No. _____

In the Supreme Court of the United States

GRIPUM LLC,

Petitioner,

v.

UNITED STATES
FOOD & DRUG ADMINISTRATION,

Respondent.

On Petition for Writ of Certiorari to the
United States Court of Appeals
For the Seventh Circuit

PETITION FOR WRIT OF CERTIORARI

J. GREGORY TROUTMAN
Counsel of Record
TROUTMAN LAW OFFICE, PLLC
4205 Springhurst Boulevard,
Suite 201
Louisville, KY 40241
(502) 412-9179
jgtatty@yahoo.com

QUESTIONS PRESENTED

The questions presented for review are:

(1) What level of judicial deference, if any, is afforded the determinations of administrative agencies which have a conflict of interest *vis-à-vis* regulated parties;

(2) Whether an agency violates the Administrative Procedure Act when it changes a key evidentiary requirement without prior notice to regulated parties after the expiration of the deadline for complying with such new requirement; and

(3) Whether an agency violates the Administrative Procedure Act when it rigidly adheres to a presumption which is overbroad and lacks evidentiary support.

PARTIES TO THE PROCEEDING

Petitioner is Gripum LLC. The Petitioner was the Petitioner-Appellant below.

Respondent is the United States Food and Drug Administration. The Respondent was the Respondent-Appellee below.

CORPORATE DISCLOSURE STATEMENT

Petitioner Gripum is an Illinois limited liability company and is neither a parent corporation nor a publicly held company owning 10% or more of another corporation's stock.

RELATED PROCEEDINGS

Gripum LLC vs FDA., 21-2840, United States Court of Appeals for the Seventh Circuit, Opinion entered on August 29, 2022.

FDA Marketing Denial Order on PM0001689, entered on September 8, 2021.

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GLOSSARY

APA	Administrative Procedure Act
ENDS	Electronic Nicotine Delivery System
FDA	United States Food and Drug Administration
FDCA	Food, Drug and Cosmetic Act
HHS	United States Department of Health and Human Services
PMTA	Pre-Market Tobacco Products Application
TCA	Family Smoking Prevention and Tobacco Control Act

PETITION FOR A WRIT OF CERTIORARI

This case concerns a novel industry and whether the United States Food and Drug Administration (FDA) violated the Administrative Procedure Act, codified as 5 U.S.C. § 551, *et. seq*., as to Gripum's Pre-Market Tobacco Application (PMTA) for flavored E-Liquids used in Electronic Nicotine Delivery System (ENDS) products.

This case concerns: (i) the deference due FDA's marketing decisions as to ENDS products given a conflict of interest and (ii) FDA's marketing decisions arbitrarily adhering to a superseded presumption that all non-tobacco flavored products equally motivate youth initiation.

OPINION BELOW

This petition seeks review of the opinion of the United States Court of Appeals for the Seventh Circuit, reported as *Gripum LLC v. FDA*, 47 F.4th 553 (7th Cir. 2022). (App. 1a – 15a, *infra*). Such opinion upheld a marketing denial order which FDA issued to Gripum. (App. 16a – 20a, *infra*).

JURISDICTION

The Court of Appeals entered its opinion on August 29, 2022. (App. 1a – 15a, *infra*). The Court has jurisdiction under 28 U.S.C. § 1254(1) to hear this case by writ of certiorari which is timely filed within the Rule 13.1 time period as extended by the December 1, 2022, order in 22A482.

STATUTORY PROVISIONS INVOLVED

A. 5 U.S.C. § 706(2): To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action. The reviewing court shall—

* * *

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

* * *

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

B. 21 U.S.C. § 387j: (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.

* * *

C. 21 U.S.C. § 387*l*(b): (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.

INTRODUCTION

This Court held in *Ward v. Monroeville*, 409 U.S. 57 (1972) that a town's mayor had an impermissible conflict of interest when operating an administrative court that imposed fines which substantially comprised its budget. This case presents a similar conflict of interest on a greater scale given FDA's financial interest in the outcome of ENDS product marketing decisions.

ENDS products came to the United States in the late 2000's. They do not contain any part of a

tobacco plant and their use does not involve combustion or many of the toxic substances associated with smoking. ENDS products use E-Liquids which are a solution of propylene glycol, vegetable glycerin, food-grade flavorings, and in some cases, nicotine of varying concentrations. Nicotine comes from tobacco plants, another plant,[1] or is made synthetically. Gripum's E-Liquids use tobacco-derived nicotine.

The industry is segmented into the open- and closed-systems which track their manufacturers' size, and the products' physical characteristics and retail channels. All first-generation products were of the closed-system variety; made by legacy tobacco companies although small companies later entered the market. Such products have two distinctive features: (1) small device size and (2) a disposable pre-filled cartridge or fully disposable device[2] with a limited variety of flavors. The device batteries are not powerful and thus customer satisfaction requires high nicotine E-Liquids. Such products are usually sold in convenience stores.

Consumer dissatisfaction with the low device power and poor E-Liquid quality of early closed-

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[1] Domino, E., *et. al.*, *The Nicotine Content of Common Vegetables*, N. ENG. J. MED., (Aug. 5, 1993) (identifying tomatoes, potatoes, cauliflower, and eggplant as plant-based nicotine sources).

[2] Disposable devices are an evolution of the closed-system segment.

system products led to the birth of the open-system segment. Its devices are larger and have powerful, rechargeable batteries; circuitry to regulate the device's thermal parameters; and interchangeable and refillable E-Liquid tanks. The increased device power allows the use of E-Liquids with a lower nicotine concentration. The advent of these devices led consumers to create their own E-Liquids; evolving into many brands and complex manufacturing operations with certified labs and clean rooms. These new products also led to a burgeoning specialty retailer sector devoted to serving an older customer base[3/4]

ENDS products have caused significant smoking reductions,[5] and FDA has a long professed their benefits. The former Director of FDA's Center for Tobacco Products (CTP), the branch which regulates tobacco products, opined in 2014 that it "would be good for public health" if

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[3] Pattinson, J., *et al., Vape shops: Who Uses Them and What Do They Do?* BMC PUBLIC HEALTH, 18:541 (Apr. 23, 2018).

[4] Miller, *V., "New FDA regulations could damage Nevada's vapor industry"*. Las Vegas Sun. Greenspun Media Group. (Aug. 28, 2016).

[5] Shu-Hong Zhu, *et al.*, *E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys*. BRITISH MED. J., 358:j3262 (Jul. 26, 2017).

adult smokers "completely switch all of their cigarettes" to an ENDS product.[6] FDA's then-Commissioner agreed.[7] FDA still professes this.[8]

FDA has stressed the importance of following a science-based approach concerning ENDS products. Such approach has stark consequences as the World Health Organization estimates that a billion people will die this century from tobacco-related illnesses.[9] This equates to approximately 530,000 Americans annually.[10] A significant association exists between ENDS product sales

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[6] FDA, Statement of Mitchell Zeller, "*Progress and Challenges: The State of Tobacco Use and Regulation in the U.S.*" at 1:59:00, (May 14, 2014).

[7] C-SPAN, *FDA Commissioner on E-Cigarettes and Public Health Concerns*, at 10:25, (Sept. 25, 2018).

[8] Perrone, M., *Insider Q&A: FDA official on vaping's "promise or peril,"* The Associated Press, (Sept. 26, 2022).

[9] Cropley, E., *Smoking could kill 1 billion this century: WHO*, Reuters, (Jul. 2, 2007).

[10] GBD 2019 Tobacco Collaborators, *Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019*, Lancet, v. 397; 10292, at 2337-2360 (Jun. 19, 2021).

and decreased cigarette use.[11] Their daily use by smokers with no plans to quit is correlated with subsequent plans to do so.[12] There are substantial benefits: avoiding 1.8 million American deaths and saving 38.9 million life years by 2060,[13] and substantially reversing the mortality risks of smokers, particularly for those under age 45.[14]

In 2016, FDA assumed regulatory authority over ENDS products pursuant to a 2009 federal law which required an application for market approval even if products pre-dated such authority. Such law exempted combustible tobacco

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[11] Selya, A., *et. al., Higher Sales of Electronic Nicotine Delivery Systems (ENDS) in the US Are Associated with Cigarette Sales Declines, according to a Trend Break Analysis*, Qeios (Oct. 24, 2022).

[12] Kasza K.A., *et. al*., *E-cigarette use and change in plans to quit cigarette smoking among adult smokers in the United States: Longitudinal findings from the PATH Study 2014-2019*. ADDICT. BEHAV., (Sept. 22, 2021).

[13] Levy, *et al*., *Public Health Implications of Vaping in the USA: the Smoking and Vaping Simulation Model*, POPUL. HEALTH METRICS, (Apr. 17, 2021).

[14] Thomson, B., *et. al., Association Between Smoking, Smoking Cessation, and Mortality by Race, Ethnicity, and Sex Among US Adults*, JAMA NETWORK OPEN, 2022;5(10) (Oct. 24, 2022).

from this requirement.[15] The success of ENDS products in converting smokers, however, poses a budgetary conflict for FDA as user fees computed upon the sale of combustible tobacco comprise more than 95% of CTP's annual budget.[16] ENDS product manufacturers do not pay user fees.

FDA thus has an incentive to maximize user fees akin to the mayor's incentive to maximize fines in *Ward*. The user fee issue means that E-Liquid manufacturers, like the parties who appeared before the mayor in *Ward*, must face an arbiter who lacks detachment and neutrality. FDA acknowledges the benefits of ENDS products for adults and the low risk of youths using the kind of products which Gripum manufactures but it then ignored these acknowledgments as to such products. George Mason's observation that "[t]he purse and the sword ought never to get into the same hands," THE RECORDS OF THE FEDERAL

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[15] The 2009 law subjected a subset of tobacco products to immediate regulation and delegated FDA authority to add more products. Gripum ponders the constitutionality of the delegation as a major question given *West Virginia v. EPA*, 597 U.S. ___, 142 S.Ct. 2587 (2022).

[16] Depart. of Health and Human Serv., *Fiscal Year 2023, Food and Drug Administration, Justification of Estimates for Appropriations Committees*, at 32.

CONVENTION OF 1787, Vol. 1, at 139-40 (M. Farrand ed. 1937), evidences the need for review.

STATEMENT OF THE CASE

Gripum is an Illinois limited liability company which manufacturers flavored open-system E-Liquids, explained *infra*. Gripum is a "co-packer," as it manufactures third-party products owned using their proprietary formulas. Understanding this case requires the Court to consider some basics about the industry.

1. Tobacco Control Act and Deeming Rule.

In June 2009, Congress enacted the Family Smoking and Tobacco Control Act (TCA), 123 STAT. 1776, codified as 21 U.S.C. §§ 387, *et. seq*. The TCA operates upon the definition of "tobacco products" found at 21 U.S.C. § 321(rr)(1). Congress subjected only four classes of tobacco products to the TCA's requirements, 21 U.S.C. § 387a(b), and authorized the Secretary of the Department of Health and Human Services to add other products through a regulatory deeming.[17] *Id.*, at § 387a(b).

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[17] The Secretary delegated the deeming authority to FDA's Commissioner, FDA Staff Manual Guide, 1410.10 (Nov. 17, 2015), who then sub-delegated such authority to the Associate Commissioner for Policy. FDA Staff Manual Guide, 1410.21 (Jul. 5, 2012).

On May 10, 2016, FDA brought ENDS products under its control through its "Deeming Rule," 81 FED. REG. 28,974 (May 10, 2016), codified as 21 C.F.R. § 1143.1, effective August 8, 2016. The Rule mandated a series of requirements, including the capstone PMTA. The PMTA process is "onerous," *Wages and White Lion Invest. v. FDA*, 16 F.4th 1130, 1134 (5th Cir. 2021), and FDA's miscalculations made the process more so.

FDA set its deadlines upon expecting 1,250 to 2,500 PMTAs;[18] an underestimate by a factor of 2,700 as it received 6,700,000 PMTAs. Yes, you read that correctly. FDA's miscalculation became apparent in November 2016 when the mass of initial product registrations overloaded its online portal. FDA responded by extending the registration deadline[19] and serially extending future deadlines. FDA's most significant extension was its August 2017 four-year delay of the PMTA deadline, as a part of a larger policy shift towards promoting less harmful tobacco products. *See* 82 FED. REG. 37,459, *et. seq*. (Aug. 10, 2017).

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[18] FDA, *Final Regulatory Impact Analysis Final Regulatory Flexibility Analysis Unfunded Mandates Reform Act Analysis*, p. 48 (May 2016).

[19] FDA, *Registration and Product Listing for Owners and Operators of Domestic Tobacco Product Establishments*, 13 (Dec. 2017) (identifying the registration extension).

FDA failed to take this regulatory step through notice-and-comment rulemaking and anti-tobacco advocates challenged the new PMTA deadline. *Amer. Acad. of Pediatrics v. FDA*, 379 F.Supp.3d 461, 494 (D. Md. 2019) held that FDA's PMTA deadline extension required notice-and-comment rulemaking. It imposed a 10-month deadline based upon FDA revision of its PMTA expectancy to 6,800;[20] a figure off by a factor of about 980.[21]

2. FDA Guidance and Review Process.

FDA did not publish a final PMTA rule until more than a year after the court-mandated deadline. FDA instead issued guidance in June 2019, which acknowledged that "limited data may exist from scientific studies and analyses" and that it did not expect applicants to conduct long-term studies to show the potential benefits and risks from information contained in the PMTA. 84 FED. REG. 27,200 (Jun. 12, 2019). In September 2019, FDA issued a *proposed* final PMTA rule which simply urged stakeholders to follow its June 2019 guidance and again reiterated the expectation that

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[20] Decl. of Mitchell Zeller, *Amer. Acad. of Pediatrics,* filed June 12, 2019, *ECF#120-1.*

[21] Such figure is curious given FDA's prior acknowledgment that over 400 million ENDS products were registered and that it was unlikely to complete a review within 1-year if a PMTA was filed for "only a portion" of those products. FDA, *Perspective: FDA's Preparations for the September 9 Submission Deadline* (Aug. 31, 2020).

PMTAs did not have to include long-term clinical studies. 84 FED. REG. at 50,619 (Sept. 25, 2019).

In August 2020, FDA crafted a memorandum (August Memorandum), some three weeks before the PMTA deadline, which articulated its historic review approach; a "bundling and bracketing" process for open-system E-Liquids. App. at 47a–48a. FDA's goal was to "increase the likelihood" of receiving a marketing order. *Id.* This was consistent with FDA's June 2019 guidance[22] and logical given the January 2020 promises by Secretary Azar that FDA would both work with the small E-Liquid manufacturers to "shepherd" their PMTAs and create a streamlined PMTA pathway for open-system E-Liquids.[23] FDA even represented in June 2021, that it had streamlined the PMTA review process.[24]

FDA published its final PMTA rule on October 5, 2021—more than a year after the PMTA

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[22] The August Memorandum did not predicate a review upon long-term studies showing an increased likelihood of smoking cessation versus tobacco-flavored E-Liquids and did not focus on whether products motivated youth initiation.

[23] *Interview with Alex Azar*, The Scott Sands Show, WSPD-AM, (Jan. 21, 2020). https://soundcloud.com/jamesjarvis-1/azar-scott-sands-show.

[24] FDA, June 2021 Webinar Transcript, at 28, 35, https://tinyurl.com/4jbhayuu.

deadline and weeks after it issued serial marketing denial orders—to be effective on November 4, 2021.[25] FDA again reiterated that it did "not expect" long-term clinical studies for each PMTA.[26] Instead, FDA articulated that it "expect[ed] that it should be able to rely on other valid scientific evidence to evaluate some PMTAs." *Id*.

3. Gripum's PMTA and FDA's Denial.

On September 8, 2020, Gripum filed a PMTA for 281 flavored E-Liquids; comprising more than 3,400 pages with citations to numerous published scientific studies which established something FDA already knew and acknowledged—the harm-reduction potential of ENDS products.

On May 25, 2021, FDA accepted Gripum's PMTA and moved it to scientific review on August 23, 2022. FDA did not conduct a review according to the August Memorandum which it abandoned without explanation. It did not conduct a scientific review but instead used a "check-the-box" routine to determine the presence of long-term studies and ended its review upon noting their absence. On September 8, 2021, FDA issued Gripum a marketing denial order. App. 16a – 20a.

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[25] FDA, *Premarket Tobacco Product Applications and Recordkeeping Requirements*, 86 FED. REG. 55,300, *et. seq*. (Oct. 5, 2021).

[26] *Id.*, at 55,387.

On October 8, 2021, Gripum timely filed a Petition for Review in the United States Court of Appeals for the Seventh Circuit. On November 4, 2021, the court stayed FDA's marketing denial order. On August 29, 2022, the court issued an opinion which denied Gripum's Petition. The court accorded deference to FDA's presumption that all flavored E-Liquids motivate youth initiation and held that FDA did not deceive Gripum in its pre-PMTA declarations. The court also refused to consider the August 2020 Memorandum.

REASONS FOR GRANTING THE PETITION

This Court has said a lot during recent terms about the scope of congressional delegations of authority to agencies; how their management is chosen; and how they operate. *See e.g.*, *Lucia* v. *SEC*, 585 U.S. ___, 138 S.Ct. 2044 (2018); *Carr v. Saul*, 593 U.S. ___, 141 S.Ct. 1352 (2021); *Seila Law LLC v. Consumer Financial Protection Bureau*, 591 U.S. ____, 140 S.Ct. 2183 (2020); *Collins v. Yellen*, 594 U.S. ___, 141 S.Ct. 1761 (2021); *American Hospital Association v. Becerra*, 596 U.S. ____, 142 S.Ct. 1896 (2022); and *West Virginia, supra*. This case presents an opportunity to add to that story regarding the deference to be afforded when agencies have a conflict of interest.

This Court recognizes deference to an agency's reasonable interpretation of an ambiguous statute, *Chevron v. Natural Resources Defense Council*, 467 U.S. 837 (1984); an agency's interpretation of its own regulations, *Auer v.*

Robbins, 519 U.S. 452 (1997); and an agency's interpretive rules, *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944). These cases did not address what deference, if any, courts should afford agency determinations when they have a conflict of interest. Gripum is not asking the Court to abandon the existing standards but instead determine that *de novo* review is applicable when a conflict of interest impairs an agency.

Finally, the Court should consider whether FDA acted arbitrarily by applying a regulatory presumption that all flavored E-Liquids motivate youth initiation. FDA's presumption was arbitrary as being contrary to both its own guidance and more contemporaneous data. A circuit split exists concerning FDA's application of its presumption to open-system flavored E-Liquid PMTAs which has ripened the legal landscape for review.

The Eleventh Circuit recently held in *Bidi Vapor LLC v. FDA*, 47 F.4th 1191 (11th Cir. 2022) that FDA arbitrarily applied a one-size-fits-all presumption concerning the risks of youths using flavored E-Liquids to both market segments.[27] The court noted that FDA's own data and guidance recognized the significantly different youth initiation risks between the two market segments.

A circuit split exists, however, regarding the arbitrariness of FDA's youth risk presumption

[27] *Bidi Vapor* involved six manufacturers and three consolidated appeals.

given the adverse opinions by the Third Circuit in *Liquid Labs LLC v. FDA*, 52 F.4th 533 (3rd Cir. 2022); the Fourth Circuit in *Avail Vapor, LLC v. FDA*, 55 F.4th 409 (4th Cir. 2022); the Fifth Circuit in *Wages and White Lion Invest. v. FDA*, 41 F.4th 427 (5th Cir. 2022),[28] the Seventh Circuit in *Gripum* and the District of Columbia Circuit in *Prohibition Juice Co. v. FDA*, 45 F.4th 8 (D.C. Cir. 2022).[29] This circuit split makes inconsistent future marketing decisions likely.

A. Agencies should be afforded no deference when they have a conflict of interest *vis-à-vis* regulated parties.

The federal courts have spoken volumes about agency deference but have not significantly questioned agency detachment and neutrality due to a conflict of interest. FDA lacked detachment and neutrality because of a budgetary stake in its regulatory decisions.

A core principle underlying our republic is that neutral and detached arbiters will adjudicate disputes. *See e.g.*, *Ward*, *supra.*, and *In re*

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[28] On January 19, 2023, the Fifth Circuit granted *en banc* rehearing of its July 18, 2022, opinion in favor of FDA and accordingly vacated such opinion.

[29] Additional cases are pending in: *Magellan v. FDA*, (Second Circuit); *BMF, LLC v. FDA*, (Fourth Circuit); *SWT v. FDA*, (Fifth Circuit); and *Lotus v. FDA*, (Ninth Circuit).

Murchison, 349 U.S. 133 (1955). Such cases, like here, involved key decisions by arbiters who lacked detachment and neutrality. This Court holds that a conflict of interest merely requires the "possible temptation" and not proof of actual bias. 409 U.S. at 60; 349 U.S. at 136.

User fees pegged to the sale of combustible tobacco[30] fund CTP's annual budget. ENDS products have helped reduce the adult smoking rate to an all-time low. This creates an extricable conflict of interest because user fees fund more than 95% of CTP's budget[31] and means it has a stake in every ENDS product regulatory decision.[32] It is not surprising that FDA predicted in May 2016 that the Deeming Rule would result in "significant [ENDS] product exit and reduced reentry."[33] It begs the question how FDA knew such fact before receiving any PMTAs. FDA ultimately fulfilled its prophesy by rejecting all flavored E-Liquids adjudicated to date.

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[30] 21 U.S.C. § 387s.

[31] Department of Health and Human Services, Fiscal Year 2023, *supra.*, at 32.

[32] FDA's conflict of interest is not limited to CTP. *See* Jewitt, C., *F.D.A.'s Drug Industry Fees Fuel Concerns Over Influence,* The New York Times (Sept. 15, 2022).

[33] FDA, *Final Regulatory Impact Analysis*, *supra.*, at 20.

FDA will no doubt disclaim any conflict of interest[34] and assert that its marketing decisions were not colored by the user fee disparity.[35] That narrative would naturally beg the question as no party alleged to have a conflict of interest can ever fairly judge the existence of a conflict or whether it affected their decisions.[36] A fox would never admit having an adverse interest to a chicken farmer. Yet, you will not see chicken farmers allow foxes to guard their hen houses for obvious reasons.

Agency conflicts of interest are not always budgetary. An agency also has a conflict of interest when its management shares a coziness with non-governmental organizations or bows to political pressure as occurred in *D.C. Federation of Civic Assn's v. Volpe*, 459 F.2d 1231 (D.C. Cir. 1971). In

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[34] FDA, *FDA Makes Significant Progress in Science-Based Public Health Application Review, Taking Action on Over 90% of More Than 6.5 Million 'Deemed' New Tobacco Products Submitted* (Sept. 9, 2021).

[35] FDA acknowledges the inability to collect user fees from ENDS product manufacturers is a significant mission challenge. *See* Reagan-Udall Foundation, *Operational Evaluation of Certain Components of FDA's Tobacco Programs*, 11 (Dec. 19, 2022).

[36] Even King David recognized this proposition centuries ago in asking "[w]ho can discern his own errors?" *Psalm* 19:12.

this instance, FDA's conflict of interest is not merely budgetary as it has bowed to pressure from legislators and non-governmental organizations when crafting regulatory decisions. In June 2021, a House oversight subcommittee grilled FDA's commissioner about the failure to adjudicate ENDS product PMTAs.[37] The subcommittee's chair then had discussions with FDA's commissioner and a key anti-vaping organization on such subject and boasted about their close alliance.[38] This political pressure explains FDA's pivot from its August 2017 harm reduction strategy and promise of a streamlined review process, its adoption of a secret review standard, and its mass issuance of marketing denials.

The Senate Judiciary Committee chair applied more pressure in June 2022 by demanding that FDA's commissioner either resign or reject all

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[37] *An Epidemic Continues: Youth Vaping in America*: Hearing before Subcomm. of H. Comm. on Oversight and Reform, 117th Cong., (Jun. 23, 2021).

[38] Parents Against Vaping E-Cigarettes, *An Update from Congressional Champions on FDA's Decision to Order JUUL Off the Market*, at 7:10 (Jun. 24, 2022). https://www.dropbox.com/s/k2j1x97ha3yd1ao/pavemp4.mp4?dl=0

remaining ENDS products.[39] The chair then communicated with FDA's commissioner and CTP's director in September 2022.[40] Shortly thereafter, CTP's director overruled FDA's Office of Science opinion that the Logic Technology menthol ENDS products were appropriate for marketing based upon scientific review.[41] The application of undue pressure is evident regarding FDA's adjudication of flavored E-Liquid PMTAs as discussed above.[42] The separation of powers does not seemingly exist between FDA and the legislative branch, and FDA's decision also suggests a policy to ban all flavored E-Liquids outside the TCA's rulemaking process. *See* 21 U.S.C. § 387g.

The Court can reasonably question the extent of deference to be afforded FDA's PMTA

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[39] Statement of Sen. Dick Durbin, *Durbin Investigation Finds More Than 750,000 Kids Have Picked Up Vaping Since FDA's Missed Deadline To Regulate E-Cigarettes*, (Jun. 22, 2022).

[40] Office of Senator Dick Durbin, *Durbin Meets with New Director of FDA's Center for Tobacco Products*, (Sept. 29, 2022).

[41] *See Logic Technology Development LLC v. FDA*, No 22-3030 (3rd Cir) at ECF #34-2, p. 2-3 and ECF #34-3, at 3, filed Dec. 12, 2022.

[42] *See also* McDonald, J., *AVM Files Senate Ethics Complaint Against Durbin*, Vaping 360 (Oct. 17, 2022).

adjudications. The question then becomes what level of deference should be afforded when an agency has a conflict of interest. Courts should not afford any deference to agency determinations which are tainted by a conflict of interest in lieu of applying a *de novo* review.

B. FDA arbitrarily abandoned its existing review process after the PMTA deadline.

Next, the Court should accept review to consider the propriety of FDA's arbitrary midstream PMTA process shift. The TCA prohibits manufacturers from introducing any "tobacco product" into interstate commerce which was not on the market prior to February 15, 2007, absent a marketing order. FDA must predicate its marketing decisions upon a tobacco product being "appropriate for the protection of public health". 21 U.S.C. § 387j(c)(4). Congress requires that FDA weigh the benefits of cessation across the "population as a whole" against the risk of initiation against the same population. *Id.*

FDA has not set any threshold metrics or identified a comparator product for measuring the benefits and risks of flavored E-Liquids as to the population as a whole.[43] FDA instead lumped all such flavored products into one basket when considering the risks of youth initiation but disregarded the statutory mandate to consider

[43] Reagan-Udall Foundation, *supra.*, at 15.

benefits to youths who use them to either stop smoking or in lieu of smoking.

This Court prohibits agencies from "depart[ing] from a prior policy *sub silentio*" or simply disregarding existing rules. *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009). Agencies must also "provide regulated parties fair warning" of what it "prohibits or requires" in enforcing regulations. *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156 (2012) (quotation omitted). These principles preclude agencies from announcing a position, lulling parties to follow it, and then creating an "unfair surprise" by pivoting to an unannounced position which penalizes reliance on the prior position. *Id.,* at 156-57 (quotation omitted). These principles apply to the agency actions based upon informal guidance. *See e.g.*, *Morton v. Ruiz*, 415 U.S. 199, 235 (1974).

FDA has made a mockery of these principles. FDA's June 2019 guidance reassured the industry that it did not expect long term studies; it promised at least one deficiency letter and an opportunity to remedy deficiencies;[44] and it articulated a streamlined PMTA review process. FDA, however, abandoned this without prior notice or explanation in lieu of an unannounced evidentiary standard which required specific proof that flavored E-Liquids were more effective at causing smoking cessation than a tobacco-flavored product, App. at

[44] *See* FDA, June 2021 Webinar, *supra*.

17a-18a. FDA expected such analysis from manufacturers but never identified a comparator product.[45]

FDA justified its pivot by a post-hoc mindset evolution of what it "learned" from "review[ing] PMTAs for flavored ENDS."[46] App. 23a and 24a. It is reasonable for FDA to change its mindset as experiences evolve. FDA, however, should have acknowledged such evolution and articulated a "detailed justification" *before* the PMTA deadline instead of abandoning its stated expectations. *Encino Motorcars, LLC v. Navarro,* 579 U.S. ___, 136 S. Ct. 2117, 2125 (2016) (quotation omitted).

FDA likely realized it could not comply with the court-imposed deadline[47] but never sought relief from such constraint and instead pulled the "surprise switcheroo" initially found by the Fifth

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[45] FDA has a "zero tolerance" youth use policy with respect to ENDS products. This is inconsistent with regulations adopted pursuant to the 1992 *Synar Amendment*, 106 STAT. 394 (Jul. 10, 1992), which set a 20% tolerance for age-related tobacco sales violations. 61 FED. REG. 1492 (Jan. 19, 1996), codified as 45 C.F.R. pt. 96. FDA disregarded such tolerance *vis-à-vis* flavored ENDS products without a rational explanation.

[46] FDA employed this same explanation in its marketing decisions for all other flavored open-system E-Liquids adjudicated to date.

[47] *See* Reagan-Udall Foundation, *supra.*, at 11.

Circuit. 16 F.4th at 1138. The Seventh Circuit erred in giving deference to FDA based upon its inherent conflict of interest and unexpected, after-the-fact evidentiary requirement.

C. FDA arbitrarily based its marketing decision upon a flawed presumption rooted in superseded data.

5 U.S.C. § 706(2)(A) looks to whether an agency acted arbitrarily. The Seventh Circuit erred because FDA applied an overbroad and flawed presumption that all flavored E-Liquids equally drive youth initiation. FDA predicated its marketing decisions upon such presumption despite its own contrary guidance and refused to recalibrate its position as new data better clarified the divergent risks as to the two market segments.

1. FDA's own guidance belies its broad-brush treatment.

In early 2020, FDA banned the sale of non-tobacco flavored closed-system products pending marketing review based upon its determination that they were the most often used by youths.[48] This was a proper balancing which considered that certain attributes of closed-system products (design and ease of concealment and purchase)

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[48] FDA, *Enforcement Priorities for Electronic Nicotine Delivery System (ENDS) and Other Deemed Products on the Market without Premarket Authorization (Revised): Guidance for Industry* (Apr. 2020). 85 FED. REG. 23,973 (Apr. 30, 2020).

appealed to youths versus the public health benefit to adults of flavored open-system products which did not have such youth-appealing attributes.

FDA abandoned this recognition as to flavored open-system E-Liquids. The Eleventh Circuit held such abandonment was arbitrary because FDA's 2020 guidance acknowledged the disparate youth initiation risks between open- and closed-system E-Liquids, particularly the latter's youth-appealing attributes.[49] 47 F.4th at 1198.

The Seventh Circuit's blithe acceptance of FDA's blanket presumption was an abdication of the "important role" of courts to ensure that an agency "engaged in reasoned decisionmaking," *Judulang v. Holder*, 565 U.S. 42, 53 (2011), by considering "the relevant factors and whether there was a clear error of judgment." *Id.*, citing *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). FDA failed to consider all relevant facts and erroneously disapproved Gripum's E-Liquids; finding that its PMTA failed to show such products "will provide a benefit to adult users that would be adequate to outweigh the risks to youth." App. 17a – 18a. FDA

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[49] *Bidi Vapor* addressed the differing youth initiation risks of the two segments *vis-à-vis* the manufacturers' marketing plans. This context was not an issue below because Gripum does not market E-Liquids. The respective risks, however, translate across the spectrum of "appropriate for the protection of public health" metric.

ignored the substantially lower risks of Gripum's flavored E-Liquids by applying its blanket youth initiation risk presumption. The Seventh Circuit erred in affording deference as FDA refused to predicate marketing decisions upon the known disparate market segment risks.

2. FDA's youth risk presumption ignored the evolution of scientific evidence.

> "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge."[50]

An agency is quintessentially arbitrary when it relies upon data-driven regulations but refuses to change course as the data evolves. FDA refused to alter its youth initiation risk presumption as new data clarified which type of products youths preferred. This violated the above cardinal rule of science and is reminiscent of the adage about the navy captain who arrogantly refused directions from the lighthouse to change course and instead ordered the lighthouse change its course.

FDA will no doubt argue the validity of its presumptions by pointing out that most youths

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[50] Hill, Austin Bradford, *The Environment and Disease: Association or Causation?* Proceedings of the Royal Society of Medicine, 58 (1965), 295-300.

who vape use non-tobacco flavored E-Liquids. This is overly simplistic for two reasons. *First*, it is logical that youths are more likely to use a flavored E-Liquid since non-tobacco flavored E-Liquids comprise the substantial product universe. FDA's assumption is akin to assuming that all Model T drivers preferred black cars. *Second*, FDA cannot overcome *Bidi Vapor*'s finding that its presumption as to flavored open-system E-Liquids was belied by scientific data and evidence.

FDA's arbitrariness is highlighted by it rooting the youth presumption upon superseded data from the 2019 National Youth Tobacco Survey (NYTS), an annual survey conducted by the Centers for Disease Control.[51] FDA refused to recalibrate its presumption as later data evidenced that youth usage decreased 29% between 2019 to 2020,[52] and another 42% between 2020 and 2021.[53] The 2021 NYTS also evidences the availability of flavored E-Liquids was a distant tertiary motivating factor

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[51] Centers for Disease Control, *Tobacco Product Use and Associated Factors Among Middle and High School Students — United States, 2019* at Table 6.

[52] McDonald, J., *Teen Vaping Declined 29% in 2020, CDC Survey Shows*, Vaping 360 (Sept. 15, 2020). (summarizing 2020 NYTS).

[53] McDonald, J., *CDC Says Youth Vaping Dropped More Than 40% in 2021*, Vaping 360 (Sept. 30, 2021). (summarizing 2021 NYTS).

and the recognition by youths that ENDS products "are less harmful than other forms of tobacco," something which FDA had to consider as a benefit.

Finally, FDA acted arbitrarily because its presumption effectively banned all flavored E-Liquids outside the rulemaking process mandated by the TCA as a predicate to adopting any tobacco product standard.[54] *See* 21 U.S.C. § 387g. FDA's policy memorandum, *supra.*, at 21, proves it acted beyond the statutorily mandated process.

FDA's ends to justify the means by pointing to youth migrating from cartridge-based products to disposable products after its 2020 guidance. *See* App. 32a. Such guidance simply caused youths to switch from one type of closed-system products to another product of the same class. In fact, FDA's Commissioner disclaimed during his term that the agency's concerns applied to open-system products.[55] *Bidi Vapor* recognized FDA's

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[54] FDA is also trying to bypass a prior Office of Management and Budget determination that it could ban flavored E-Liquids in the proposed Deeming Rule.
See https://www.regulations.gov/document/FDA-2014-N-0189-83193 (identifying the OMB changes to the proposed Deeming Rule).

[55] Florko, N., *Former FDA Commissioner Calls for a Full Ban on Pod-Based E- Cigarettes*, STAT. (Nov. 12, 2019).

conflation as any elasticity of demand was confined solely to closed-system products.

FDA's implementation of the Deeming Rule and its review of flavored E-Liquid PMTAs has been ever-shifting sands. FDA did not just move the goalposts; it moved the field beneath the industry's feet during the game. The Seventh Circuit's acceptance of FDA's regulatory tact is inconsistent with this Court's precedents. Review is thus appropriate given the circuit split and need to define a standard of review of agency decisions which are tainted by a conflict of interest.

CONCLUSION

Gripum's petition for a writ of certiorari should be granted for the reasons set forth above.

Respectfully submitted,

J. GREGORY TROUTMAN
Counsel of Record
TROUTMAN LAW OFFICE, PLLC
4205 Springhurst Blvd, Suite 201
Louisville, KY 40241
(502) 412-9179
jgtatty@yahoo.com

January 2023

APPENDIX A
Opinion of Seventh Circuit Court of Appeals
[Filed August 29, 2022]

In the
United States Court of Appeals
For the Seventh Circuit

No. 21-2840
GRIPUM, LLC,

Petitioner,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondent.

On Petition for Review of a Final Marketing Denial Order by the U.S. Food and Drug Administration. No. PM0001689

ARGUED APRIL 20, 2022 — DECIDED AUGUST 29, 2022

Before WOOD, HAMILTON, and KIRSCH, *Circuit Judges*.

WOOD, *Circuit Judge*. Gripum, LLC, manufactures and dis- tributes hundreds of

flavored liquids for use in e-cigarette devices. Seeking to take its products to market, Gripum submit- ted a "premarket tobacco product application" to the federal Food and Drug Administration (FDA) in September 2021. But the agency denied the application, reasoning that Gripum had failed to demonstrate public-health benefits as required by the Family Smoking Prevention and Tobacco Control Act (the Act), see 21 U.S.C. § 387j. We now deny Gripum's petition for review of the FDA's decision, finding that the agency's approach to adjudicating the application was both reasoned and consistent with the Act.

I

A

Commonly known as "e-cigarettes," electronic nicotine delivery systems (called ENDS in bureaucratese) vaporize nicotine-laden "e-liquid" for users to inhale. Users have a choice of devices that accomplish that function and thus allow "vaping." The delivery systems come in an open form, which takes refillable cartridges, and a closed form, which requires single-use cartridges. There is a huge number of flavor options for the cartridges. Some e-liquids mimic traditional cigarette flavors such as tobacco or menthol. Others, like the e- liquid products at issue in this case, taste like candy, fruit, or baked goods. All, however, are laced with nicotine.

Under the Act, manufacturers of a "new tobacco product"—defined as a product that was not on the market as of February 15, 2007—must receive authorization from the FDA prior to marketing

that product. As concern grew over the dangerous health consequences of vaping and e-cigarette use, the FDA promulgated the "Deeming Rule" in May 2016. See 81 Fed. Reg. 28,974 (May 10, 2016). This brought all "tobacco" products, including e-cigarettes and their delivery systems, under the Act's premarket-authorization requirements.

Most relevant for our purposes is the Act's command that the Secretary of Health and Human Services "shall deny an application" to market a new tobacco product if the manufacturer fails to show that the product would be "appropriate for the protection of public health." This is commonly referred to as the "APPH" standard, but in the interest of using plain English, we will call it the "appropriateness" standard. 21 U.S.C. § 387j(c)(2). To determine whether a product meets the appropriateness standard, the Secretary must consider "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." *Id.* That assessment, in turn, must take into account the "increased or decreased likelihood that":

(A) "existing users of tobacco products will stop using such products"; and

(B) "those who do not use tobacco products will start using such products."

Id. § 387j(c)(4). In other words, the Secretary must weigh a product's risks of hooking new users (typically youth) into the world of tobacco, broadly defined, against its potential to help existing users (typically adults) wean themselves from tobacco's

unhealthier forms (namely, combustible cigarettes).

As a matter of enforcement discretion, the FDA specified in its 2016 Deeming Rule that manufacturers would be given two to three years to prepare market applications for the e-cigarette products already on the market. See 81 Fed. Reg. at 28,978. Soon thereafter, youth e-cigarette use exploded across the country. From 2017 to 2018, the number of high schoolers using e-cigarettes rose by over seventy-five percent. See FDA, *Results From 2018 National Youth Tobacco Survey Show Dramatic Increase in E-Cigarette Use Among Youth Over Past Year* (Nov. 15, 2018). With the urgency of the situation in mind, the FDA began around late 2017 to step up its enforcement efforts against products that targeted youth. See *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry* 6–7 (Apr. 2020) (hereinafter 2020 Guidance).

In 2019, the FDA issued a guidance document to help manufacturers prepare applications. See *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry* (June 2019) (2019 Guidance). In that document, the FDA stated that it "understands that limited data may exist from scientific studies and analyses." *Id.* at 12. To address the paucity of data, it indicated that it "intends to re- view" "information on other products (*e.g.*, published literature, marketing information)" provided by an

applicant, so long as the application also included "appropriate bridging studies" tying extant data to the applicant's own products. *Id.*

By 2020, nearly twenty percent of high-school students were active users of e-cigarettes, making e-cigarettes "the most widely used tobacco product among youth by far." FDA, *Technical Project Lead Review of PMTAs* (2020). The agency adjusted its enforcement priorities accordingly and publicized those changes in a guidance document issued that year. It announced that it planned to pay particular attention to flavored, cartridge-based e-cigarettes given their "extraordinary popularity" among youth. See 2020 Guidance at 13 (describing how ninety-three percent of e-cigarette users aged 12–17 reported that their first e-cigarette was a flavored product). The guidance document also recounted the many efforts undertaken by both the agency and manufacturers to reduce youth access. Regrettably, measures such as age-limited sale restrictions had failed to stem the tide, even after the FDA had sent over 6,000 warning letters and 1,000 civil monetary penalty complaints to retailers accused of illegal sales to minors. See *id.* at 7. Because youths often obtain e-cigarettes from friends rather than by direct purchases, sales restrictions proved to be largely ineffective. The 2020 Guidance also clarified that the agency would "make enforcement decisions on a case-by-case basis" and that it "retains discretion to pursue enforcement action at any time against any deemed new tobacco product marketed without premarket authorization." *Id.* at 11.

B

Since 2013, petitioner Gripum has manufactured and dis- tributed flavored e-liquids for use in open-system devices (that is, the refillable cartridges). It claims to have had 291 private label e-cigarette products under contract as of January 2022. On September 7, 2020, Gripum submitted a premarket application to the FDA seeking authorization to market hundreds of its flavored e-liquids, which carried colorful and evocative names such as "Peanut Butter Milk Pie," "Bad Mon- key Giovanni," and "Sunshine Vape Dragon Berry Balls." In its application it included a review of the scientific literature and consumer surveys assessing trends in the use of e-cigarettes, though none of these materials discussed or referred to Gripum's own products.

About a year later, on September 8, 2021, the FDA issued a "marketing denial order" for Gripum's application, explaining that "the new products … lack sufficient evidence to demonstrate that the marketing of these products is appropriate for the protection of public health." The denial order went on to say that "robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers." Reliable evidence, the denial order explained, could have taken the form of a "randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS." Although Gripum's application mentioned randomized controlled trials and longitudinal cohort studies of *other products*,

Gripum never explained how or why its products were sufficiently similar to those other products so that the latter were relevant to its application. In other words, it failed to provide a "bridge" between the data about other products and its own proposed offering. In addition, the denial order concluded that the alleged public-health benefits of Gripum's products were too speculative to outweigh the risks of youth initiation. The agency thus concluded that it was required to deny Gripum's application in its entirety.

On October 8, 2021, Gripum timely filed its petition for re- view of the denial order pursuant to 21 U.S.C. § 387*l*(a)(1)(B). Seeking emergency relief from this court, Gripum filed a motion for a stay pending review on October 17, 2021. On November 4, 2021, we entered an order granting Gripum the re- quested relief.

Since Gripum lodged its petition, similar challenges to e- cigarette marketing denial orders have percolated across the courts of appeals. Not long after we entered our stay, the Sixth Circuit denied a stay pending review in one such case. See *Breeze Smoke, LLC v. FDA*, 18 F.4th 499, 503 (6th Cir. 2021). The Sixth Circuit petitioners then sought a stay from the Supreme Court, but that was denied. See *Breeze Smoke, LLC v. FDA*, 142

S. Ct. 638 (2021) (mem.). We are informed that Breeze Smoke has now voluntarily withdrawn its petition in the Sixth Circuit challenging its marketing denial order. In another case, the Fifth Circuit entered a stay of the marketing denial

orders before it, see *Wages & White Lion Invs., LLC v. FDA*, 16 F.4th 1130 (5th Cir. 2021), but later the merits panel sided against the flavored e-cigarette manufacturers and upheld the agency's decisions, see *Wages & White Lion Invs., LLC v. FDA*, Nos. 21-60766 & 21-60800 (5th Cir. July 18, 2022). The Eleventh Circuit issued an opinion that was the mirror image of the Fifth Circuit's. In *Bidi Vapor LLC v. U.S. Food and Drug Admin.,* No. 21-13340 (11th Cir. Aug. 23, 2022), a panel majority vacated denial orders relating to six different companies, because it concluded that the agency had failed adequately to consider the companies' marketing and sale-access-restriction plans; the dissenting judge thought that the agency had said enough, and that in any event any error was harmless. Finally, the D.C. Circuit recently upheld FDA orders denying market authorization for certain flavored e-cigarette products. See *Prohibition Juice Co. v. FDA*, Nos. 21-1201, 21-1203, 21-1205 & 21-1207 (D.C. Cir. July 26, 2022). (There are also some additional pending challenges. See https://vaping360.com/vape-news/111563/vape-companies-challenging-fda-marketing- denials/.)

II

This case arises under section 912(a)(1)(B) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 387*l*(a)(1)(B)), which provides that any person adversely affected by the FDA's issuance of a marketing denial order may file a petition for review either in the D.C. Circuit or in the circuit in which the person resides or has its principal place of business. Gripum's principal place of business is

in Skokie, Illinois, and so its challenge to the marketing denial order is properly before us.

Because denial orders are reviewed in accordance with section 706(2)(A) of the Administrative Procedure Act (APA), an order may be held unlawful and set aside only if it is found to be "arbitrary, capricious, an abuse of discretion, or other- wise not in accordance with law." 5 U.S.C. § 706(2)(A); see 21 U.S.C. § 387*l*(b). To meet the APA's arbitrary-and-capricious standard, "the agency must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); see also *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021) ("The APA's arbitrary-and-capricious standard requires that agency action be reasonable and reasonably explained.").

Gripum advances three theories for why the FDA's adjudication of its application was arbitrary: (1) the agency failed to announce ascertainable standards prior to its adjudication of the application; (2) the agency quietly shifted the evidentiary standard after inviting reliance on an earlier, easier-to- meet standard; and (3) it failed to undertake an individualized approach to the application, instead applying generalized, and thereby arbitrary, presumptions.[1] We address

[1] We note in this connection that in our case Gripum did not present the argument that persuaded the Eleventh Circuit in *Bidi Vapor*,

these points in that order.

A

Gripum first argues that the FDA's failure to promulgate rules governing the premarket application process, or other- wise to announce ascertainable standards, rendered its adjudication of Gripum's application arbitrary. But the relevant standard applied by the agency—that benefits to adult users must outweigh the risk of fomenting youth use—flows directly from the Act, and the agency reasonably could have thought that no further elaboration on that point was needed. As the statute says, the FDA must evaluate "the risks and benefits to the population as a whole, including users and nonusers"; and to carry out that task, it must weigh "the increased or decreased likelihood that existing users of tobacco products will stop" against "the increased or decreased likelihood that those who do not use tobacco products will start." 21 U.S.C. § 387j(c)(4). That language expressly orders the agency to conduct the described balancing process and to consider both the risks and benefits attendant to each application that it adjudicates. The statute does not, contrary to Gripum's contention, obligate the agency to define threshold levels of likelihoods or the minimum number of users who must be aided for a product to pass muster. Indeed, bright lines of this sort

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namely, that the FDA's analysis was flawed because it did not explain why it placed no weight on the companies' marketing and sales-access-restrictions. Gripum has thus waived, or at a minimum forfeited, this point.

would be difficult to square with the statute's comparative language.

Furthermore, Congress's intent to allow the FDA to develop its premarket policy through a flexible, case-by-case ad- judicative approach is apparent in the structure of the Act. The statute delegates broad authority to the agency to regulate the marketing of tobacco products both through rulemaking, see 21 U.S.C. § 387g(a)(3), and through individual adjudications, see *id.* § 387j(c). It also obligates the agency to issue interpretative rules and regulations in some contexts. See, *e.g.*, 21 U.S.C. § 387e(j)(3)(B) (specifying that the FDA "shall issue regulations" with respect to the registration of tobacco manufacturers); *id.* § 387k(*l*)(1) (specifying that the FDA "shall issue regulations or guidance" with respect to the review of "modified risk tobacco products"). But in the premarket-ad- judication context of section 387j(c), there is no such obligation for the FDA to promulgate implementing regulations.

In a related vein, Gripum argues that the agency's adjudicative approach was inconsistent with the statutory appropriateness standard, and instead amounted to an ersatz "product-efficacy assessment" borrowed from the drug-review provision of 21 U.S.C. § 355(b)(1)(A)(i). Under such an "efficacy" standard, an applicant needs to show that a product is effective at meeting some fixed result (say, the killing of a bacterium at a minimum rate). But all the FDA required Gripum to do here is to show that its flavored e-cigarette products were *relatively better* at reducing rates of

tobacco use than products already on the market. The agency properly applied the comparative standard mandated by the statute; Gripum simply failed to meet it.

B

Gripum next claims that the FDA changed course by re- quiring product-specific clinical studies to meet the appropriateness standard. It contends that in so doing, the agency failed to respect the reliance interests that manufacturers had in the administrative guidance they had received, and thus it acted arbitrarily. See *DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913 (2020) ("When an agency changes course, … it must be cognizant that longstanding polices may have engendered serious reliance interests that must be taken into account."); *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 514– 16 (2009). But like our sister circuits, we conclude that the FDA's e-cigarette guidance materials have consistently reflected that product-specific long-term data are required only if existing studies are inadequately related to the proposed product.

In 2019, the FDA issued a nonbinding guidance document stating that "in general, FDA does not expect that applicants will need to conduct long-term studies to support an application." 2019 Guidance at 13. Gripum makes much hay of that sentence. But the broader document tells a more complicated story. It begins by describing how "[n]onclinical studies alone are generally not sufficient to support" the statutory showing. *Id.* at 12. It then describes how "in some cases, it may be

possible to support a marketing order for an [e-cigarette] product without conducting new nonclinical or clinical studies," though that depends on whether "an established body of evidence … can be adequately bridged to [the] product, such as data from the published literature or government-sponsored databases." *Id.* at 46. This explanation underscores the case-by-case and open-ended nature of FDA review. Nowhere does it confer blanket permission to forego product-specific testing.

As the Sixth Circuit concluded, the agency indicated only that "it *might* accept evidence other than long-term studies, if that evidence had sufficient scientific underpinnings." *Breeze Smoke*, 18 F.4th at 506–07. So too the D.C. Circuit read the 2019 Guidance as "nowhere guarantee[ing] that unspecified other forms of evidence would necessarily be sufficient—only that they might be." *Prohibition Juice Co.*, Nos. 21-1201 etc. at 23. We conclude the same.

C

Gripum also argues that the agency failed to conduct a careful, individualized review of its evidence and instead relied on a general presumption that e-liquids increase youth tobacco use. But according to Gripum, the belief that young people will be attracted to its e-liquids rests on a more tenuous base than the agency thinks, in part because evidence demonstrates that young users prefer closed-system devices to open-system ones.

Gripum's arguments rest on a questionable reading of both the agency's marketing denial order and the statutory burden. The Act requires the denial of an application unless the manufacturer can affirmatively demonstrate that it meets the appropriateness standard through the section 387j(c) comparative assessment. Even if Gripum is right when it asserts that young people are much less interested in e-liquids in open-system devices than they are in closed-system ones, the FDA reasoned that the marketing and sale of open-system de- vices still are responsible for *some portion* of youth initiation. To succeed under the appropriateness standard—a comparative one, as we have stressed—Gripum had the burden of demonstrating that its flavored e-liquids would "switch" some users of combustible cigarettes over to e-cigarettes. But as we already have noted, Gripum failed to provide evidence specific to its products. And though it did include studies of other products, those studies did not even compare tobacco- flavored e-cigarette products (which we will assume do have a "switching" effect) to flavored products resembling those Gripum wants to offer.

Before concluding, we have one unusual new item of business that requires our attention. Almost four months after the oral argument in this case, Gripum filed something it called an "Opposed Motion To Correct Administrative Record." In that motion, it asked us to re-open the underlying administrative record and add a memorandum dated August 19, 2020, entitled "*Bundling and Bracketing Approach for Review of ENDS Open E-*

Liquid PMTAs." This document, it contended, had just come to its attention when it was released by the FDA in response to a third party's freedom-of-information request. We invited the FDA to respond, which it has now done. Aside from remarking that, despite calling the motion "opposed," Gripum had not communicated with the agency before filing its motion, the FDA noted that Gripum has not identified anything that would undermine the presumption of regularity that attaches to an agency's certification of its record, see *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 415 (1971). On the merits, the FDA pointed out that Gripum's petition founders on the utter lack of evidence showing that the benefits of its products outweigh the harms. The further scientific review process described in the memorandum is triggered only for cases that pass that first threshold.

We agree with the FDA that the time has long passed for amendments or changes to the administrative record in the present case, and that the 2020 memorandum is in any event of dubious relevance. We therefore deny Gripum's motion.

* * *

In adjudicating Gripum's application, the FDA hewed to the statutory standard and issued a reasoned marketing denial order. Its determination that Gripum's products lack a clear benefit to current tobacco users was not arbitrary or un- reasonable. We therefore DENY Gripum's petition for review.

APPENDIX B
FDA Marketing Denial Order (Excerpt)
[Filed September 8, 2021]

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

September 8, 2021

Denial

GRIPUM LLC
Attention: Raul Onu, President
7825 Gross Point Rd
Skokie, IL 60077

FDA Submission Tracking Numbers (STNs):
PM0001689, see Appendix A

Dear Mr. Onu:

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

Based on our review of your PMTAs[1], we determined that the new products, as described in your applications and specified in Appendix A, lack sufficient evidence to demonstrate that the marketing of these products is appropriate for the protection of the public health (APPH). Therefore, you

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

cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

If you choose to submit new applications for these products, you must fulfill all requirements set forth in section 910(b)(1). You may provide information to fulfill some of these requirements by including an authorization for FDA to cross-reference a Tobacco Product Master File.[2] You may not cross-reference information submitted in the PMTAs subject to this Denial. Based on review of your PMTAs, we identified the following key basis for our determination:

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

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

> flavored ENDS. Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. We did not find such evidence in your PMTAs. Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

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

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

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

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

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

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

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

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

unable to accept regulatory submissions by e-mail.

If you have any questions, please contact Deema Slim, Regulatory Health Project Manager, at (301)796-1058 or Deema.Slim@fda.hhs.gov.

Sincerely,
Digitally signed by Matthew R. Holman -S
Date: 2021.09.08 09:04:46 -04'00'
Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

APPENDIX C
FDA Technical Project Lead (Excerpt)
[Prepared September 8, 2021]

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

New Products Subject of this Review[i]	
Submission tracking numbers (STNs)	PM0001698, see Appendix A
Common Attributes	
Submission date	September 8, 2020
Receipt date	September 8,2020
Applicant	GRIPUM LLC
Product	GRIPUM LLC
Application type	Standard
Product category	ENDS (VAPES)
Product	ENDS Component
Cross-Referenced Submissions	
All PMTAs	MF0000470, MF0000397, MF0000401
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):
Dale C. Slavin, Ph.D.
Supervisory Science Policy Analyst

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

Office of Science
Signatory Decision:
Matthew R. Holman, Ph.D.
Director
Office of Science

* * *

1. EXECUTIVE SUMMARY

These applications for flavored ENDS[ii] products lack evidence to demonstrate that permitting the marketing of these products would be appropriate for the protection of the public health (APPH). Given the known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use, applicants would need reliable and robust evidence of a potential benefit to adult smokers[iii]

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

[iii] The standard described in Section 910 requires an accounting of the risks and benefits to the population as a whole, balancing the potential impacts to both

that could justify that risk. Accordingly, in order to show that a flavored ENDS is APPH, the applicant must show that the benefit to adults switching from or reducing cigarettes outweighs the risk to youth.

Based on existing scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined for these applications that, to effectively demonstrate this benefit in terms of product use behavior, only the strongest types of evidence will be sufficiently reliable and robust —most likely product specific evidence from a randomized controlled trial (RCT)[iv] or longitudinal cohort study, although

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current tobacco users and non-users. This review is focused on the risk to youth nonusers as well as the potential benefit to adult smokers as current users, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth.

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

other types of evidence could be adequate, and will be evaluated on a case-by-case basis.[v]/[vi]

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

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

[vi] For example, we would consider evidence from another study design if it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco flavored products. In our review of PMTAs for flavored ENDS so far, we have learned that, in the absence of strong evidence generated by directly observing the behavioral impacts of using a flavored product vs. a tobacco-flavored product over time, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth.

reducing their smoking.

We have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate APPH. Our review determined that the subject PMTAs do not contain evidence from a randomized controlled trial, longitudinal cohort study, or other evidence regarding the impact of the ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over tobacco-flavored ENDS. As a result, the applicant has failed to provide evidence to overcome the risk to youth and show a net population health benefit necessary to determine that permitting the marketing of the new tobacco product is APPH.

* * *

2.3.1 **The Risk to Youth of Flavored ENDS Products**

As noted, the APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood[5]

and thus youth are at particular risk of tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and

established during adolescence when the developing brain is most vulnerable to nicotine addiction. Indeed, almost 90 percent of adult daily smokers started smoking by the age of 18.[6] Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood.[7] On the other hand, youth and young adults who reach the age of 26 without ever starting to use cigarettes will most likely never become a daily smoker.[6] Because of the lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

2.3.1.1. Youth use of flavored ENDS

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

The evidence shows that the availability of a broad range of flavors is one of the primary reasons for the popularity of ENDS among youth. The

majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time. In the 2014 National Youth Tobacco Survey (NYTS), 65.1% of high school and 55.1% of middle school e-cigarette[x]

users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xi] increased to 84.7% of high school users and 73.9% of middle school users.[3] Among high school e-cigarette users, the most common flavors used in 2020 were fruit (73.1%); mint (55.8%); menthol (37.0%); and candy, dessert, or other sweets (36.4%).[3] Among middle school e-cigarette users, the most common flavors used in 2020 were fruit (75.6%); candy, desserts, or other sweets (47.2%); mint (46.5%); and menthol (23.5%).[3]

Youth ENDS users are also more likely to use flavored ENDS compared to adult ENDS users. In PATH Wave 5.5 from 2020, 66.8% of youth ENDS users aged 13 to 17 reported using fruit, followed by 53.8% for mint/menthol[xii] 23.5% for candy/dessert/other sweets, and 13.3% for tobacco

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

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

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

flavor (internal analysis). In the 2020 PATH Adult Telephone Survey, 51.5% of adult ENDS users[11] 25 and older used fruit, 30.4% used mint/menthol, 23.8% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal analysis). Youth current ENDS users were also more likely than adult current ENDS users to use more than one flavor and to use combinations that did not include tobacco flavors.[12]

Studies show that flavors influence youth initiation of ENDS use. In particular, data show that flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a flavored product. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first e-cigarette that they used was flavored.[13] In another PATH study, more youth, young adults and adults who initiated e-cigarette use between Wave 1 and Wave 2 reported use of a flavored product than a non-flavored product.[14] Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older.[15]

In addition, nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason.[16/17] In fact, among Wave 4 youth current ENDS users, 71% reported using ENDS "because they come in flavors I like."[14]

One explanation for this high prevalence and increase in frequency of use is that flavors can influence the rewarding and reinforcing effects of e-liquids, thereby facilitating ENDS use and increasing abuse liability. Research shows that flavored ENDS are rated as more satisfying than nonflavored ENDS, and participants will work harder for and take more puffs of flavored ENDS compared to non-flavored ENDS.[18] Research also shows that flavors can increase nicotine exposure by potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use.[19] Together, this evidence suggests flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth, particularly due to the vulnerability of the developing adolescent brain, which is discussed further below.

Finally, existing literature on flavored tobacco product use suggests that flavors not only facilitate initiation, but also promote established regular ENDS use. In particular, the flavoring in tobacco products (including ENDS) make them more palatable for novice youth and young adults, which can lead to initiation, more frequent and repeated use, and eventually established regular use. For example, regional studies have found that the use of flavored e-cigarettes was associated with a greater frequency of e-cigarettes used per day among a sample of adolescents in Connecticut in 2014[20] and continuation of e-cigarette use in a sample of adolescents in California from 2014-2017.[21] Use of non-traditional flavors (vs. tobacco,

mint/menthol, flavorless) was associated with increased likelihood of continued use and taking more puffs per episode.[20] Data from a regional survey in Philadelphia, PA found initial use of a flavored (vs. unflavored or tobacco-flavored) ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months.[22] Finally, similar effects have been found in the nationally representative PATH study among young adults (18-24 years), where "ever use" of flavored ecigarettes at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2.[23] In sum, flavored ENDS facilitate both experimentation and progression to regular use, which could lead to a lifetime of nicotine dependence.

2.3.1.2. The appeal of flavors across ENDS devices

The role of flavors in increasing the appeal of tobacco products to youth — across tobacco product categories — is well-established in the literature.[24/25/26/27] The published literature is sufficient to demonstrate the substantial appeal to youth of flavored ENDS, because it is robust and consistent. As described above, the preference for use of flavored ENDS among youth is consistently demonstrated across large, national surveys and longitudinal cohort studies.

National surveillance data suggest that, within the ENDS category, there is variability in the popularity of device types among youth,

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

It is also worth noting that the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace, that is, the options, especially flavors, that are available for consumers to choose from. Some evidence for this was observed in the trends both leading up to, and coinciding with, the shifting marketplace following the 2020 Enforcement Priorities Guidance. In particular, the enormous rise in youth ENDS use from 2017-2019 coincided with the ascendance of JUUL (and copy-cat devices) in the marketplace, suggesting a relationship between the availability of JUUL as an option, and the sudden popularity of pod-based

devices.[xiii]

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

* * *

2.3.1.6. Conclusion

The exponential growth in youth ENDS use observed from 2017 to 2019, and the enduring prevalence of youth ENDS use in the U.S. is alarming. Despite a reduction in youth use of ENDS from 2019 to 2020, there were still 3.6 million youth ENDS users in 2020 and the majority used a flavored ENDS product. Youth

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

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

users are more likely to use flavored ENDS than adult ENDS users. Flavors are associated with ENDS initiation and progression among youth. The full extent of the harms of ENDS use are not yet known, but evidence to date suggests they include permanent effects of nicotine on the developing adolescent brain and the risk of nicotine addiction. Studies indicate an additive effect of e-liquid flavorings on the rewarding and reinforcing effects of nicotine containing e-liquids.

Studies also demonstrate that e-liquid flavors affect nicotine exposure. Among youth who use ENDS, there is a risk of progression to other tobacco products with greater health risks including combustible cigarettes. Finally, though long-term health risks are not fully understood, studies suggest an association between never-smoking ENDS users and respiratory and cardiovascular health effects. This evidence demonstrates that flavored ENDS pose a significant risk to youth. Cross-sectional surveys examine these relationships at a single point in time, and as a result, do not establish causality.

2.3.2 Balancing Known Risks to Youth with a Potential Benefit to Adults

Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product

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

2.3.2.1. Potential benefit of new flavored ENDS

Current scientific literature demonstrates that ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than combustible cigarettes, and biomarker studies demonstrate significantly lower exposure to HPHCs among current exclusive ENDS users than current smokers.[28] However, whether this is true for any particular new ENDS product, and the implications for health risks from a particular product, are considered on a case-by-case basis during the course of FDA's scientific review of a PMTA.

FDA also considers the potential that current cigarette smokers may experience a reduction in health risks if they switch completely to an ENDS, or if they use both products but substantially reduce their cigarette smoking. For a flavored ENDS product, assuming that the evaluation of the product shows the likelihood for lower HPHC exposure, then to demonstrate the likely individual and population benefit, applicants must demonstrate that current smokers are likely to start using the new ENDS product exclusively or predominantly (e.g., dual use with a significant smoking reduction).[29]

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

FDA's PMTA review includes an evaluation of any potential benefits of the product for the likely users, such as a possible reduction in health risks. In general, as FDA stated in its guidance for PMTAs for ENDS, an assessment of how a new product may be used by current smokers can be derived from a variety of sources. FDA may consider direct behavioral evidence on the specific products under review or indirect evidence derived from studies of behavioral intentions; pharmacological studies of nicotine delivery, abuse liability, and/or use topography; and bridging from studies based on comparable products. Further, in the case of a flavored ENDS product, to demonstrate that the marketing of the new product is APPH, the magnitude of the likely benefit would have to be substantial enough to overcome the significant risk of youth uptake and

use posed by the flavored ENDS product.

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

For flavored ENDS, the known and substantial risk to youth in particular is high. Therefore, to show a net population health benefit, FDA has determined that these applications must demonstrate potential benefits to smokers from marketing such products with robust and reliable evidence – including both robust study design and methods and the strength of the study results. In other words, because the potential benefit to adults is gained through its impact on smoking behavior, FDA is reviewing these applications to determine whether they demonstrate that a benefit of a new product is significant enough to overcome the risk to youth. In particular, FDA's

review of these applications has considered the degree of benefit for a flavored ENDS product over a tobacco flavored variety in facilitating smokers completely switching or significantly reducing their smoking, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. Note that applications with this type of information may still not be APPH: applications containing this evidence would still be evaluated to determine that the totality of the evidence supports a marketing authorization. As it relates to the risk to youth, for example, this assessment includes evaluating the appropriateness of the proposed marketing plan.

We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS products. Our substantive review of PMTAs for ENDS and our completion of numerous scientific reviews over the last 10 months have deepened our understanding of the APPH evaluation with respect to behavior. In these reviews, the expectations for scientific evidence related to potential adult benefit can vary based on demonstrated risk to youth. Although indirect evidence or bridged data from the literature may still be appropriate for many new products, including tobacco-flavored ENDS, robust and direct evidence demonstrating potential benefit has been needed when the known risks are high as with all flavored ENDS products. At the same time, we have learned from experience that, in the absence of strong direct evidence, we are unable to reach a conclusion that the benefit outweighs the

clear risks to youth. For instance, applicants who do not conduct their own behavioral studies must rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. To date, that approach has not been sufficient in our evaluation of flavored ENDS PMTAs because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions--the evidence regarding the role of flavors 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 flavors differentially promote switching amongst ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due, at least in part, to differences in the products studied. Therefore, given the state of the science on flavored ENDS, and the known risks to youth, FDA has reviewed these applications for any acceptably strong product-specific evidence.

More specifically, in order to adequately assess whether such an added benefit has been demonstrated, FDA has reviewed these applications for product-specific evidence that would enable a comparison between the applications' new flavored products and an appropriate comparator tobacco-flavored product (both ENDS) in terms of their impact on tobacco use behavior among adult smokers. Consistent with section 910(c)(5), evidence generated using either an RCT design or longitudinal cohort study design is mostly likely to demonstrate such a

benefit, although other types of evidence could be adequate if sufficiently reliable and robust, and will be evaluated on a case-by-case basis.

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

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

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

While RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity; cohort studies enable stronger generalizability because conditions are closer to real-world. We are aware of these as trade-offs and generally do not favor one type over the other for addressing this question. To be informative, a study using one of these two designs would measure the impact of use of the new or appropriate comparator product tobacco-flavored ENDS and flavored products on adult smokers' tobacco use behavior over time; include outcomes related to ENDS use and smoking behavior to assess switching and/or cigarette reduction; and enable comparisons of these outcomes based on flavor type. In some cases, evidence on each individual flavor option may not be feasible; bridging data from one of the applicant's flavors to other flavors of the applicant's in the same flavor category (e.g., "fruit") may be appropriate. Furthermore, consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging. Likewise, if a flavor is tested

with one nicotine concentration, it may be feasible for the applicant to bridge the study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging.

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

2.3.2.3. Conclusion

Given the known and substantial risk to youth posed by flavored ENDS, FDA has reviewed these applications for the presence of particularly reliable product-specific evidence to demonstrate a potential for benefit to adult smokers that could justify that risk. Based on our current understanding, a demonstration with sufficiently reliable and robust evidence that the flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS.

* * *

Note: Remainder of text omitted. Endnotes from text follows.

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APPENDIX D
FDA Memorandum (Excerpt)
[Prepared August 19, 2020]

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: File

From: Sharyn Miller, MPS, GWCPM
Senior Regulatory Health Project Manager
Office of Science, CTP
Digitally signed by Sharyn E. Miller-5
Date: 2020.08.19 08:53:08 -04'00'

Through: Matthew Holman, Ph.D.
Director
Office of Science, CTP
Digitally signed by Matthew R. Holman -5
Date: 2020.08.19 09:23:21 -04'00'

Subject: Bundling and Bracketing Approach for Review of ENDS Open E-liquid PMTAs

Background

The United States District Court for the District of Maryland ordered FDA to require that premarket authorization applications for all deemed new tobacco products on the market as of August 8,

2016,[1] be submitted to the Agency by September 9, 2020, and provided a one-year period during which products with timely received applications might remain on the market while FDA considers their applications ("compliance period").[2/3]Applicants are required to submit a premarket application for each new tobacco product including each ENDS open e-liquid with different characteristics such as characterizing flavor (CF), nicotine concentration, and propylene glycol to vegetable glycerin (PG:VG} ratio. FDA anticipates that a substantial portion of PMTA ENDS submissions[4] during the compliance period will consist of open e-liquids that contain hundreds to thousands of products with variations in CF, nicotine concentration, and

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[1] The order applies to deemed tobacco products that meet the definition of a 'new tobacco product' (defined in section 910(a)(l)) and were on the market on August 8, 2016, the effective date for the final deeming rule (81 FR 28976)

[2] American Academy of Pediatrics, et al. v. Food and Drug Administration, et al., No. 8:18-cv-883 (PWG), 2019 WL 3067492, at *7 (D. Md. July 12, 2019) (Dkt. No. 127)

[3] American Academy of Pediatrics, et al. v. Food and Drug Administration, et al., Case No. 8:18-cv-883 (PWG), (D. Md. Apr. 22, 2020), Dkt. No. 182

[4] A 'PMTA submission' can refer to an applicant's submission of individual PMTAs and/or a grouped submission for multiple tobacco products that share a significant amount of application content (e.g., a submission for products in the same subcategory such as ENDS open e-liquids).

PG:VG ratio based on the tobacco ingredient listing submitted by tobacco product manufacturers and importers. To increase the likelihood that more tobacco products will be reviewed and receive marketing orders before the end of the compliance period, the Office of Science (OS) is implementing a bundling-bracketing review approach for ENDs open e-liquids PMTAs.

Bundling refers to the process of dividing an applicant's PMTA submission into smaller subsets ("bundles") for scientific review. Since the start of OS review of premarket submissions for tobacco products, OS has been bundling PMTAs, SE Reports, and EX REQs. Additionally, OS has been conducting limited bracketing during scientific review (e.g., applicant X makes cigarette with three different but similar cigarette papers, where the worst-case scenario paper data was bridged to the other two papers). Historically, bundling has occurred before initiation of scientific review while bracketing has occurred during scientific review.

Bracketing refers to the process of individually evaluating the highest and lowest variation of a given characteristic within the bundle (i.e., the highest and lowest nicotine concentration for purposes of this memo) and bridging the findings and conclusions to all other products within the bracket (e.g., products with nicotine concentrations between the highest and lowest nicotine concentration). The application of the bundling and bracketing approaches to the unique challenges of ENDS open e-liquids is the focus of this memo.

There is an expectation that applicants may submit applications that include numerous flavor combinations, nicotine concentrations, and solvent combinations that will exceed the capacity of the reviews to complete in a timely manner. Each of these combinations are considered new products but have many common characteristics that would best be reviewed using bracketing approaches. However, before reviewers can apply these approaches, the scientific review bundles will need to be developed to ensure proper representation of products. To accomplish this, while maintaining a fair and unbiased selection of products that will be reviewed, the bundle will be comprised of randomly selected open e-liquids proportional to the flavor categories represented in the overall PMTA submission. The updated OS approach described in this memo combines bundling and the identification of the bracketing products into a single process that occurs before scientific review.

Discussion

Role and Responsibilities

• Bundling and the identification of bracketing products will be conducted by the Division of Regulatory Project Management (DRPM) before the start of scientific review. Conclusions for the products identified to create the brackets will be extrapolated to all of the products within the bundle during DPS and DNCS scientific review.

• Due to the nature of their disciplines' reviews, Division of Population Health Science (DPHS) and Division of Individual Health Science (DIHS)

reviewers will continue to review the entire PMTA in order to reach conclusions for any portion of the submitted products. As a result, DI HS/DP HS will review all the CFs in the PMTA and provide a comprehensive DIHS/DPHS review that indicates the findings of the review may apply across all tobacco products in the submission.

○ The reviewers will clearly identify and organize deficiencies that apply to the tobacco products bundle, and separate deficiencies that apply to the remaining tobacco products in the submission.

○ When there are subsequent bundles from a submission that has already been reviewed, abbreviated, focused DIHS and DPHS reviews should be completed. If the conclusions of the reviews still stand, then the reviews can simply reference the original reviews and state that the conclusions do not change from the original reviews. If there are changes to the conclusions in the original reviews to reflect CTP's current thinking and/or new information, the review should state the new conclusions and explain why the conclusion is different.

Criteria

• The approach will be applied only to ENDS open e-liquid[5] PMTAs that contain:

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[5] Based on OS experience and the available scientific literature, the bracketing-bundling approach is applicable for ENDS open eliquids only. OS will consider expanding the product scope as more experience and knowledge is gained.

○ More than 24 tobacco products;

○ Two levels of nicotine concentrations; and

○ More than one PG:VG ratio

• Some ENDS open e-liquid PMTAs will contain many products with numerous CFs.[6] Each CF can be categorized into common flavor categories (e.g., tobacco, menthol/mint, fruit, dessert) based on the color wheel (Figure 1) [omitted].

• Division of Product Science (DPS) and Division of Nonclinical Science (DNCS} reviewers are able to conduct individual scientific review on a maximum of 24 CFs within any single PMTA due to resource limitations. However, there is no limit to the maximum number of tobacco products per PMTA for which the conclusions can be bridged.

Assumptions

• Open ENDS e-liquids in the same PMTA will contain the same-sourced ingredients (e.g., nicotine, PG:VG) in varying amounts, with the only distinct ingredients being flavor ingredients.

• PMTAs will contain representative harmful and potentially harmful constituent (HPHC) data for each tobacco product flavor.

Process

1. After a PMTA is accepted and filed, it is placed

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[6] Characterizing flavor is based on the labeling and identifying information stated by the applicant in the application.

in the queue for triage randomization before the start of scientific review. If selected for scientific review, the application is reviewed to identify CFs and variations of nicotine concentration and PG:VG ratio.

2. Assign submitted CFs to flavor categories based on flavor wheel (Figure 2, Step 1) [omitted].

• For flavor categories and respective CFs, refer to Figure 1. Flavor wheels have been used as tools to classify flavors and aromas in the food, alcohol, and fragrance industries and can be adapted as a systematic tool for flavor classification in e-liquid tobacco products.

o If a flavor category is not immediately apparent from the applicant-provided CF, tobacco product name, or brief descriptor (e.g., characterizing flavors such as unicorn blood or blue jazz), the assigned flavor category will be "Other."

• After classifying CFs by flavor category, similar CFs should be grouped together (e.g., fruit flavors will be grouped together; "Other" flavors will be grouped together).

• Less common flavor categories can be combined to create fewer flavor categories (e.g., "nuts" and "spices" may be combined into the "Other" category) on a case-by-case basis.

3. Calculate the percentage of tobacco products in each of the flavor categories within the application (Figure 2, Step 1) [omitted].

$$\frac{\textit{Total\# products within a flavor category}}{\textit{Total\# products in the application}} \text{ x100}$$

This calculation is done so that bundles can be representative of flavor categories present in the overall PMTA submission.

4. Randomly select 24 CFs, proportional to the percentage of flavor categories in the PMTAs based on step 3 (Figure 2, Step 2) [omitted].

Recall, the maximum number of individual tobacco products that can be scientifically reviewed in a bundle is 24. For each of the selected CFs, OS is only going to scientifically review two individual tobacco products, and bridge the conclusions to all remaining products in that CF.

All of the nicotine variations and PG:VG ratios within each of the selected 24 CFs will enter scientific review as a single bundle.

5. Bracket products by reviewing two products for each of the 24 selected CFs: the highest and lowest nicotine concentrations, both with the highest VG[7]

[7] If 100% VG is the bracket, the reviewer should consider looking at the HPHC data for at or closest to 30:70 PG:VG.

within PG:VG ratios (Figure 2, Step 3a, 3b).[8/9/10/11] [omitted]

• Conclusions for the two individually scientifically reviewed products will be bridged to all other products in the bracket (Figure 2 and Figure 3). [omitted]

• In certain situations, a bracketing product[12] with the highest nicotine concentration may head towards a marketing denial order (MOO). If this occurs, the next appropriate nicotine concentration (e.g., the product with the next highest nicotine concentration) should be reviewed

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[8] N Engl J Med 2015; 372:1575-1577, DOI: 10.1056/NEJMc1502242

[9] FDA CTP CDRH Research project (VG degradation data showed highest levels of acrolein, formaldehyde, and acetaldehyde with increasing levels of VG)

[10] Tobacco products with the same CFs which contain variations in other characteristics (such as salt formulation), will not be bracketed due to changes in product composition and therefore, would require individual review.

[11] FDA CTP CDRH Research project (VG degradation data showed highest levels of acrolein, formaldehyde, and acetaldehyde with increasing levels of VG)

[12] "Bracketing products" are those that represent the highest and lowest nicotine concentrations. "Bracketed products" are those that fall in between the highest and lowest nicotine concentrations.

by DPS and DNCS as the bracketing product.

Public Health Benefits

Bundling divides PMTA submissions into more manageable subsets that will result in increased availability of OS review resources and increase the likelihood that more PMTA reviews will be completed during the one-year compliance period. Bracketing will facilitate efficiency in substantive

scientific review as FDA can take action on a larger number of tobacco products than the actual number of tobacco products that are individually reviewed (through bridging) within the 180-day PMTA review timeline. The bundling-bracketing approach will increase the likelihood that FDA issues a greater number of marketing orders for tobacco products within the compliance period. This will benefit public health in two ways as it will (1) increase the likelihood that a variety of products for which marketing is determined to be APPH will be legally marketed by the end of the compliance period; increasing availability of tobacco products that help adult current TP users switch to potentially less harmful products; and (2) increase the likelihood that a greater number of TPs for which marketing was determined to not be APPH be removed from the market.

Conclusion

We anticipate that many PMTA submissions for ENDS open e-liquids during the one-year compliance period will contain hundreds to thousands of open e-liquids with variations in characteristics such as characterizing flavor (CF),

nicotine concentration, and propylene glycol to vegetable glycerin (PG:VG) ratios. OS is implementing a bundling-bracketing approach for ENDS open e-liquids that will reduce the size of each PMTA submission by dividing it into smaller review bundles and will reduce the need for individual scientific review for each ENDS open e-liquid product due to characteristic variations. The current approach will increase the likelihood that FDA can issue more marketing orders on a greater number of tobacco products which would provide public health benefit.

APPENDIX E
FDA News Release
[September 26, 2020]

FDA News Release

FDA Denies Marketing of Logic's Menthol E-Cigarette Products Following Determination They Do Not Meet Public Health Standard

Company Must Stop Marketing Unauthorized Products or Risk Enforcement

For Immediate Release: October 26, 2022

Today, the U.S. Food and Drug Administration issued marketing denial orders (MDOs) for several e-cigarette products currently marketed by Logic Technology Development LLC (Logic). The currently marketed products include the Logic Pro Menthol e-Liquid Package and Logic Power Menthol e-Liquid Package. As a result, the company must not market or distribute these products in the United States or risk enforcement action by the FDA. These are the first menthol e-cigarette products to receive a marketing decision based on a full scientific review from the FDA.

"Ensuring new tobacco products undergo premarket evaluation is a critical part of the FDA's work to reduce tobacco-related disease and death," said Brian King, Ph.D., M.P.H., director of the FDA's Center for Tobacco Products. "We remain committed to

evaluating new tobacco products based on a public health standard that considers the risks and benefits of the tobacco product to the population as a whole."

After reviewing the company's premarket tobacco product applications (PMTAs), the FDA determined that the applications lacked sufficient evidence to demonstrate that permitting the marketing of the products would be appropriate for the protection of the public health, the applicable standard legally required by the 2009 Family Smoking Prevention and Tobacco Control Act. The evidence provided within the application does not demonstrate that these menthol-flavored e-cigarettes are more effective in promoting complete switching or significant cigarette use reduction relative to tobacco-flavored e-cigarettes among adult smokers. The company may resubmit applications or submit new applications to address the deficiencies for the products that are subject to these MDOs.

Before permitting the marketing of a product under the PMTA pathway, among other things, the agency reviews a tobacco product's components, ingredients, additives, constituents, design, harmful and potentially harmful constituents and health risks, as well as how the product is manufactured, packaged, and labeled. Under the PMTA pathway, applicants must demonstrate to the agency that permitting the marketing of a new tobacco product would be appropriate for the protection of the public health. In reviewing PMTAs for tobacco products, the FDA

evaluates the risks and benefits of those tobacco products to the population as a whole, including users and nonusers of the tobacco product, and takes into account, among other things, the likelihood that those who do not currently use tobacco products will start using those tobacco products.

For non-tobacco-flavored e-cigarettes, including menthol-flavored e-cigarettes, existing evidence demonstrates a known and substantial risk with regard to youth appeal, uptake and use. Recent data from the 2022 National Youth Tobacco Survey found most (84.9%) youth who used e-cigarettes in the past 30 days used non-tobacco-flavored e-cigarettes, and of them, 26.6% used menthol-flavored e-cigarettes. Additionally, data indicate tobacco-flavored e-cigarettes do not have the same appeal to youth and therefore do not pose the same degree of risk of youth uptake. Given these existing differences in youth risk, applicants need to provide robust evidence to demonstrate that using their menthol-flavored e-cigarette products are likely to promote complete switching or are likely to significantly reduce cigarette use in adult smokers beyond that facilitated by tobacco-flavored e-cigarette products.

"The FDA conducts a rigorous, scientific review of submitted premarket tobacco product applications, evaluating the data for each product to determine if it meets the public health standard," said Dr. King. "In this case, the applicant did not provide sufficient scientific evidence to show that

the potential benefit to adult smokers outweighs the risks to youth."

The MDO letter that Logic, LLC received today is not limited to the two products named above; in general, the FDA publicly names only products that the applicant is marketing to avoid potential disclosure of confidential commercial information. Any products subject to an MDO may not be offered for sale or distributed in the United States, or the FDA may take enforcement action. These products cannot be legally introduced into interstate commerce in the U.S. without risking FDA enforcement. In March, the FDA authorized several tobacco-flavored e-cigarette products from the company under the Logic Vapeleaf, Logic Power and Logic Pro brands, including devices.

In addition to ensuring that Logic complies with this order, as with unauthorized products generally, the FDA intends to ensure compliance by distributors and retailers. Specifically, the FDA notes that all new tobacco products on the market without the statutorily required premarket authorization are marketed unlawfully and their distribution or sale is subject to enforcement action. Retailers should contact Logic with any questions about products in their inventory.

Today's issuance of these MDOs is just one of the many actions the FDA has taken to ensure any tobacco products that are marketed undergo science-based review and receive marketing determinations by the FDA. The agency has completed the review of and made determinations

on more than 99% of the nearly 6.7 million deemed products for which applications were submitted by the Sept. 9, 2020 deadline. To date, the FDA has authorized 23 tobacco-flavored e-cigarette products and devices. [Note: FDA has not authorized any non-tobacco flavored products or devices to date.]