco will start using the new products.

- The applicant provided a short review of published studies on youth initiating tobacco use with ENDS and suggested that estimates of youth ENDS initiation varied widely.

- In 2021, Logic products were not among the top five brands reported for use among youth (despite being one of the options available for selection in the 2021 NYTS survey) (Park-Lee et al., 2021). However, use of the new products by youth ENDS users might substantially change, depending on the availability of other products on the market (Cullen et al., 2019).

- To address initiation of the new products, or ENDS generally, among former tobacco users, the applicant provided a summary of information from the literature and suggested that ENDS use among former smokers is relatively low. Studies suggest that some adult former smokers do use ENDS, but data from both the PATH and National Health Interview Survey (NHIS) suggest that ENDS use among adult former smokers is less common than among current adult smokers.

3.4.1.4 Vulnerable populations (other than youth)

Per the social science and epidemiology reviews:

- The applicant did not provide information on use of the new products among vulnerable populations—i.e., groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation. Evidence from the published literature indicates that all age groups with substance use or mental health issues are more likely to use ENDS compared to those without these conditions (Cho et al., 2018; Conway et al., 2018; Riehm et al., 2019). Additionally, the prevalence of ENDS use is higher among other vulnerable populations (e.g., pregnant persons, and lesbian, gay, and bisexual individuals) (Azagba, Latham, & Shan, 2019; Buchting et al., 2017; Hawkins, Wylie, & Hacker, 2020; Obisesan et al., 2020; Wheldon & Wiseman, 2019). While

the evidence indicates that some vulnerable populations experience disproportionate ENDS use, there is a lack of currently available evidence to show whether the new products would help facilitate adult CC smokers from vulnerable populations to completely switch or significantly reduce CPD.

Per the BCP review:

- No clinical studies were provided or reviewed by the applicant addressing use of the new products among vulnerable populations. The applicant submitted five clinical studies (LP001-LP005) indicating lower abuse liability among adult CC smokers for the new products relative to CC, which suggests the new products may not pose greater risk of progression to regular use and addiction among vulnerable populations other than youth compared to CC. Nevertheless, these studies did not specifically assess vulnerable populations, and from a BCP perspective, the impact of the new products on abuse liability and product use behavior in vulnerable populations other than youth is unknown.

3.4.1.5 Actions taken to mitigate risk to nonusers, including youth

- Before determining that permitting the marketing of a new tobacco product would be APPH, FDA considers the impact of marketing restrictions and other mitigation efforts that aim to reduce the

risk of youth initiation and tobacco use. Marketing restrictions include advertising and promotion restrictions intended to limit youth exposure to and appeal of tobacco product marketing (e.g., measures such as limiting advertising to platforms that are predominantly used by adults and using advertising content and methods that are not known to resonate with youth, or even eliminating advertising in certain media channels altogether) and sales access restrictions intended to restrict youth access to tobacco products (e.g., measures such as selling products only in face-to-face interactions, in adult-only facilities, or via websites that require robust age verification). In recent years, there have been efforts to develop novel and potentially more effective mitigation measures aimed at reducing youth initiation risks, such as device access restrictions (e.g., technologies that require adult user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product). FDA evaluates these measures in the context of the overall public health evaluation of the product, weighing the known risks to youth against the benefit to adults. For example, as discussed in section 3.4.2 below, in the case of flavored ENDS, the risk of youth initiation and use is well-documented and substantial and thus more stringent restrictions are needed in order to meaningfully mitigate that risk.

Restrictions on advertising and promotion include measures such as: limiting advertising in various media channels like point-of-sale, print, TV, radio,

digital media such as Internet websites, mobile applications, social media platforms like Facebook, Twitter, Instagram (e.g., placing advertising only in media with audience compositions of at least 85% adults 21+; limiting social media promotion to only platforms with age-gating controls; not advertising on billboards located within 500 feet of any elementary or secondary schools, youth-oriented facilities, childcare facilities, or hospitals; requiring point-of-sale advertising be placed only in areas of the facility that cannot be seen outside); limiting the timing, frequency, or overall amount of advertising (e.g., advertising on TV and radio only during certain hours; airing no more than one advertisement per half hour of programming with a minimum 20-minute separation between spots); limiting the use of certain advertising and promotional tactics (e.g., sending direct e-mail communication to only age-verified customers who have opted to receive such content; avoiding the use of direct mail advertising; avoiding use of influencers; avoiding use of product giveaways and product samples; avoiding use of sponsorships and events); developing advertising content that is intended to appeal to adults and avoid themes and images known to resonate with youth (e.g., avoiding use of cartoons; avoiding use of content depicting youth culture or lifestyle appeal; avoiding use of user-generated social media content featuring under age users; using only models who will be and appear to be ages 25+ in advertising); and utilizing product labeling and packaging designs

intended to reduce youth appeal (e.g., avoiding use of confectionary or candy-like naming conventions or images, limiting use of colors and imagery, using only black and white labels). The purpose of these restrictions is to reduce youth exposure to and appeal of tobacco product images, which in turn reduces product appeal among youth, which in turn reduces the desire to buy and/or try products, which in turn reduces the likelihood of youth initiation and youth use. Because these restrictions are intended to curb youth appeal but do not directly prevent youth use, they do not in themselves provide enough assurance of a sufficient reduction in youth use to mitigate the substantial risk that flavored ENDS pose to youth, a risk that is supported by direct, robust and reliable data of behavioral outcomes (e.g., actual youth initiation rates and youth use rates). Accordingly, for flavored ENDS, these promotion and advertising restrictions do not have the potential to reduce the magnitude of adult benefit required to establish APPH. In other words, for flavored ENDS, these promotion and advertising restrictions do not reduce the risk of youth initiation and use to a material enough degree that FDA could find that a product is APPH in the absence of robust evidence of a countervailing benefit to adults.

Restrictions on sales access include measures such as: complying with local, state, and federal minimum age of sale restrictions; requiring age- and identity-verification prior to selling products

online; utilizing independent and reliable age- and identity-verification services; selling products only in face-to-face interactions; selling products only in adult-only facilities; using trace and verify QR codes linked to the purchaser's driver's license; setting limits on the number of products that can be purchased in a single transaction; requiring retailers and distributors to sign written agreements stating they will cooperate with "secret shopper" programs and audits; penalizing retailers and distributors for underage sales; conducting retailer training programs; participating in responsible retailing programs (e.g., We Card); and monitoring distribution channels for compliance. These measures tend to be more direct than advertising and promotion restrictions in that they are intended to curtail access to products. However, FDA has found that to date these restrictions do not by themselves mitigate the high risk to youth posed by flavored ENDS to a degree material enough to establish that a product is APPH in the absence of robust and reliable evidence of benefit to adults. This is because youth have been able to obtain products, including flavored ENDS, despite sales restrictions.

As FDA explained in the 2020 Enforcement Priorities Guidance, from April 2018 to August 2019, the agency sent more than 6,000 warning letters and more than 1,000 civil money penalty complaints to online and brick-and-mortar retailers for illegal sales of e-cigarettes to minors

(FDA, 2020). FDA also asked manufacturers to propose measures they could implement to help restrict youth access to e-cigarettes (FDA, 2020). The proposed measures included the use of age-verification technology for online sales, enhanced monitoring of retailer compliance with age-verification requirements, and contractual penalties for retailers that failed to comply with sales restrictions (FDA, 2020).

Youth continue to be able to access to e-cigarettes, despite legal prohibitions and voluntary actions by some manufacturers (FDA, 2020). This is due in substantial part to the fact that the majority of youth do not purchase e-cigarettes themselves from retail locations, but rather they obtain them from social sources, including from friends or family members, steal them, or use someone else's product (Gentzke et al., 2022; Liu et al., 2019; Meyers et al., 2017; Tanski et al, 2019). In addition, with respect to youth who do attempt to purchase e-cigarettes themselves, one study (Meyers et al., 2017) found that some e-cigarette users <18 years of age reported having last obtained e-cigarettes from adult-only locations or those that should have had age verification procedures in place (i.e., smoke shops, liquor stores). Only one-quarter of youth who tried to buy tobacco products were refused sale because of their age (Liu et al., 2019).

Therefore, FDA has found to date that these sales access restrictions do not in themselves provide

enough assurance of a sufficient reduction in youth use to mitigate the substantial risk flavored ENDS pose to youth. Accordingly, for flavored ENDS, these sales access restrictions do not have the independent potential to reduce the magnitude of adult benefit needed to show APPH.

In contrast, in recent years there have been efforts to develop novel and potentially more effective mitigation measures such as device access restrictions. These include implementation of device technologies, such as age-gating technologies that require user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product or geo-fencing technologies (e.g., technologies that make it impossible to operate a tobacco product in a particular location such as a school or playground). In contrast to advertising and promotion and sales access restrictions discussed above, FDA believes that these novel device access technologies may offer a potential to sufficiently mitigate the risk to youth if they can be shown to restrict product access in a way that cannot be disabled or defeated. The use of device access restrictions in the current marketplace is limited, and FDA continues to assess them.

In conclusion, before determining that permitting the marketing of a new tobacco product would be APPH, FDA considers the impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and

tobacco use. FDA evaluates these measures in the context of the overall public health evaluation of the product, weighing the known risks to youth against the possible benefit to adults. The assessment for flavored ENDS is different from other tobacco products because of (1) the substantial risk of youth initiation and youth use as shown by well-established data, and (2) the lack of robust evidence in the scientific literature regarding the potential of flavored ENDS to benefit adult smokers, particularly when compared to alternatives posing less risk to youth, such as tobacco-flavored ENDS. Given those considerations, as well as the information discussed above regarding advertising, promotion and sales access restrictions, we have thus far determined that restrictions on advertising and promotion and sales access have not been adequate to mitigate the risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit needed to show APPH. In contrast, only the most stringent mitigation measures could provide sufficient assurance of such risk mitigation. To date, the only such measures identified with the potential for that kind of impact have been device access restrictions. Nonetheless, consistent with the concerns expressed by certain federal courts, FDA is reviewing all applicant-proposed marketing restrictions and mitigation measures to ensure that there are no other types of novel and materially different proposals.

- OHCE reviewed the relevant marketing submissions and drafted a consult dated 11/22/2021. The marketing plan information submitted by the applicant includes very limited information on its intended labeling, advertising, marketing, and promotion for the new products for at least the first year the products would be marketed after receiving an order. Based on the limited information submitted by the applicant and review of publicly available information online, it appears that the applicant uses, or has used: an owned e-commerce website; social media marketing (Facebook, Instagram, YouTube); TV and radio advertising; paid digital advertising; point-of-sale advertising; out-of-home advertising (e.g., mass transit, billboards, cinema); tradeshows; events; and sponsorships. The applicant does not clarify if it intends to continue marketing via the above channels and tactics. The applicant did describe some measures intended to mitigate youth initiation risks such as: discontinuing online sales via its owned website; restricting access to its owned website to only registered, age-verified adult users 21+; eliminating its social media accounts; avoiding the use of social media influencers and paid social media promotion; using only models over the age of 30 in its consumer marketing materials; avoiding the use of characterizing words (e.g., "sweet," "candy," "cool," "naturally flavored"); avoiding the use of cartoon imagery or images of foods marketed to youth; requiring adult consumers to participate in mandatory

age-verification before any in-person interactions with Logic products; providing retailer trainings; supporting the We Card program; and restricting age-verified Logic accounts from ordering more than 35 refill packages in a 30-day rolling time period and 6 Logic devices within a 12-month rolling time period.

- Overall, OHCE concluded that, if the products are otherwise authorized to be marketed, the marketing granted order should include additional marketing requirements and recommendations.

- However, as TPL I find that these menthol-flavored ENDS should not otherwise be authorized. The applicant did not propose any novel or materially different measures from those that FDA has previously considered and found insufficient. Consistent with the explanation above, I find that the applicant-proposed measures do not have the potential to mitigate the substantial risk to youth from flavored ENDS sufficiently to establish that the new products are APPH in the absence of robust evidence of added benefit to adults compared to less risky alternatives. Thus, the marketing plans and restrictions are not sufficient to overcome the deficiency related to the lack of evidence for added benefit to adult smokers.

3.4.1.6 Labeling, packaging, and advertising

Per the social science review:

- Per 21 CFR 1143.3, packages and advertising of covered tobacco products other than cigars must bear the statement "WARNING: This product contains nicotine. Nicotine is an addictive chemical." (nicotine warning statement). As noted in the DPAL memo finalized on January 16, 2020, some of the submitted materials do not include the nicotine warning statement. The leaflet for Logic Power Menthol Rechargeable Kit does not bear the nicotine warning statement on any page (*e-1-1-men-recharge-kit-leaflet-pwr*). The applicant provided a $2 off coupon for Logic Vapeleaf Caps (*e-2-cartridge-caps-refill-coupon-vlf*) and a $1 off coupon provided for Logic Pro Menthol cartridges (*e-3-refill-coupon-pwr*). Neither coupon contains the nicotine warning statement.

- On February 28, 2020, the applicant submitted new information about product labeling for Logic Pro and Power products, which included images of the product user guide insert. The amendment received on February 28, 2020 does not address the concerns raised in the DPAL memo about the required nicotine warning statement.

- The leaflet/user guide submitted with the Logic Vapeleaf products described the product as "A unique combination of vapor technology and real

tobacco provides satisfying taste with no smoke smell and no ash." In addition, the Point-of-Sale advertisement for the Logic Vapeleaf Menthol Green products included a similar statement: "Real Tobacco. No Smoke Smell. No Ash." Also, the capsule shelf carton shows a statement "No Ash, No Smoke Smell" on one side of the package, above the image of the device. Based on the information presented at this time, there is insufficient information to conclude that the above statements on the Logic Vapeleaf materials submitted with the application, or any other information in the applicant's other labeling/advertising for Logic Vapeleaf products do in fact convey modified risk. Accordingly, Social Science does not conclude that this labeling/advertising would cause the new tobacco products to be modified risk tobacco products.

- The applicant assessed comprehension of overall package labeling and marketing materials (specifically, the warning label) for the new products in the Consumer Perception Studies. The overall comprehension score for the new products' labeling and marketing materials appears adequate.

- As described below, the applicant provided proposed labeling. Based on the information presented at this time, we have not concluded that the proposed labeling is false or misleading in any particular.

Appendix C

In order to assess the statements "A unique combination of vapor technology and real tobacco provides satisfying taste with no smoke smell and no ash." and "Real Tobacco. No Smoke Smell. No Ash." on the Logic Vapeleaf packaging, a meeting with chemistry and engineering disciplines was held. The PMTA Internal Meeting Record dated December 17, 2019 with chemistry and engineering disciplines concluded:

- Because the tobacco is heated, and not combusted, it should not produce ash or a smoke smell under normal use conditions.

- The lower HPHC levels in the Logic Vapeleaf Menthol Green product's aerosol (compared to CC) also suggest that the tobacco is not combusted and therefore will not produce ash or a smoke smell.

- Although CTP does not have specific data at the time to indicate that such statements are modified risk claims, they may convey modified risk.

3.4.2. Synthesis

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 places the burden on the applicant to make the required showing by providing that FDA "shall deny an application" for a product to receive a PMTA marketing authorization if, "upon the basis of the information submitted to the Secretary as

part of the application and any other information before the Secretary with respect to such tobacco product," FDA finds that "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." Section 910(c)(2)(A). The statute further 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. My review of whether the marketing of the new products is APPH takes into account the information from the discipline reviews described above as well as other relevant information.

For the marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be outweighed by a sufficient benefit to adult users, and as the known risks increase, so too does the burden of demonstrating a substantial enough benefit. For flavored ENDS, including menthol-flavored ENDS, the known and substantial risk to youth in particular is high, as outlined in the section below. Therefore, to show a net population health benefit, the evidence should demonstrate that the benefit of the new products is significant enough to overcome that high risk to youth. In particular, such evidence should permit FDA to assess whether there is any added or incremental benefit to a flavored ENDS over a tobacco-flavored variety in facilitating smokers completely switching or significantly reducing their smoking. Without

evidence of such an incremental benefit, there would be insufficient justification to find the marketing of such products APPH, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. The availability of other products that provide similar opportunities for switching also informs the weight given to the asserted benefits of the subject products for adult smokers. As the statutory text makes clear, it is the applicant's burden to make a "showing"—with sufficient supporting information—that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole. The applicant did not carry its burden because the PMTAs for the new products did not include sufficient evidence of benefits to adult smokers.

Previously, FDA excluded menthol products from application decisions to allow more time to consider whether any factors unique to menthol would affect the APPH assessment. Among other things, FDA considered the potential significance of the fact that menthol-flavored combustible cigarettes currently remain on the market, unlike other non-tobacco characterizing flavors that are prohibited in combustible cigarettes. FDA conducted a thorough examination of the peer-reviewed scientific literature on this subject to determine whether it established that menthol-flavored ENDS provide a sufficient benefit for adult smokers relative to that of tobacco-flavored ENDS.

Appendix C

As discussed in the section entitled "*Evidence Provided in the PMTAs,*" the scientific literature suggests that menthol smokers show a preference for menthol-flavored ENDS, relative to non-menthol flavored ENDS. Based on this literature, FDA explored whether that preference for menthol-flavored ENDS among menthol smokers would be sufficient to demonstrate a benefit to adult smokers that outweighs the increased youth risks relative to tobacco-flavored ENDS, such that FDA could authorize the marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS products. However, the existing literature does not demonstrate that menthol-flavored ENDS differentially facilitate switching or cigarette reduction, and this is the behavioral outcome measurable with available methods that most directly and most robustly determines the potential benefit to users. In addition, flavored ENDs, including menthol, pose substantial risk of youth appeal and use. Ultimately, FDA has concluded that the existing scientific literature does not demonstrate a benefit to adult smokers that outweighs the increased youth risks relative to tobacco-flavored ENDS, such that FDA could authorize the marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS. Thus, the approach to the APPH analysis for menthol-flavored ENDS is the same as for other non-tobacco-flavored ENDS, in that, to overcome the risk to youth, an applicant must provide evidence demonstrating their menthol-flavored ENDS products provide an added benefit for adult smokers relative to tobacco-flavored ENDS.

Appendix C

The Risk to Youth of Flavored ENDS, Including the New Products

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 and thus youth are at particular risk of tobacco initiation. 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. 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. 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 daily smokers. 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.

The published literature demonstrates that non-tobacco-flavored ENDS pose substantial risk in youth appeal and use. In 2021, 11.3% of high school students and 2.8% of middle school students reported current ENDS

use (Park-Lee et al. 2021). It is possible that the number of youth who were current ENDS users was higher than reported in 2021; approximately half of students took the survey at home, which may have resulted in an under-reporting of tobacco use behaviors (Biglan et al., 2004; U.S. Department of Health and Human Services, 2012). The majority of youth who use ENDS report using a non-tobacco-flavored ENDS product, and the use of non-tobacco-flavored ENDS has increased over time (Cullen et al., 2019). In the 2014 National Youth Tobacco Survey (NYTS), 65.1% of high school and 55.1% of middle school ENDS users reported using non-tobacco-flavored ENDS, including menthol-flavored ENDS (Corey et al., 2015). By the 2022 NYTS, the percentage of ENDS users reporting using a non-tobacco-flavored product was 85.5% of high school users and 81.5% of middle school users (Cooper et al., 2022). In 2022, among youth who currently used flavored e-cigarettes, the most commonly used flavor type was fruit (69.1%), followed by candy, desserts, and other sweets (38.3%), mint (29.4%), and menthol (26.6%) (Cooper et al., 2022). The published literature shows that youth ENDS users are also more likely to use non-tobacco-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,[11] 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,

11. 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.

23.8% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal analysis). Youth current ENDS users were also more likely than adult current ENDS users to use more than one flavor (Schneller et al., 2019).

Additionally, the published literature shows that flavors influence youth initiation of ENDS use. In particular, data show that non-tobacco flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a non-tobacco-flavored product. For instance, in Wave 1 of the PATH Study from 2013-2015, over 81% of youth aged 12-17, 71% of young adults 18-24, and 53% of adults 25 and older reported that the first ENDS that they used was non-tobacco-flavored (Villanti et al., 2019). In another PATH study, more youth, young adults, and adults who initiated ENDS use between Wave 1 and Wave 2 reported use of a non-tobacco-flavored product than a tobacco-flavored product (Rose et al., 2020). 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 non-tobacco-flavored compared to 54.9% among adult ever users 25 and older (Rostron, Cheng, et al., 2020).

Existing literature on non-tobacco-flavored tobacco product use suggests that non-tobacco-flavored products not only facilitate initiation, but also promote established regular ENDS use. In particular, non-tobacco flavoring in tobacco products (including ENDS) make them more palatable for novice users, including 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 non-tobacco-flavored ENDS was associated with a greater frequency of ENDS used per day among a sample of adolescents in Connecticut in 2014 (Morean et al., 2018). Use of non-traditional flavors (defined in the study as flavors other than tobacco, mint/menthol, or flavorless) was associated with increased likelihood of continued use and taking more puffs per episode (Leventhal, Goldenson et al., 2019). Data from a regional survey in Philadelphia, PA found initial use of a non-tobacco-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 (Audrain-McGovern et al., 2019). Finally, similar effects have been found in the nationally representative PATH study among young adults (18-24 years), where "ever use" of non-tobacco-flavored ENDS at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2 (Villanti et al., 2019). In sum, there is evidence that non-tobacco flavors, including menthol, may influence the rewarding and reinforcing effects of flavored ENDS in adults, thereby facilitating ENDS use and increasing abuse liability, which may increase concerns of addiction in youth.

Per the epidemiology and social science reviews, the evidence from the peer-reviewed literature demonstrates that, while youth use of ENDS is common, the proportion of youth who report the new products as their usual brand is low. However, the evidence indicates that the preference for device types and popularity of certain

styles is likely fluid and affected by the marketplace, particularly the options, especially flavors, that are available for consumers. Data from the 2019 NYTS indicated that youth overwhelmingly preferred cartridge-based ENDS (Cullen et al., 2019) as these products are easy to conceal, can be used discreetly, and may have high nicotine content. ENDS use more than doubled among middle school and high school students from 2017 to 2019 (Miech et al., 2021); this substantial increase among youth coincided with the availability of non-tobacco-flavored cartridge-based and pod-based ENDS in the marketplace. Following FDA's prioritized enforcement of premarket review requirements for certain ENDS[12] such flavored cartridge-based or pod-based ENDS, use for these types of ENDS declined while a substantial increase in use of disposable flavored ENDS, which were not subject to the prioritized enforcement, was observed. Findings from the 2020 NYTS data showed that disposable ENDS were used by 26.5% of high school e-cigarette users (up from 2.4% in 2019) and 15.2% of middle school ENDS users (up from 3.0% in 2019) (Wang et al., 2020). Furthermore, more than 8 out of 10 youth ENDS users report use of non-tobacco-flavored products, with fruit, mint, candy, and menthol among the most commonly used. Disposable use and flavor use continued to be high in 2021 among ENDS users. For example, in 2022, disposable ENDS continued to be the most widely used type of ENDS among middle and high school students with 57.2% of high school

12. Guidance for Industry: Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised). May 2019. https://www.fda.gov/media/133880/download

e-cigarette users and 45.8% of middle school e-cigarette users using disposable ENDS (Cooper et al., 2022). 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 youth appeal and use of ENDS.

Although the applicant did not submit direct product-specific data on youth, the applicant attempted to address youth concerns by providing data from the 2019 NYTS. These data show low prevalence of Logic ENDS products use among youth. The latest NYTS data from 2022 show that about 4.3% of middle and high school e-cigarette users reported Logic as one of the e-cigarette brands they had used in the past 30 days (Cooper et al., 2022). These new menthol products could be particularly appealing to youth, and use of the new products by youth ENDS users might substantially change, depending on the availability of other products on the market. Additionally, the data from the NYTS are not specific to the Logic products subject to these PMTAs.

The social science review states that menthol-flavored ENDS are less appealing to youth than some other flavors and concludes that the menthol-flavored new products do not rise to a level of concern from the reviewer's perspective. Therefore, the review did not identify a deficiency. As TPL, I disagree with this conclusion because the scientific evidence demonstrates that menthol-flavored ENDS pose a substantial risk of youth appeal and use greater than tobacco flavor and similar to flavors

such as candy, desserts, sweets, and mint, regardless of whether they may be less appealing than fruit-flavored ENDS. The 2022 NYTS data clearly demonstrate that youth use of menthol-flavored ENDS (26.6% of past 30-day flavored ENDS users) is similar to that of flavors such as mint (29.4%) and candy/desserts/sweets (38.3%) (Cooper et al., 2022). Indeed, the literature described above substantiates that menthol-flavored ENDS pose a known and substantial risk to youth. The clear evidence of substantial use of menthol-flavored ENDS products among youth also reflects evidence beyond what was available at the time that FDA 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." The 2019 NYTS survey instrument for the data cited in the guidance grouped mint- and menthol-flavored products together, so it was not possible to differentiate youth use of mint and menthol flavors separately. Data from the Monitoring the Future Survey were available to separate out mint and menthol use at the time, but only for JUUL products specifically; these data showed greater youth use of mint, as compared to menthol-flavored JUUL products. By contrast, the 2022 NYTS survey measured youth use of mint- and menthol-flavored ENDS separately and found the rates to be similar. As noted above, menthol-flavored ENDS were used by 26.6% of middle- and high-school users of flavored ENDS, which is similar to the use rates for mint (29.4%) and candy/desserts/sweets (38.3%) (Cooper et al., 2022).

The findings described above demonstrate that menthol-flavored ENDS, such as the new products, pose a substantial risk of youth initiation and use similar to the risk presented by ENDS with flavors such as mint and candy/desserts/sweets.

Type of Evidence Needed to Outweigh the Risk to Youth[13]

Given the known and substantial risk to youth of the new products, sufficiently reliable and robust evidence that these flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or significantly reducing their cigarette use is needed to show a potential benefit to current adult users that would outweigh the new products' risk to youth.

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 flavored ENDS, including menthol flavor, would be APPH in the face of the significant risks to youth. In order to

13. This framework applies to flavored ENDS PMTAs for which FDA has found that the applicant-proposed marketing restrictions and related measures cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH. See section 3.4.1.5 for details.

adequately assess whether such an added benefit has been demonstrated, product-specific[14] evidence should be submitted to demonstrate the extent to which the product is likely to promote switching and to enable a comparison between the applicant's flavored ENDS and appropriate comparator tobacco-flavored ENDS in terms of their impact on tobacco use behavior among adult smokers. Consistent with section 910(c)(5), the strongest types of evidence could be generated from an (1) RCT or (2) LCS. Although 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. FDA is aware of these trade-offs and generally does 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 and appropriate comparator product (e.g., flavored ENDS and tobacco-flavored ENDS) on adult smokers' tobacco use behavior over time[15]; include outcomes related to

14. Product-specific evidence is derived from or based on studies using the specific new products that are the subject of the applications.

15. 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

ENDS use and smoking behavior to assess complete switching and/or significant 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 the RCT or LCS 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. Consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging.[16] Likewise, if a flavor is tested with one nicotine concentration, it may be feasible for the applicant to bridge the RCT or LCS study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging. Data from one of these studies could support a benefit to adult users if the findings showed that, compared to the new tobacco flavored product, use of (each) new flavored product is associated with greater likelihood of either of these behavioral outcomes for adult smokers: (1) complete switching from cigarettes to exclusive new product use or (2) significant reduction in CPD. There are no specific duration requirements for an RCT or LCS; the appropriate duration of an RCT or LCS depends on the effect being investigated.

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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.

16. Bridging is discussed in FDA's 2019 Guidance to Industry cited above (fn 18).

Appendix C

It may be possible in some contexts for applicants who do not conduct their own behavioral studies to rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. However, that approach is insufficient here because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions regarding the risks of the category as a whole—the evidence regarding the role of flavored products in promoting switching among adult smokers is far from conclusive. In fact, the findings are quite mixed and, as a result, the literature does not establish that flavored ENDS as a category differentially promote complete switching among ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due to the fact that 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 user. For these reasons, bridged data from the current literature on flavors generally cannot suffice to demonstrate a sufficient benefit of these products, and instead robust and direct product-specific evidence demonstrating potential benefit is needed. Given the state of the science on flavored ENDS, and the known risks to youth, direct product-specific evidence is needed to support the statutorily required showing. In the absence of strong direct evidence, FDA is unable to conclude that the benefit of the subject products outweighs the clear risks to youth.

Appendix C

CTP will also consider other types of evidence if they are sufficiently robust and direct to demonstrate the impact of the new ENDS on complete adult switching or significant 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 and report on their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Consumer perception studies (surveys or experiments) typically assess outcomes believed to be precursors to behavior, such as preferences or intentions related to the new products, but are not designed to directly assess actual product use behavior.

Evidence Provided in the PMTAs

The applicant provided several studies that aimed to address factors related to the likelihood of product use. Three clinical studies investigated the abuse liability of Logic Power Menthol (PM0000539.PD1; LP001), Logic Vapeleaf Menthol Green (PM0000528; LP002), and Logic

Pro Menthol (PM0000534.PD1; LP003) products under controlled laboratory conditions, compared to UB CC smoking, representative ENDS, and nicotine gum or inhaler. Two 60-day RCTs were conducted to examine toxicant exposure and subjective effects of new products (LP004, LP005). Note, these studies were not designed to address direct comparisons between Logic's menthol-flavored ENDS and tobacco-flavored ENDS (or any other flavor combinations) with respect to reductions in CPD or rates of complete switching. At the end of the 60-day studies, exit interviews (LOGIC-CMA-EI-001) were conducted, which included information on participants' overall experience with the new products, intention to use the new products, and perceptions of the new products' flavors. In addition, three consumer perception studies (LOGIC-CMA-CPS-003, LOGIC-CMA-CPS-004, LOGIC-CMA-CPS-005), cross-sectional online surveys, examined perceived health risks of the new products, likelihood to use the new products, and comprehension of the new products' labeling and advertising among current tobacco product users, former tobacco product users, and never users.

As TPL, I agree with the epidemiology, social science, and BCP reviews which conclude that current CC smokers (who become dual users upon initiation of ENDS) are the most likely population to use the new products, although the risk that youth non-users initiate with these products remains high. This conclusion is based on the applicant-submitted clinical study data on intentions to use the new products, actual use behavior, and abuse liability, as well as conclusions from the literature about ENDS in

general. Similarly, the applicant's Consumer Perception Studies suggest that dual and current tobacco users are the most likely user populations to purchase, try, and use the new products (regardless of characterizing flavor). The Consumer Perception Studies inform the conclusion about the likely users of these products but are not designed to address patterns of use (i.e., product switching), which is better assessed in a study involving actual product use.

The applicant-submitted clinical data (from the RCTs) also suggest that dual use will be common and that dual users will significantly decrease their CPD upon use of the new products (regardless of characterizing flavor). In the applicant's clinical trials, CC consumption decreased to 1-2 CPD in all new product cohorts (regardless of characterizing flavor and Logic sub-brand). Participant (CC smokers) compliance was low and differed slightly (although significance was not tested) across sub-brands and characterizing flavors. LP004 and LP005 required that CC smokers be randomized to a new product, and participants' ENDS characterizing flavor preference was not considered in the study's randomization scheme. The study was not designed to directly compare menthol to tobacco or other flavors and thus the applicant did not conduct these statistical comparisons. However, given that all study cohorts decreased CPD (following 60 days of new product use) to a similar degree, these data suggest that all new products (regardless of characterizing flavor or Logic sub-brand) are equally viable substitutes to CC smoking. These data do not show a differential effect for switching or reduction in CPD for the menthol-flavored new products compared to tobacco flavored

Logic products (not subject to this PMTA review). Thus, although the applicant submitted RCTs in the PMTAs, the findings from these studies did not provide evidence to suggest that the menthol-flavored new products will more effectively promote complete switching or significant cigarette reduction among adult CC smokers relative to tobacco-flavored ENDS. Thus, the evidence provided in the PMTAs regarding the potential benefit to adult users is not adequate to make the required showing.

Additional applicant-provided evidence suggests that availability of menthol characterizing flavors in the new products may appeal to current tobacco users. For example, in the Exit Interviews conducted with participants in the 60-day clinical trial studies who used the new products (and upon significant reductions in CPD), these new products were rated positively. Additionally, in the Exit Interviews, the Logic Power Menthol new product (PM0000539.PD1) had higher ratings of intention to use (upon significant reductions in CPD) than the other non-menthol Logic Power products (not subject to this PMTA); Logic Power and Vapeleaf products with menthol characterizing flavors had higher appeal and impression scores (upon significant reductions in CPD) than the other non-menthol Logic Power and Vapeleaf products (not subject to this PMTA). However, as described above, there was no evidence in the clinical trial studies submitted by the applicant that menthol-flavored products were more effective in helping smokers completely switch or significantly reduce CPD compared with smokers randomized to receive the tobacco-flavored varieties. One approach to evaluate whether the menthol-

flavored varieties are more effective than tobacco-flavored varieties at increasing complete switching or significant reductions in CPD, would have been to conduct a study that randomized smokers of menthol cigarettes to receive either the menthol- or tobacco-flavored variety.

In addition to reviewing the applicant-submitted information, and in light of the fact that menthol-flavored cigarettes currently remain on the market, unlike other non-tobacco characterizing flavors that are prohibited, FDA conducted a thorough examination of the peer-reviewed scientific literature on this subject.[17] FDA evaluated whether that literature established that menthol-flavored ENDS provide a sufficient benefit for adult smokers relative to that of tobacco-flavored ENDS.

As noted in the social science discipline review, the peer-reviewed literature supports that menthol CC smokers indicate more enjoyment, satisfaction, and intent to use menthol-flavored ENDS compared to tobacco-flavored ENDS after ENDS trial (DeVito et al., 2020; Goldenson et al., 2020; Rosbrook & Green, 2016; Voos et al., 2020). In addition, menthol/mint-flavored ENDS are more likely to be used by menthol CC smokers than

17. In May 2022, FDA proposed a product standard to prohibit menthol as a characterizing flavor in cigarettes. Tobacco Product Standard for Menthol Cigarettes, 87 Fed. Reg. 26454 (May 4, 2022). That rulemaking proceeding remains pending. Considerations such as a final rule going into effect in the future and whether it would have any impact on the assessment of menthol-flavored ENDS did not factor into the analysis here due to their entirely speculative nature at this time.

by non-menthol CC smokers, including by those who have completely switched from CC to ENDS (Brian L Rostron et al., 2021). The social science review also points to behavioral economics experiments which suggest that menthol CC users will most commonly substitute menthol CC with menthol ENDS—in scenarios where menthol ENDS are available—compared to other tobacco products, including tobacco-flavored ENDS (Denlinger-Apte et al., 2021; Shang et al., 2020). Together, these data demonstrate that adults who use menthol cigarettes prefer menthol-flavored ENDS over tobacco-flavored ENDS. However, these studies were not designed to evaluate behavior change and thus do not directly address the outcomes of complete switching or cigarette reduction. Actual product use is critical in the evaluation of product switching because the ability of a product to promote 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 user. Moreover, uptake and transition to ENDS use is a behavioral pattern that requires assessment at more than one time point. Therefore, evaluating the behavioral outcomes needed to show any benefit of the product requires observing the actual behavior of users over time. With both RCT and cohort study designs, enrolled participants are followed over a period of time, with periodic and repeated measurement of relevant outcomes. In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked

to recall their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Finally, 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.[18]

Although the current literature also includes some studies examining the impact of menthol ENDS use on smoking behavior over time, these studies do *not* substantiate that menthol-flavored ENDS provide a benefit to adult smokers sufficient to outweigh the increased risks to youth relative to tobacco-flavored ENDS, i.e., that they are more effective in promoting complete switching or significant cigarette reduction among current smokers (including menthol smokers). For instance, a longitudinal

18. Though behavioral intentions can be useful to address some questions in the PMTA assessment, there are limits to their utility as a predictor of future behavior when it comes to predicting sustained behavior change, such as product switching (Rothman et al., 2011; O'Connor et al., 2018). Indeed, the FDA Guidance, "Principles for Designing and Conducting Tobacco Product Perception and Intention Studies" (2022) notes the importance of actual use studies when evaluating patterns of use such as switching: "However, whereas a [Tobacco Product Perception and Intention] study may address how a participant intends to use the product, participants may have limited ability to forecast their future patterns of use behavior. Accordingly, patterns of use may be better assessed with data from behavioral studies, including actual use studies. For instance, behavioral study data can address a tobacco user's likelihood of completely switching to the new product and quitting smoking cigarettes."

study of menthol and non-menthol cigarette smokers who purchased JUUL pods found that non-menthol cigarette smokers who primarily used menthol/mint flavored JUUL pods (vs. tobacco-flavored pods) had higher odds of switching (aOR: 1.14; 95% CI: 1.04-1.25) at the 12-month follow-up (Goldenson et al., 2022). Although there was an association between using menthol-flavored devices and switching among non-menthol smokers, this alone does not constitute robust evidence of increased effectiveness sufficient to outweigh the known risks to youth. In particular, there was no association between using menthol/mint-flavored devices and switching overall (for all smokers), or for menthol smokers, in particular, which is the group theoretically expected to show differential success with product switching when using a menthol-flavored product. Likewise, an analysis from this study at the 30-day follow-up found that there was no significant association between use of menthol-flavored JUUL pods and increased switching rates away from cigarettes at 30-day follow-up among adult smokers (aOR: 1.04; 95% CI: 0.93-1.16) (Goldenson et al., 2021). Similarly, in a secondary analysis of Black and Latinx menthol smokers from an RCT examining ENDS flavors and switching, Nollen et al. (2022) observed that these menthol smokers were more likely to select menthol-flavored (vs. non-menthol flavored) ENDS, but that there was no difference in terms of cigarette reduction by flavor used. In sum, to provide a meaningful benefit to menthol smokers, menthol ENDS products must be shown to facilitate complete switching or significant cigarette reduction better than tobacco-flavored ENDS products. An applicant cannot satisfy its burden by relying on current scientific literature, which

does not provide robust support for such a benefit, but must instead conduct its own studies to determine whether the standard can be met.[19]

The epidemiology review also evaluated the potential benefit to adult smokers. I note that neither the epidemiology review nor the social science review identified a deficiency associated with these menthol-flavored products with respect to evidence related to adult switching at a rate beyond tobacco. Further, the epidemiology and social science reviews grouped menthol- and tobacco-flavored products together when citing a deficiency for other non-tobacco flavors in terms of needing evidence of greater complete switching or significant reduction in cigarettes smoked per day than either the tobacco or menthol flavored varieties. This grouping of tobacco and menthol together (in the epidemiology and social science reviews) reflected the perspective, at that time, that the menthol ENDS products might not necessitate the same strength of product-specific evidence of benefit that other flavored ENDS require relative to tobacco flavored ENDS, due to the potential that menthol-flavored ENDS could serve as a more effective substitute

19. Moreover, given FDA's product application review knowledge and understanding of the variability in ENDS products in terms of adult switching behavior, even if direct behavioral data regarding switching or significant cigarette reduction were to become available for products other than those in an application, product-specific data would likely still be needed to demonstrate that the specific products under review provide a benefit to adult smokers in terms of completely switching or significantly reducing cigarette use beyond that of a tobacco-flavored ENDS.

for menthol cigarettes and the social science reviewer's conclusion that menthol-flavored ENDS are less appealing to youth than some other flavors. However, as described above, the scientific literature does not demonstrate that menthol-flavored ENDS are more effective in promoting complete switching or significant cigarette reduction relative to tobacco-flavored ENDS among adult smokers (including menthol smokers). Furthermore, as noted in the section titled "*The Risk to Youth of Flavored ENDS, Including the New Products,*" I disagree with the social science reviewer's conclusion and conclude that flavored ENDS, including menthol-flavored ENDS, such as the new products, pose substantial risk to youth.

Regarding adult non-tobacco users, findings from the Consumer Perception Studies indicate low intent (among these adult non-tobacco users) to use the new products, although the findings are limited in generalizability because of methodological limitations.

Given the risk of youth use of flavored ENDS products, and given that the existing literature does not demonstrate a benefit to adult smokers that outweighs that risk, FDA could not authorize the marketing of menthol-flavored ENDS with less robust product-specific evidence than expected for other types of flavored ENDS products. Accordingly, for these menthol-flavored ENDS products, the applicant must provide a similar level of reliable and robust evidence of benefit to adult smokers as required for other types of non-tobacco-flavored ENDS products.

Because the applicant's studies and the available information do not show a differential effect for complete

switching or significant reduction in CPD for the menthol-flavored new products compared to tobacco-flavored ENDS products, the applicant has not demonstrated that the menthol-flavored new products demonstrate sufficient added benefit to adult smokers, relative to tobacco-flavored ENDS, to outweigh the known and substantial risks to youth (see Section 3.4.1.3.).

Regarding product labeling, packaging, and advertising, there are insufficient data at this time to conclude that the statements "A unique combination of vapor technology and real tobacco provides satisfying taste with no smoke smell and no ash" and "Real Tobacco. No Smoke Smell. No Ash." are misleading, and the statements do not contain scientifically false information from an engineering or chemistry perspective. Therefore, I conclude that PM0000528 should not be denied under 910(c)(2)(C) of the FD&C Act (see Section 3.4.1.6. and 3.8.3.).

As TPL I agree with the social science review that, if the new products were to be marketed, the applicant would have to include the mandatory nicotine warning statements on packages and advertising for their nicotine-containing products and kits, including but not limited to coupons for Logic Vapeleaf menthol green capsules and e-liquid cartridges (applicable for PM0000528.PD1 and PM0000528) and Logic Pro and Power e-liquid package (applicable for PM0000534 and PM0000539). However, I do not agree that the new products' user guides would require the nicotine warning because, per 21 CFR 1143.3, the warning applies to package labels and advertising; the user guides do not qualify as package labels or advertising.

I also conclude that all product labeling and marketing information has appropriate comprehension scores.

Overall, as TPL, I conclude that the applicant has not provided sufficiently reliable and robust evidence to support a finding that the menthol-flavored new products demonstrate an added benefit to adult smokers, relative to tobacco-flavored ENDS, sufficient to outweigh the known and substantial risks to youth. With respect to youth appeal and mitigation, thus far, experience shows that advertising and promotion restrictions and sales access restrictions cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH.[20] Rather, for flavored ENDS, only the most stringent mitigation measures have such mitigation potential; to date, the only such measures identified with the potential for that kind of impact have been device access restrictions. The marketing restrictions and other mitigation measures that the applicant proposed cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH, as explained in Section 3.4.1.5. Therefore, I recommend a deficiency to cite the finding that these applications

20. *See* FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry* 44 (Apr. 2020) ("The reality is that youth have continued access to ENDS products in the face of legal prohibitions and even after voluntary actions by some manufacturers."); *see also id.* at 45 (noting "data that many youth obtain their ENDS products from friends or sources in their social networks").

lack sufficient evidence demonstrating that the menthol-flavored new products have the potential to benefit adult smokers, who switch completely or significantly reduce their cigarette use, that would outweigh the substantial risk to youth (Section 5.1.; Deficiency 1).

3.5. TOXICANT EXPOSURE

The toxicology discipline evaluated in vitro genotoxicity and cytotoxicity studies that compared all new products to the 3R4F research cigarette. They also compared chemical constituents (HPHCs) from the new products' aerosol, the reference ENDS (VUSE Vibe Original and blu PLUS Classic Tobacco) and conduced a toxicity assessment.

The BCP discipline evaluated BOE from the forced switch, 60-day clinical studies (LP004, LP005).

3.5.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.5.1.1 Toxicity

Per the toxicology review:

- The CC, Pall Mall Red Kings, used as a comparison product, did not induce genotoxicity in the in vivo micronucleus assay. This result is inconsistent with in vitro data showing that CC smoke from

both the comparison product Pall Mall Red Kings and the reference cigarette 3R4F induced cytotoxicity and genotoxicity at the same cigarette smoke concentrations tested in vivo. Differences in results may be due to experimental issues related to the lack of systemic exposure leading to low sensitivity to detect DNA damage vs. in vitro system tested.

- The genotoxicity study indicates that total aerosol collected matter (ACM) and gas vapor phase (GVP) from all new products, under the conditions of the study, had no mutagenic potential in vitro in a bacterial reverse mutation assay (Ames test) at any concentration tested, either with or without metabolic activation. In contrast, total particulate matter (TPM) from 3R4F reference cigarette and CC Pall Mall Red Kings smoke produced a positive result in five strains of bacteria used in the Ames test after metabolic activation. In addition, for all new products, no evidence of mutagenic toxicity was observed in in vitro and in vivo micronucleus assays; and there was no evidence of cytotoxicity in neutral red uptake (NRU) assay under the conditions of these studies.

- In general, exposure of CC mainstream smoke tested at all the concentrations (low, mid, and high) produced toxic effects that were more severe than those produced by the new products.

- The ingredients and structural materials for the new products are in the TPMF and the provided

information is acceptable from a toxicological perspective.

- There are some caveats in comparing ENDS to combusted tobacco products: 1) these two types of tobacco products are greatly different (e.g., constituents and the ways they are used); 2) different consumer topographies and different testing regimens are used to compare them. Due to the differences, not all HPHCs reported for the new products were reported for the CC and vice versa.

- Chromium was detected in the aerosols of the new products and the comparison ENDS but was not present at sufficient levels for quantification in the CC mainstream smoke. High levels of heavy metals are known to be involved in respiratory and gastroenterology pathology and are carcinogenic. However, overall HPHCs are lower in all new products' aerosols compared to a combusted cigarette, Pall Mall Red Kings. On per TPM weight basis, HPHC levels were lower in new products' aerosols by 70%-100% compared to the CC. These HPHC levels for the new products were also lower (83%-100%) when compared to the CC levels on per nicotine yield basis.

The applicant submitted a risk assessment for the identified, partially identified, and unknown simulated leachable compounds in the new products. The applicant concluded that the potential risks to consumers from identified and partially identified

leachable compounds are acceptable but risk for the unknown leachable compound was above the benchmark value of 1.0 which indicates potential risks of concern. Although the simulated leachable compounds for all new products can be hazardous, at the low levels present, if there is any contribution towards cancer hazard, they are likely outweighed by the reduction of HPHCs by 83-99% in all new products.

3.5.1.2 Biomarkers of exposure

Per the BCP review:

- ENDS exposure increased during the course of the 60-day clinical studies (LP004, LP005), evidenced by the significant increase in urinary PG concentration in all new product cohorts.

- In LP004 and LP005, total nicotine equivalents (TNeq) were not different between PM0000528. PD1, PM0000534.PD1, PM0000539.PD1 and UB CC cohorts. TNEq was significantly lower in the Logic Vapeleaf Menthol Green product cohort compared to UB CC cohorts, indicative of the low nicotine delivery associated with the Logic Vapeleaf Menthol Green product.

- The applicant-submitted clinical studies (LP004, LP005) showed that BOEs (e.g., TSNAs, volatile organic compounds [VOCs], s-phenylmercapturic acid [S-PMA], and carboxyhemoglobin [COHb]) are generally lower in CC smokers who used the

new products compared to CC smoking cohorts. NNN, however, was not significantly lower in any of the Logic product cohorts on day 59, compared to CC cohorts; however, the NNN t1/2 (half-life; the time it takes for a drug to reach half of its initial concentration in the body) in humans is unknown.

- Although complete switching from UB CC to the new products is low, the literature and applicant-sponsored clinical studies (LP004, LP005) demonstrate that CC smokers who initiate ENDS use and significantly decrease CPD (i.e., dual users) are generally exposed to lower levels of multiple BOEs.

Per the epidemiology review:

- Biomarker data from observational studies generally show that ENDS users have higher exposure to nicotine, some VOCs, and TSNAs than do non-tobacco users (Goniewicz et al., 2018; Rubinstein, Delucchi, Benowitz, & Ramo, 2018). Some biomarker data from observational studies have also found that dual users can have higher levels of certain BOE than exclusive CC smokers (Goniewicz et al., 2018; B. L. Rostron et al., 2019).

3.5.2. Synthesis

I agree that most HPHCs and other constituents are lower in aerosol yields (from both regimens tested) from the new products compared to CC smoke yields

(see Section 3.2.1.4.). Chromium levels are significantly higher in new product aerosols compared to CC smoke, but the chemistry discipline review noted that the levels are analytically equivalent to the representative ENDS, suggesting that their presence is due to the metal components in ENDS. Furthermore, the higher chromium levels in the new products, compared to CC, are outweighed by the decreases in HPHCs associated with the new products. Nevertheless, the impact of metal exposure from ENDS has not been evaluated in the long-term health risk literature. These results are reflected in the BOE evaluated in the clinical 60-day switching studies that showed the new products are associated with lower levels of many BOE compared to CC smoking cohorts. The BCP review concluded that these lower BOE are evident even upon dual use of the new products and CC, when CC smoking decreased; indeed, the peer-reviewed literature suggests that reductions in BOE are dependent upon decreased CPD. Although the likelihood of exclusive new product use is low given the new products' low abuse liability (see Section 3.3.1.), it is likely that exclusive new product users who switch from CC would experience greater reductions in many BOE.

The toxicology review concluded that: (a) the ingredients and structural materials for the new products are acceptable; and that (b) although the simulated leachable compounds for all new products can be hazardous, at the low levels present, if there is any contribution towards cancer hazard, they are likely outweighed by the reduction of HPHCs by 83-99% in all new products. As FDA continues to explore the genotoxicological implications of

various chemical ingredients and constituents in ENDS products, the breadth of its understanding continues to develop. Here, information came to light after the toxicology review was finalized in March 2022 that suggests that the hazard associated with some ingredients and leachables associated with the new products may be greater than understood at the time of the review. Because FDA has already found that the applicant has failed to include evidence that is capable of showing a sufficient benefit to adult smokers that could outweigh the known and substantial risk to youth from flavored ENDS, FDA is denying the PMTA on that basis. In light of that determination, and because FDA's thinking with respect to toxicological risks continues to develop, it is therefore both unnecessary and premature for FDA to reach any final conclusions regarding toxicology at this time.

3.6. HEALTH EFFECTS

The toxicology discipline evaluated results from 90-day nose-only repeated inhalation non-clinical studies (95019D, 95019B, 95019F) that were conducted with adult male and female rats to evaluate toxicity endpoints, including survival, body weight, respiratory physiology, and gross observations. All new product aerosols were tested at various concentrations and compared to Pall Mall Red Kings CC smoke.

The short-term health effects of new products were evaluated through the applicant-submitted clinical studies and literature review. The BCP discipline evaluated nicotine and non-nicotine BOE in LP004 and LP005. The

medical discipline evaluated adverse experience (AE) data in all applicant-submitted clinical studies and evaluated physiological effects and BOPH associated with the new products compared to CC smoking and cessation cohorts in the clinical 60-day switching studies (LP004, LP005). In addition, they evaluated FDA's internal databases of voluntary reports related to Logic ENDS in general. Furthermore, the medical discipline evaluated the applicant-submitted literature search about ENDS and their associated health effects.

3.6.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.6.1.1 Toxicology

Per the toxicology review:

- Studies submitted by the applicant indicate that 90 days of non-clinical, repeated inhalation exposure to all new products' aerosols is associated with concentration-dependent exposure to biomarkers such as nicotine and cotinine when compared to control, demonstrating systemic exposure to nicotine. There was no accumulation or sex dependent differences observed in the non-clinical studies (95019D, 95019B, 95019F) submitted by the applicant.

- Data submitted by the applicant from 90-day inhalation studies with rats indicates that repeated

exposure to the Pall Mall Red Kings CC smoke affected body weight, increased presence of proinflammatory markers in the lungs, produced some evidence of liver toxicity, affected differential blood counts, and altered lung physiology. These changes were either not observed, or were significantly less severe, in male and female rats repeatedly exposed to all new products' aerosols. Similarly, while rats exposed to all new products' aerosols exhibited histopathological changes like hyperplasia, metaplasia, and tissue degeneration, those changes were generally less severe than those observed in rats exposed to CC smoke.

- There are several limitations to these non-clinical studies (95019D, 95019B, 95019F). No biomarkers such as reactive oxygen species (i.e., oxidative stress) or cardiovascular parameters were measured or discussed. In fact, published data suggest that user exposure to ENDS is a potential concern for cardiovascular toxicities (Buchanan et al., 2020). The applicant provided absolute and relative heart weights and gross and histopathological findings for heart and aorta. Although the applicant did not provide enough details regarding a statistical analysis plan (including the statistical power analysis) for absolute and relative heart weights in male and female Sprague Dawley rats, it follows the OECD guidelines (No. 413) of utilizing 10 male and 10 female rats in the 90-day sub-chronic study. The statistical analyses from both the applicant and a CTP statistical consult did not find significant

differences in heart weight between the study groups. In addition, there were no gross or histopathological findings in the heart or aorta of the core and recovery groups exposed to any new products' aerosol. Therefore, the toxicological evaluation determined that the applicant has adequately addressed the concerns from the toxicology perspective.

- Repeated exposure to the new products and the CC resulted in increased plasma nicotine and cotinine in a dose-dependent manner. There are no apparent sex differences or accumulation in the systemic exposure of nicotine and cotinine. Differences in time of exposure to all new products correlated with Tmax. The nicotine concentrations (AUCs) measured at the no observable effect level (NOEL) from exposure to all new products were approximately 2-fold higher than that of the CC at the lowest concentrations tested; however, HPHCs were lower for all new products when compared to the HPHCs from the CC.

- The applicant provided supporting data from ENDS published literature on cancer risk, cardiovascular effects, and other health effects (respiratory). The new products deliver similar nicotine (or less for the Logic Vapeleaf Menthol Green [PM0000528.PD1] product) than Pall Mall Red Kings, and generally have lower or non-measurable levels of unwanted HPHCs, than Pall Mall Red Kings CC.

- The evaluation of the health risks of the new products is based on a comparison to CC. However, there are some caveats in comparing ENDS to combusted tobacco products: 1) these two types of tobacco products are greatly different (e.g., constituents and the ways they are used); 2) different consumer topographies and different testing regimens are used to compare them. Due to the differences, not all HPHCs reported for the new products were reported for the CC and vice versa.

3.6.1.2 BIMO inspection findings

FDA conducted BIMO inspections for two of the five applicant-submitted clinical studies (LP004, LP005). The first site was involved in LP004 and LP005: George S. Stoica, MD at Bioclinical Research. The second site was involved in LP005: Charles S. Tomek, MD at Celerion Inc. OCE concluded there were no human subjects concerns at either site. However, OCE classified Dr. Stoica's site as Voluntary Action Indicated due to investigational findings, including missing data and inadequate documentation of blood and urine storage, that may affect data reliability. Such findings likely do not have a major impact on the overall conclusions drawn in LP004 and LP005 because the conclusions from these studies are supported by other applicant-submitted data. Dr. Tomek's site was classified as NAI and there were no data integrity concerns. These findings were considered in disciplines' assessments of the data and outcomes.

Appendix C

No BIMO inspections were recommended or conducted during 2nd cycle scientific review.

3.6.1.3 Addiction as a health endpoint

Per the BCP review:

- The abuse liability of all new products is lower than that of CC. Current CC smokers (i.e., the applicant's stated intended user population for the new products) largely dual-use the new products with CC but reduce their CPD upon initiating use of the new products. In the actual use clinical studies, TNeq was not different between CC smoking and PM0000534.PD1 and PM0000539. PD1 cohorts upon dual use. Therefore, current CC smokers are likely to maintain their nicotine addiction severity via dual use of the Logic Pro and Power Menthol products and CC. TNeq was significantly lower in the Logic Vapeleaf Menthol Green (PM0000528.PD1) cohort upon dual use compared to CC smoking cohorts, suggesting that current CC smokers may decrease their nicotine addiction severity via dual use of Logic Vapeleaf Menthol Green products and CC.

- The risks of addiction associated with the new products are similar to risks associated with using other ENDS.

Appendix C

3.6.1.4 Short and long-term health effects (clinical and observational)

Per the medical review:

- Applicant-submitted clinical studies (LP004, LP005) assessed physiological effects following a 5-day, 30-day, and 60-day switch to all new products, compared to continued CC smoking. Physiological endpoints included blood pressure, pulse rate, and lung function. For all new products, there were no distinct, clear, or consistent trends in systolic or diastolic blood pressure or pulse rate that emerged from study data over the 60-day study period after switching to the new products. Lung function measurements were largely unchanged after switching to the new products. Statistically higher forced expiratory flow 25-75% values were observed in the Logic Pro Menthol (PM0000534. PD1) product cohort after 60 days, compared to continued use of UB CC, which may be indicative of improved lung function. However, the long-term clinical implications of these changes have not been determined. Other lung parameters generally did not show significant differences.

- Elevated transaminases were noted among study participants using all new products in the 60-day clinical studies (LP004, LP005). The clinical significance of these abnormal liver enzymes is unclear. The applicant performed a liver safety assessment to address these observations which

indicated the incidence was below what could be expected in a true signal of liver toxicity. Although this conclusion was based on the criteria used for new medical drugs, no similar criteria has been established for tobacco products. This evaluation also did not consider the limited exposure participants had to the new products. The effect(s) of using these new products for more than 60 days cannot currently be determined. It may be possible for a signal to emerge with use in the broader population.

- The differences in BOPH between the Logic Power Menthol product, CC, and tobacco cessation cohorts were typically small and not statistically significant. There are currently no known definitive markers of health effects for ENDS and it remains unclear how the changes in BOPH associated with ENDS use impact long-term human health. Thus, the selected BOPH are inadequate for predicting short-term or long-term disease risk.

- The 60-day clinical studies (LP004, LP005) had extensive dual use with CC and were not powered to detect any patterns of AEs or examine long-term health consequences and are unlikely generalizable to other populations. However, it is possible that within a larger population, there could be differences among flavors for the prevalence of users affected by AEs, or the potential for abuse liability. Overall, there was not a clear, strong, and consistent pattern within

the context of the applicant-submitted clinical studies (LP004, LP005) to suggest that the new products are particularly likely to directly contribute to tobacco-related disease. The likelihood of completely switching to the new products, as compared to continuing to use CC, leading to reduced incidence of chronic tobacco-related diseases such as pulmonary disease, cardiovascular disease, or cancer in CC smokers has not been established.

Per the epidemiology review:

- The applicant did not provide conclusions or final assessments of their findings from the submitted studies or the peer-reviewed literature on the long-term health risks associated with use of the new products or for ENDS as a product class.

- The applicant relied on short-term health effect findings from two clinical studies (LP004, LP005) to describe health effects and outcomes related to use; however, the applicant did not provide justification for how short-term health effect information can be bridged to long-term outcomes.

- Some published literature suggests that ENDS use compared to never tobacco use may be associated with a higher likelihood of some health outcomes such as cardiovascular disease, respiratory disease, and oral health (although temporality may be an issue with some of these studies) (Giovanni,

Keller, Bryant, Weiss, & Littman, 2020; Osei et al., 2020; Osei et al., 2019).

- A meta-analysis found that compared to heavy CC smokers, those who reduce their CPD by at least 50% had a significant reduction in lung cancer risk (Chang, Anic, Rostron, Tanwar, & Chang, 2021). However, reductions in CC smoking have not been found to lower the risk of all-cause mortality, all-cancer risk, or other smoking/tobacco related cancers (Chang et al., 2021).

- Switching and CC smoking reduction likely reduce exposure to tobacco related toxicants (Goniewicz et al., 2017; B. L. Rostron, Corey, et al., 2020).

3.6.1.5 Likelihood and effects of product misuse

Per the medical review:

- There were no AEs reported in the applicant-submitted clinical studies (LP001-LP005) suggesting accidental exposure. It is possible that some of the AEs such as burns may represent product misuse.

- There were no AEs reported in the submitted clinical studies related to secondary exposure to the new products.

Appendix C

Per the BCP review:

- The likelihood of misuse (using the product in ways other than intended such as product modifications, dripping, and stealth use) among all new products is low. The new products are all closed ENDS with replaceable cartridges or capsules. The applicant stated that all AEs in the new product cohorts throughout the applicant-submitted clinical studies were due to product misfunction and not misuse. There are no published reports that describe misuse of the new products in the literature.

3.6.1.6 Adverse experiences

Per the medical review:

- The TPST Safety Reporting Portal search for AEs reported by the public showed six unique entries for Logic ENDS for reports submitted prior to May 18, 2021. Of the six entries, three described a health problem – one a cough, one of gingival bleeding, and one of hypoxia requiring intubation. Reviewer assessment of these problems determined that these reports were possibly related to product use. It is unknown whether the most significant health problem – hypoxia requiring intubation - is associated with the patient's reported use of a Logic ENDS. Two of the other entries were notable for the potential to

be associated with an adverse health experience – one was a product problem of a fire, and the other an environmental issue where a discarded part caused a flat tire while driving.

- An updated TPST search was conducted on February 02, 2022 to identify potential AEs reported by the public since the last search. No unique entries were for Logic ENDS were found.

- FDA is aware of several health issues regarding the use of ENDS, specifically e-cigarette or vaping product use-associated lung injury (EVALI), seizures, and thermal burns:

    - EVALI is a potential respiratory health effect that could occur in individuals who use vaping products. There were no reports of EVALI in the applicant-submitted clinical studies and there did not appear to be any subjects who experienced the constellation of symptoms indicative of EVALI as an AE that required hospitalization. However, since EVALI is associated with use of vaping products, CTP is interested in evaluating any additional information related to respiratory illness in association with ENDS and specifically the new products.

    - Participants in the applicant-submitted clinical studies (LP004, LP005) reported some neurological AEs (they were associated with

products not subject to this PMTA review), but seizures were not reported. While this data is insufficient to fully evaluate the potential association of the new products with seizures, CTP is interested in monitoring an on-going evaluation of this potential health consequence of ENDS use.

- o A few participants reported thermal burns during use; data were not provided to determine whether these were due to a product problem, product misuse, or other cause. However, the risk is still an issue regarding ENDS use overall.

- Across all new products, data showed elevated transaminases, indicative of possible hepatocellular injury in some study participants after use of the new products.

- There were no AEs reported in the submitted clinical studies related to secondary exposure to the new products.

- In the applicant-submitted clinical studies (LP004, LP005), for all new products, the majority of product emergent AEs were non-serious and reported to be either mild or moderate in severity. Almost all had improved or resolved by the study end.

Appendix C

3.6.2. Synthesis

As TPL, I agree with the toxicology discipline conclusions that the non-clinical data suggest responses to the non-clinical inhalation studies were milder and less severe than responses from CC exposure. However, the implications of these findings are undetermined at this time, as discussed above (Section 3.5.2), and this review does not reach final conclusions about the overall toxicological profile of the new products. In addition, the incidence of elevated liver enzymes (see below) merits further monitoring, particularly given its prevalence in the LP004 and LP005 clinical studies (see Section 3.6.1.4. and below).

As TPL, I agree with the BCP review that when CC smokers partially switch to the new products, and reduce CPD, total nicotine exposure stays the same (Logic Pro Menthol and Logic Power Menthol products; PM0000534.PD1, PM0000539.PD1) or is lower (Logic Vapeleaf Menthol Green product; PM0000528.PD1) than CC cohorts. Thus, the risk for addiction is mostly maintained upon dual use with the new products, although the addiction risk may be reduced in Logic Vapeleaf Menthol Green product users.

The medical review concluded that most reported AEs in the applicant-submitted clinical studies were mild and expected. Furthermore, no new product-specific AEs were identified in the TPST searches. Limited data are available related to the short-term health effects of all new products. For example, although participants in the new product cohorts had elevated liver enzymes,

their clinical significance and associations with the new products are unclear. One reason that the significance of elevated liver enzymes with new product use is unclear is that elevated liver enzymes were also observed in the CC cohort. It seems likely that there is a concomitant condition that leads to elevated liver enzymes. Elevated liver enzymes were also present in some non-clinical 90-day inhalation studies (95019D, 95019B, 95019F); because the effects were partly reversed upon exposure removal, the applicant determined them to be not toxicologically relevant.

Although no seizures were reported in the applicant-submitted clinical studies (LP004, LP005), the peer-reviewed literature suggests that seizures may be related to ENDS use. The medical review also noted that, although not reported in the applicant-submitted clinical studies, EVALI is a serious concern related to vaping product use.

Furthermore, the submitted BOPH data from the applicant-submitted 60-day clinical studies (LP004, LP005) are limited in their ability to assess the impact of the new products on human disease risk; yet it is unclear whether any currently available BOPH are appropriate to assess health risks associated with ENDS use. Furthermore, there is no data about the long-term effects of the new products and limited data about the long-term effects of ENDS, in general.

However, I also recognize that some short-term health outcomes (e.g., lung function) associated with ENDS use are significantly better than CC smoking for

individual users. Furthermore, although the long-term impacts of lower BOE or BOPH associated with ENDS is unclear (particularly with dual use), it is unlikely that these reduced exposures pose a greater health risk than continued CC smoking to individuals. While the long-term health effects of dual use were not assessed, significant reductions in systemic exposures after short-term switching and the available evidence suggest that daily use of the new products with concomitant reduction in CPD may reduce an individual's exposure to HPHCs relative to continued CC smoking alone. Furthermore, there is no information to suggest that the expected AEs or short- or long-term health risks associated with the new products differ in incidence or severity compared to other representative ENDS.

Adults who initiate the new products are likely to use them with CC (see Section 3.4.1.2.); the literature on health outcomes for CC smokers who dual use and reduce CPD is mixed. The epidemiology review noted that some dual users who drastically decrease CPD may see some health benefits, particularly for those whose long-term goal is cessation. However, use of the new products may still pose significant long-term health risks to non-tobacco users. Past Surgeon Generals' reports have suggested that reductions in smoking may lead to long-term health benefits (U.S. Department of Health and Human Services, 2014); however, the benefits associated with complete switching from CC to ENDS are much more substantial (U.S. Department of Health and Human Services, 2020). Thus, the peer-reviewed literature suggests that individual CC smokers will receive a greater health

benefit when switching to exclusive ENDS use compared to dual use, but given the lower BOE (see Section 3.5.1.2) and short-term effects (see Section 3.6.1.4.) associated with the new products, I conclude that dual use (as is likely to occur with these new products) associated with significantly reduced CPD (as evidenced in LP004 and LP005) will support lower health risks and provide health benefits by reducing HPHC exposures to CC smokers who initiate use of the new products and decrease their CPD. Because the Consumer Perception Studies indicated that intention to use among adult never tobacco users was low (see Section 3.4.1.3.), the increased health risks associated with ENDS use compared to no tobacco use among adults are outweighed by the decreased health risks among current adult CC smokers. However, this same potential benefit to smokers may be achieved by using tobacco-flavored ENDS products. As described in section 3.4.2., like other non-tobacco flavors, menthol-flavored ENDS are more appealing to youth than tobacco-flavored ENDS products and the scientific literature demonstrates they pose a known and substantial risk for youth initiation. Accordingly, the assessment for menthol-flavored ENDS is the same as for other flavored ENDS, in that, to overcome the risk to youth, an applicant must provide evidence demonstrating their menthol-flavored ENDS products provide an added benefit relative to tobacco-flavored ENDS. Such evidence has not been provided for the products that are the subject of this review.

Lastly, no significant issues of misuse were identified, and given that the new products require closed e-liquids, the potential for tampering with the new products and

associated risks of accidental exposure are minimal. Furthermore, the risk of accidental exposures among children is also minimal given the child-protective packaging and adequate testing (in nicotine-containing products). The applicant also provided adequate instructions about how the new products should be used and warnings against misuse in the products' leaflets.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

The following discussion is based on the key findings provided in the epidemiology review:

3.7.1.1 Population health impact (PHI) model

The population model submitted by the applicant used appropriate U.S. data sources for inputs, conducted data analyses using PATH data, and generally used reasonable assumptions (with some exceptions). However, it is likely that the model may have overestimated the benefits of the new products; while the applicant refers to the new products, it appears that they modeled use of all ENDS and not just the new products. The potential overestimation of the population health benefit limits the utility of the model. The population model also does not characterize the potential public health benefit for any specific new product. Further, the applicant did not present novel information from the population health model to clearly demonstrate that the menthol flavored products that

are the subject of this review increase the likelihood of complete switching or significant CC reduction among adult CC smokers compared to the tobacco-flavored new products from an epidemiology perspective.

3.7.2. Synthesis

As TPL, I agree with the limitations of the applicant-submitted population model as described in the epidemiology review: the model did not characterize the potential public health benefit for the new products. Thus, the model is not particularly informative in the evaluation of whether the new products are appropriate for the protection of the public health.

Although the applicant's population health model may have overestimated the anticipated health benefits associated with the new products' marketing, these new products are likely to be associated with a population health benefit if CC smokers completely switch to them. However, population harm would likely occur when non-tobacco users, including youth who otherwise would not have used tobacco products initiate with them (particularly when they then transition to CC smoking) and when CC smokers who would have otherwise quit all tobacco use switch to them instead.

The applicant-submitted data do not suggest that CC smokers will completely switch to the new products and dual use is the most likely use behavior; because the greatest health benefit to CC smokers is associated with cessation, the population health model may overestimate

the impact actual use of these products has on population health.

3.8. STATUTORY REQUIREMENTS

3.8.1. Public health conclusion

Based on the findings and evaluations discussed in Sections 3.1-3.7, I find that the applicant has not demonstrated that permitting the marketing of the new products would be appropriate for the protection of the public health.

3.8.2. Tobacco product manufacturing practices[21]

The PMTAs contain sufficient information to characterize the products' design and adequate processes and controls to help ensure that the new products meet the manufacturer's specifications. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in Section 906(e) of the FD&C Act.

3.8.3. Labeling

For all PMTAs, the applicant provided proposed labeling. Based on the information presented at this time, we have not concluded that the proposed labeling is false or misleading in any particular way.

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21. FDA has not promulgated a tobacco product manufacturing practices (TPMP) rule.

Appendix C

3.8.4. Product standards

There are no applicable product standards for these PMTAs.

4. ENVIRONMENTAL DECISION

4.1. DISCIPLINE FINDINGS

Environmental science concluded that the environmental assessments for all PMTAs qualified a type of Categorical Exclusions under 21 CFR 25.35(b) because they may not be introduced or delivered for introduction in interstate commerce. As TPL, I agree with this conclusion.

4.2. ENVIRONMENTAL CONCLUSION

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 tobacco product may not be introduced or delivered for introduction into interstate commerce (i.e., a marketing denial order, MDO) 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.

Appendix C

5. CONCLUSION AND RECOMMENDATION

Section 910 of the FD&C Act requires that, for a product to receive a PMTA marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute specifies that, in assessing whether the marketing of the new products would be APPH, FDA must 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. Section 910(c)(4). The APPH standard requires a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. In determining whether permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching).

Based on the information provided in the application and as described in this Technical Project Lead review, I find that the applicant has not demonstrated that permitting the marketing of the new products in the PMTAs listed above would be APPH.

This review finds a deficiency in these applications that relates to the lack of sufficient evidence demonstrating that the new products have a potential benefit to adult smokers who switch completely or significantly reduce their cigarette use that would outweigh the risk to youth. The APPH determination includes evaluating the risks and benefits to the population as a whole. For flavored ENDS, including menthol flavor, existing evidence demonstrates that the known and substantial risk to youth in particular is high. As discussed throughout this TPL review, the evidence indicates that non-tobacco-flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth. There is also a known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use.

The PMTAs provide insufficient evidence to diminish or dispel those risks in connection with the new products. The applicant did not propose any novel or materially different marketing restrictions or other mitigation measures from those that FDA has previously considered and found insufficient to mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to show APPH. Thus, the new products could be appropriate for the protection of the public health only if the PMTAs present reliable and robust evidence of a potential added benefit to adult smokers completely switching from or significantly reducing cigarette use that could outweigh that risk to youth. To effectively demonstrate the potential benefit to adult smokers in terms of product use behavior, the PMTAs would likely need to provide product-specific evidence from an RCT, LCS, or other similarly reliable

sources. FDA evaluates the sufficiency of such evidence on a case-by-case basis to determine if it makes the statutorily required showing. Moreover, tobacco-flavored ENDS may offer the same type of public health benefit claimed by flavored ENDS, i.e., increased complete switching and/or significant reduction in smoking, without posing the same degree of risk of youth uptake. Therefore, to evaluate the potential benefit to current users, FDA has reviewed the PMTAs for any acceptably strong evidence that the new products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking.

I have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate APPH. Although the PMTAs contained evidence from RCTs that evaluated the impact of the new products on switching and cigarette consumption, these studies did not demonstrate that the menthol-flavored new products were more likely to promote complete switching or significant cigarette reduction compared to tobacco-flavored products that present less risk of youth initiation and use. The other evidence provided in the PMTAs regarding the potential benefit to adult users is likewise inadequate to make the required showing, due to the absence of robust, product-specific evidence of actual behavior change, in the form of complete switching or significant reduction in CPD among adult CC smokers, beyond that of tobacco-flavored ENDS products.

Appendix C

Together, based on the information provided in the PMTAs and the available evidence, the PMTAs lack sufficient evidence to show that the new products have the potential to benefit adult smokers that would outweigh the risk to youth.

Based on my review of the PMTAs, as TPL, I determined that the new products as described in the applications and specified in Appendix A, lack sufficient evidence to demonstrate that permitting the marketing of the subject products would be appropriate for the protection of the public health. Because these new products lack premarketing authorization, 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.

Because the applicant has not demonstrated that permitting the marketing of the new products would be appropriate for the protection of the public health, a Denial letter should be issued to the applicant, citing a deficiency.

5.1. DEFICIENCIES

The following deficiency should be conveyed to the applicant:

> Your PMTAs lack sufficient evidence demonstrating that the new products have a potential to benefit adult smokers in terms

of complete switching or significant cigarette use reduction, that would outweigh the risk to youth.

There is substantial evidence that the use of menthol flavors in tobacco products, like the menthol flavors in the new products, has significant appeal to youth and is associated with youth initiation of such products. The marketing restrictions and other mitigation measures that you proposed cannot mitigate these risks to youth sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH. In light of the known risks to youth of marketing flavored ENDS (including menthol flavor), 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, longitudinal cohort study, or other evidence demonstrating the benefit of the new products to adult smokers relative to tobacco-flavored ENDS products. Such evidence should include an appropriate comparator tobacco-flavored ENDS. Reliable and robust data are needed to evaluate the impact of the new products as compared to tobacco-flavored products on adult smokers' complete switching or significant reduction in cigarette use over time because tobacco-flavored products have not been shown to present the same risks to youth as tobacco products with

other characterizing flavors. Whether other products give adult smokers comparable options for complete switching or significant cigarette reduction bears on the extent of the public health benefit that the new products arguably provide to that population. Finally, although this evidence is necessary to demonstrate that the subject ENDS provide benefits for adult smokers, it may not be sufficient to demonstrate that the marketing of the subject ENDS is appropriate for the protection of the public health: having established the benefit to adults, applications containing this evidence would still be evaluated to determine that the totality of the evidence supports a marketing authorization.

Although your PMTAs include use behavior information from randomized clinical trial studies LP004 and LP005, those studies did not demonstrate that your menthol-flavored new products are more likely to promote complete switching or significant cigarette reduction compared to tobacco-flavored products. In addition, the published literature on the role of menthol-flavored ENDS and smoking cessation or reduction is limited and does not demonstrate that menthol-flavored ENDS are more effective in promoting complete switching or significant cigarette reduction relative to tobacco-flavored ENDS.

Thus, based on your applicant-sponsored studies and the peer-reviewed studies in the literature, FDA is unable to determine whether or to what extent your menthol-flavored new products facilitate complete switching or significant cigarette reduction as compared to tobacco-flavored ENDS products. Given the known risks to youth of marketing flavored ENDS, FDA would have needed this information to demonstrate that your menthol-flavored new products (PM0000528.PD1, PM0000534.PD1, and PM0000539.PD1) would provide a benefit to adult smokers sufficient to outweigh their risk to youth.

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7. APPENDICES

7.1.1. Appendix A. New Products[22],[23]

Common Attributes of PMTAs	
Submission date	August 19, 2019
Receipt date	August 19, 2019
Applicant	Logic Technology Development LLC
Product manufacturer	Logic Technology Development LLC
Product category	ENDS (VAPES)

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

23. Effective April 14, 2022, FDA's authority to regulate tobacco products was extended to include tobacco products containing nicotine from any source. As such, nicotine source is considered a required property for unique identification. https://www.congress.gov/bill/117th-congress/house-bill/2471

Attributes	**New Tobacco Product**
STN	**PM0000528.PD1**[24]
Product name	Logic Vapeleaf Menthol Green Cartridge/ Capsule Package
Product subcategory	ENDS Other
Package type	Blister Pack
Package quantity	5 Capsules
Characterizing flavor	Menthol
Nicotine source	Tobacco
Additional properties	Mass of flavored tobacco granules per capsule: 310 mg, Nicotine Content: < 48.4 mg-dry base/g
STN	**PM0000534.PD1**
Product name	Logic Pro Menthol e-Liquid Package
Product subcategory	Closed E-Liquid

24. PD numbers were not used in previously issued letters.

Appendix C

Package type	Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Menthol
Nicotine concentration	20.0 mg/mL
E-liquid volume	1.5 mL
PG/VG ratio	70/25
Nicotine source	Tobacco
STN	**PM0000539.PD1**
Product name	Logic Power Menthol e-Liquid Package
Product subcategory	Closed E-Liquid
Package type	Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Menthol
Nicotine concentration	27.0 mg/mL
E-liquid volume	1.2 mL
PG/VG ratio	69/25
Nicotine source	Tobacco

7.1.2. Appendix B. Amendments Received.

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
September 25, 2019	September 25, 2019	PM0000545	PM0000528. PD1	Yes	Response to FDA's September 18, 2019 information request
		PM0000546	PM0000539. PD1	Yes	
		PM0000547	PM0000534. PD1	Yes	
October 22, 2019	October 22, 2019	PM0000569	PM0000528. PD1	Yes	Response to FDA's October 15, 2019 information request
		PM0000570	PM0000534. PD1	Yes	
		PM0000571	PM0000539. PD1	Yes	

Appendix C

November 1, 2019	November 1, 2019	PM0000574	All	Yes	Response to FDA's October 24, 2019 information request
		PM0000575	All	Yes	
		PM0000576	All	Yes	
November 18, 2019	November 18, 2019	PM0000578	All	Yes	Final Site Inspection Agenda
December 20, 2019	December 20, 2019	PM0000581	All	Yes	Final Site Inspection Logistics
February 27, 2020	February 27, 2020	PM0000625	PM0000534. PD1 and PM0000539. PD1	Yes	New product label information

Appendix C

July 9, 2020	July 9, 2020	PM0000825	All	Yes	Request for extension to June 26, 2020 Deficiency letter
December 17, 2020	December 17, 2020	PM0004435	All	Yes	Response to June 26, 2020 Deficiency letter

APPENDIX D — DENIAL OF REHEARING OF THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT, FILED DECEMBER 15, 2023

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 22-3030

LOGIC TECHNOLOGY DEVELOPMENT LLC,

Petitioner

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION

(FDA-1 : PM0000528.PD1,
FDA-1 : PM0000534.PD1,
FDA-1 : PM0000539.PD1)

SUR PETITION FOR REHEARING

Present: CHAGARES, *Chief Judge*, JORDAN, HARDIMAN, SHWARTZ, KRAUSE, RESTREPO, BIBAS, PORTER, MATEY, PHIPPS, FREEMAN, MONTGOMERY-REEVES, CHUNG, and AMBRO*, *Circuit Judges*

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*. Senior Judge Jordan's Vote is limited to Panel Rehearing Only.

Appendix D

The petition for rehearing filed by Petitioner Logic Technology Development LLC in the above-entitled case having been submitted to the judges who participated in the decision of this Court and to all the other available circuit judges of the circuit in regular active service, and no judge who concurred in the decision having asked for rehearing, and a majority of the judges of the circuit in regular service not having voted for rehearing, the petition for rehearing by the panel and the Court en banc, is denied.

BY THE COURT,

s/ Cheryl Ann Krause
Circuit Judge

Dated: December 15, 2023

APPENDIX E — RELEVANT STATUTORY PROVISIONS

21 U.S.C. 387j provides:

Application for review of certain tobacco products

(a) In general

(1) New tobacco product defined

For purposes of this section the term "new tobacco product" means—

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

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

(2) Premarket review required

(A) New products

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

(i) the manufacturer has submitted a report under section 387e(j) of this title; and the Secretary has issued an order that the tobacco product—

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

(II) is in compliance with the requirements of this chapter; or

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

(B) Application to certain post-February 15, 2007, products

Subparagraph (A) shall not apply to a tobacco product—

(i) that was first introduced or delivered for introduction into interstate commerce for commercial distribution in the United States after February 15, 2007, and prior to the date that is 21 months after June 22, 2009; and

(ii) for which a report was submitted under section 387e(j) of this title within such 21-month period,

except that subparagraph (A) shall apply to the tobacco product if the Secretary issues an order that the tobacco product is not substantially equivalent.

(3) Substantially equivalent defined

(A) In general

In this section and section 387e(j) of this title, the term "substantially equivalent" or "substantial equivalence" means, with respect to the tobacco product being compared to the predicate tobacco product, that the Secretary by order has found that the tobacco product—

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

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

(B) Characteristics

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

(C) Limitation

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

(4) Health information

(A) Summary

As part of a submission under section 387e(j) of this title respecting a tobacco product, the person required to file a premarket notification under such section shall provide an adequate summary of any health information related to the tobacco product or state that such information will be made available upon request by any person.

(B) Required information

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

(b) Application

(1) Contents

An application under this section shall contain—

(A) full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products;

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

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

(D) an identifying reference to any tobacco product standard under section 387g of this title which would be applicable to any aspect of such tobacco product, and either adequate information to show that such aspect of such tobacco product fully meets such tobacco product standard or adequate information to justify any deviation from such standard;

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

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

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

(2) Referral to Tobacco Products Scientific Advisory Committee

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

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

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

(c) Action on application

(1) Deadline

(A) In general

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

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

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

(B) Restrictions on sale and distribution

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

(2) Denial of application

The Secretary shall deny an application submitted under subsection (b) if, upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product, the Secretary finds that—

(A) there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health;

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

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

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

(3) Denial information

Any denial of an application shall, insofar as the Secretary determines to be practicable, be

accompanied by a statement informing the applicant of the measures required to remove such application from deniable form (which measures may include further research by the applicant in accordance with 1 or more protocols prescribed by the Secretary).

(4) Basis for finding

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

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

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

(5) Basis for action

(A) Investigations

For purposes of paragraph (2)(A), whether permitting a tobacco product to be marketed would be appropriate for the protection of the public health shall, when appropriate, be determined on the basis

of well-controlled investigations, which may include 1 or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product.

(B) Other evidence

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

(d) Withdrawal and temporary suspension

(1) In general

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

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

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

(C) that the applicant—

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

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

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

(D) on the basis of new information before the Secretary with respect to such tobacco product, evaluated together with the evidence before the Secretary when the application was reviewed, that the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or installation of such tobacco product do not conform with the requirements of section 387f(e) of this title and were not brought into conformity with such requirements within a reasonable time after receipt of written notice from the Secretary of nonconformity;

(E) on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when the application was reviewed, that the labeling of such tobacco

product, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary of such fact; or

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

(2) Appeal

The holder of an application subject to an order issued under paragraph (1) withdrawing an order issued pursuant to subsection (c)(1)(A)(i) may, by petition filed on or before the 30th day after the date upon which such holder receives notice of such withdrawal, obtain review thereof in accordance with section 387*l* of this title.

(3) Temporary suspension

If, after providing an opportunity for an informal hearing, the Secretary determines there is reasonable probability that the continuation of distribution of a

tobacco product under an order would cause serious, adverse health consequences or death, that is greater than ordinarily caused by tobacco products on the market, the Secretary shall by order temporarily suspend the authority of the manufacturer to market the product. If the Secretary issues such an order, the Secretary shall proceed expeditiously under paragraph (1) to withdraw such application.

(e) Service of order

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

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

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

(f) Records

(1) Additional information

In the case of any tobacco product for which an order issued pursuant to subsection (c)(1)(A)(i) for an application filed under subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, as the Secretary may by regulation, or by order with respect

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

(2) Access to records

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

(g) Investigational tobacco product exemption for investigational use

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

Appendix E

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

Judicial review

(a) Right to review

(1) In general

Not later than 30 days after—

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

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

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

(2) Requirements

(A) Copy of petition

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

(B) Record of proceedings

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

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

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

(C) Definition of record

In this section, the term "record" means—

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

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

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

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

(v) any other information identified by the Secretary, in the administrative proceeding held

with respect to such regulation or order, as being relevant to such regulation or order.

(b) Standard of review

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

(c) Finality of judgment

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

(d) Other remedies

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

(e) Regulations and orders must recite basis in record

To facilitate judicial review, a regulation or order issued under section 387f, 387g, 387h, 387i, 387j, or

387p of this title shall contain a statement of the reasons for the issuance of such regulation or order in the record of the proceedings held in connection with its issuance.