No. 22-708

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

REPLY BRIEF FOR PETITIONER

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Ultimately, this case concerns whether Congress the United States Food and Drug Administration (FDA) have unbalanced the separation of powers' delicate equilibrium. This happened because courts: (1) allow Congress to "announce vague aspirations" and delegate the realization of its goals. *Gundy v. U.S.*, 588 U.S. ___, 139 S.Ct. 2116, 2133 (2019) (Gorsuch, J., dissenting), and (2) extend deference to agency decisions. *See e.g., Chevron v. Natural Resources Defense Council*, 467 U.S. 837 (1984); *Auer v. Robbins*, 519 U.S. 452 (1997); and *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944). The Framers spoke against the dangers of such paradigm: recognizing the government's most dangerous power was enacting laws which restrict liberty,[1] and that allowing Congress through broad delegations would render constitutional equilibrium meaningless.[2]

The Family Smoking and Tobacco Control Act (TCA), codified as 21 U.S.C. § 387, *et. seq*., is an example: Congress defined "tobacco products," 21 U.S.C. § 387a(b), but delegated authority to FDA to decide which products would come under its regulatory control. This delegation allowed FDA to sweep away 99% of an entire industry segment—a

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[1] THE FEDERALIST NO. 48, pp. 306-308 (C. Rossiter ed. 1961) (J. Madison).

[2] Lawson, *Delegation and Original Meaning*, 88 VA. L. REV. 327, 340 (2002).

$7 billion dollars annual market.[3] Some would argue this represents a "major question". *See FDA v. Brown & Williamson Tobacco Corp.,* 529 U.S. 120 (2000).[4]

Congress' delegation of lawmaking authority to FDA, and its flawed, inconsistent and arbitrary regulatory actions, represent a microcosm of the dangers of allowing broadly delegation of lawmaking function and then deferring to agency decisions. This highlights the wisdom of Justice Alito's observation in *Gundy,* 139 S.Ct. at 2130 – 31, that it is time to re-examine the jurisprudence which has allowed "agencies to adopt important rules pursuant to extraordinary capricious standards".

A. The Court Should Await the Fifth Circuit's *En Banc* Decision in a Parallel Case.

Rule 10(a) lists a conflict among the circuits as a primary reason for granting certiorari. Four circuits have upheld FDA's adjudication of Electronic Nicotine Delivery System (ENDS) product Pre-Market Tobacco Applications

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[3] Grand View Research, *U.S. E-cigarette & Vape Market Size, Share & Trends Analysis Report By Product (Disposable, Rechargeable), By Component (E-liquid, Vape Mod), By Distribution Channel, And Segment Forecasts, 2021 – 2028*, January 2021.

[4] This Court held in *Brown & Williamson* that the regulation of tobacco products was a major question which only Congress could answer. 529 U.S. at 159-60. It logically follows that identifying the tobacco products to be regulated is also a major question.

(PMTAs) and one circuit has ruled against FDA. Another circuit, the Fifth Circuit, initially ruled for FDA in *Wages and White Lion Invest. v. FDA*, 41 F.4th 427 (5th Cir. 2022) but vacated its ruling, 58 F.4th 233 (5th Cir. 2023), upon granting *en banc* review.[5]

Likely foreshadowing its *en banc* ruling in the *Wages and White Lion*, the Fifth Circuit recently found unpersuasive the rulings of the Third, Fourth, Seventh and District of Columbia Circuits. *See R.J. Reynolds Vapor Company v. FDA*, ___ 4th ___ (5th Cir. Mar. 23, 2023); Reply App. 1a-19a. The court found that FDA likely violated the Administrative Procedure Act, 5 U.S.C. § 551, *et. seq*. (APA), and the TCA by adopting a *de facto* ban on non-tobacco flavored E-Liquids without notice-and-comment rulemaking. Reply App. at 6a. This issue is argued in the pending *en banc* case and was argued below. *See Gripum v. FDA*, No. 21-2840, ECF #24 at 46 – 53.

The Fifth Circuit also found that FDA arbitrarily changed its review standard in disregard of reliance interests. Gripum advanced the same argument below. *See Gripum v. FDA*, No. 21-2840, ECF #24 at 42 – 46. The court next found that FDA arbitrarily failed to consider the health benefits to youths who use ENDS products to quit smoking or in lieu thereof. Gripum made the same argument below. *See Gripum v. FDA*, No. 21-2840, ECF #47 at 11 - 18. Finally, the court noted the argument asserted in the pending *en banc* case

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[5] *En banc* review is scheduled for oral argument on May 16, 2023, before the Fifth Circuit.

that the TCA's deeming provision violates the "major questions doctrine." Reply App. at 13a, fn 8.

This case is ripe for adjudication given the existing circuit split. The Fifth Circuit's upcoming *en banc* decision will better clarify the landscape and better inform this Court about the scope of the underlying dispute. The Court should thus defer its decision on Gripum's Petition pending the Fifth Circuit's *en banc* opinion in *Wages & White Lion*.

B. FDA Does Not Refute its Inherent Conflict-of-Interest.

Gripum is not, as FDA claims, asserting its conflict-of-interest argument for the first time. Gripum asserted the argument below, *see Gripum v. FDA*, No. 21-2840, ECF #47 at 31-32, and the court specifically addressed the question at oral argument.[6]

On the merits, FDA asserts this case has nothing to do with *Chevron* and *Auer*. FDA misses the point. It matters not whether an agency has a conflict-of-interest when interpreting a statute (*Chevron*), its own regulations (*Auer*), or informal guidance (*Skidmore*). FDA's argument is curious given its insistence below and in other appeals that the "comparative efficacy standard" is a product of it interpretating the TCA, thus implicating *Chevron*.

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[6] *See Gripum v. FDA*, oral argument at 1:10 – 1:54. http://media.ca7.uscourts.gov/sound/2022/gw.21-2840.21-2840_04_20_2022.mp3

Further, FDA does not refute the existence of a conflict-of-interest or the effect on its deference. FDA claims the TCA's provision for the calculation of tobacco user fees could not have affected its judgment because they are not tied to the sale of combustible tobacco products.[7] Such fees are collected from domestic manufacturers and importers of cigarettes, snuff, chewing tobacco, roll-your-own tobacco, cigar, and pipe tobacco. 21 U.S.C. § 387(b)(2)(B). FDA calculates the user fees upon "market share"[8] which 7 U.S.C. § 518d(e)(1) defines as the prorated portion of each manufacturer's or importer's share of "gross domestic volume." This is consistent with the definition of "market share" as being "[t]he percentage of total sales in a particular market segment represented by the sales of a particular product." Nisberg, J., *The Random House Handbook of Business Terms* 184 (1988).

Since 2005, the number of American smokers has fallen from 20.9% to 12.5%,[9] and sales have

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[7] FDA does not refute that its inability to collect user fees upon ENDS products poses a "significant mission challenge." Reagan-Udall Foundation, *Operational Evaluation of Certain Components of FDA's Tobacco Programs*, 11 (Dec. 19, 2022).

[8] FDA, *FDA: User Fees Explained* (Oct. 3, 2022). https://www.fda.gov/industry/fda-user-fee-programs/fda-user-fees-explained

[9] Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, *Tobacco*

fallen significantly in the past 20 years.[10] Such circumstance proves the tautology that if market share is dictated by total sales, and if user fees are based upon total sales, then any products which reduce total sales without paying user fees creates a conflict-of-interest. The user fee disparity is thus clearly relevant as the millions of PMTAs strained FDA's resources without any contribution to the regulatory costs and compromised FDA's ability to "make clear and timely product decisions that withstand judicial scrutiny." Reagan-Udall Foundation, *supra*. at 16.

It thus cannot be merely coincidental that the former Director of FDA's Center for Tobacco Products, Mitch Zeller, left FDA in April 2022, and has now joined the advisory board of Qnovia, Inc., a pharmaceutical company which is pursuing approval of a virtually identical product.[11] Director Zeller proclaimed in 2014 that it would be good for public health if smokers completely switched to ENDS products[12] and then oversaw FDA's

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Product Use Among Adults — United States, 2020 (March 18, 2022).

[10] Truth Initiative, *Cigarette sales continued declining in 2021*, Jun. 22, 2022.

[11] Catronuovo, C., *Ex-FDA Tobacco Head Advising Company on Smoking Cessation*, Bloomberg Law, Mar. 31, 2023.

[12] 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).

rejection of flavored products. Now, Zeller proclaims a need to offer "something new and innovative" to adult smokers.[13] Yet, several million Americans now call themselves "former smokers" because of ENDS products.

Such circumstance compromises the public's confidence in the integrity of the regulatory process.[14] It is hard to fathom something more compromising than a former agency manager overseeing the market denial of flavored E-Liquids and then joining a regulated company to promote an almost identical technology. "[J]ustice must satisfy the appearance of justice." *Offutt v. U.S.*, 348 U.S. 11, 13 (1954). There is no justice in a technology being unacceptable when controlled by one group, but wholly acceptable when controlled by another.

This Court's jurisprudence does not address the deference to be afforded when an agency has a conflict-of-interest. The outcome below would have been different if the Seventh Circuit was constrained in the deference it gave FDA. The need for clarity on such question makes this case ripe for review.

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[13] Foley, K, *et. al., Former FDA tobacco head: Smokers need a new tool to quit*, Politico, Apr. 4, 2023.

[14] Meghani, Z., *et. al.*, *The "Revolving Door" between Regulatory Agencies and Industry: A Problem That Requires Reconceptualizing Objectivity*, J. AGRI. AND ENVIR. ETHICS 24:6, 575 – 599 (Sept. 17, 2010).

C. FDA Fails to Refute its Inconsistent Regulation of Flavored Open-System E-Liquids.

The textbook example of arbitrary action is an agency which says one thing internally then regulates in an opposite manner. FDA fails to refute the arbitrariness of its review standard which diverges from its pre-PMTA guidance and the accompanying reliance interests.

FDA's June PMTA guidance stated that that it did not expect the necessity of long-term studies. FDA, *Guidance for Industry, Premarket Tobacco Applications for Electronic Nicotine Delivery Systems* (Jun. 2019) at 13. FDA repeated this in its Proposed and Final PMTA Rules. 84 FED. REG. 50,566, 50,619 (Sept. 25, 2019); 86 FED. REG. 55,300, 55,387 (October 4, 2021). FDA instead argues the Seventh Circuit read its guidance more narrowly. FDA Brief at 7.

The Fifth Circuit deconstructed such argument in *R.J. Reynolds, supra*. based upon a comparison of FDA's aforementioned assurances against its July 2021 Fatal Law memorandum,[15] *See* Reply App. 3a, 13a-14a. The court found the latter imposed "a heightened evidentiary standard" which "bears all the hallmarks" of a substantive rule, thus necessitating notice-and-comment rulemaking. *Id*. at 16a.

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[15] An excerpt of FDA's Fatal Flaw Memorandum is found at Reply App. 20a – 23a.

The Fifth Circuit specifically found that the Fatal Flaw Memorandum:

- was "binding on its face;"
- applied by FDA as binding; evidenced by the myriad of marketing denial orders which refer to common "fatal" deficiencies;
- removed reviewers' discretion to consider the merits of PMTAs and instead required a cursory, box checking review; and
- affected the rights of literally hundreds of thousands of applicants whose PMTAs were denied.

Reply App. at 16a. The resemblance of the Fatal Flaw Memorandum to a substantive rule was "not a close call." *Id*. Those same questions are at issue here.

The establishment of a "tobacco product standard" places the burden on FDA to demonstrate its appropriateness for the protection of public health. 21 U.S.C. § 387g(a)(3). A tobacco product standard pertains to the "ingredients, additives, [and] constituents" of a tobacco product. *Id*., at § 387g(a)(4)(B)(i). The Fifth Circuit concluded that FDA has enforced a *de facto* ban on flavored ENDS products through PMTA adjudications instead of the prescribed rulemaking process. This improperly shifted the burden of proof from FDA to PMTA applicants.

FDA knew the truth about the benefits of flavored ENDS products before the PMTA deadline and its Fatal Flaw analysis. In March 2020, six months before the PMTA deadline, FDA

published an internal report which detailed the ENDS product "state of the science."[16] This report was recently revealed from a Freedom of Information Act request.

Therein, FDA relied upon two qualitative[17]/[18]and two survey[19]/[20] studies which concluded that adult smokers perceive the availability of flavored ENDS products as an important aspect of completely switching. *Id*. at

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[16] FDA, *Interdisciplinary OS State of the Science on Electronic Nicotine Delivery Systems (ENDS)*, Mar. 31, 2020. https://www.dropbox.com/s/8sahhizjczl5km8/ENDS_State_of_the_Science_Spring_2020.pdf?dl=0

[17] Duarte D., *et. al*., *Isn't there a bunch of side effects?": A focus group study on the beliefs about cessation treatments of non-college educated young adult smokers*, J. SUBST. ABUSE TREAT. 112:36-41 (May 2020).

[18] Barbeau A., *et. al*., *Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach*. ADDICT. SCIENCE & CLINICAL PRAC. 8:5 (Mar. 5, 2013).

[19] Goldberg R., *et. al*., *Older Smokers' Beliefs About e-Cigarettes and Intent to Quit Conventional Cigarettes*, J. GERONT. NURS. 44(12):17-24 (Dec. 1, 2018).

[20] Farsalinos K., *et. al., Impact of flavour variability on electronic cigarette use experience: an internet survey*, INT'L J. ENV. RES. AND PUB. HEALTH 10(12):7272-7282 (Dec. 17, 2013).

121. Another study of youths and young adults found that using two or more combined flavors was associated with a greater likelihood of quitting smoking.[21] *Id*. This represented a baseline public health benefit. Further, using multiple flavors at the time of initiation in conjunction with mint and menthol flavors leads to longer exclusive ENDS product use.[22] *Id*.

FDA's report represents a diametrically opposed policy statement from its Fatal Flaw Memorandum. The former explains why FDA disclaimed the need for long-term studies. FDA's fatal flaw analysis was pervasive in ***all*** of its marketing decisions for flavored ENDS products. Reply App. at 14a, fn 9.

The Fifth Circuit is not alone in questioning FDA's actions. The House Oversight Committee transmitted a letter to FDA on March 28, 2023 asserting its failure to promulgate ascertainable PMTA standards, echoing Gripum's arguments below,[23] and expressing "deep concerns" that FDA

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[21] Camenga D., *et. al., Current and Former Smokers' Use of Electronic Cigarettes for Quitting Smoking: An Exploratory Study of Adolescents and Young Adults*, NICOTINE TOB. RES. 19(12):1531-1535 (Nov. 7, 2017).

[22] Jones D., *et. al., Flavored ENDS Use among Adults Who Have Used Cigarettes and ENDS, 2016-2017*, TOB. REGUL. SCI. 5(6):518-531 (Nov. 2019).

[23] U.S. House of Representatives, Committee on Oversight and Accountability, *Comer Probes FDA's Tobacco and Nicotine Regulatory Programs Riddled with Uncertainty* (Mar. 28, 2023).

had allowed decisions to be "influenced by political concerns rather than scientific evidence," pointing to FDA employee revelations in the Reagan-Udall report, *supra*.

The collective take-away is that FDA has employed a flawed and arbitrary review process which contradicts its own understanding of the net public health benefits of flavored ENDS products.

D. FDA Fails to Refute the Overbredth and Flaws of its Presumption About the Motivating Role of Flavored Open-System E-Liquids.

Finally, FDA fails to refute the overbredth and flaws of its presumption about the role of flavored open-system E-Liquids in motivating youth use. FDA hangs its hat on the Seventh Circuit's findings that Gripum misread the TCA and the marketing denial order, and failed to show the propriety of its E-Liquids. FDA Brief at 9 -10. FDA errs for three reasons.

First, FDA's "comparative efficacy standard" improperly shifted the burden of showing the appropriateness for the protection of public health. The Fifth Circuit soundly rejected FDA's position in *R.J. Reynolds, supra.*, thus creating a circuit split which warrants review.

Second, FDA also fails to refute the two flaws of comparative efficacy. The first flaw is that any efficacy must be measured against the "population as a whole," 21 U.S.C. § 387j(c)(4), which would necessitate smokers using a flavored ENDS product to prove an enhanced likelihood of smoking reduction. Youths are a part of the "population as a whole," but it would be illegal to include them in an efficacy test. *See* 21 U.S.C. §

387f(d)(3)(a). Gripum would thus have to violate the law to satisfy FDA's requirement. The Fifth Circuit exposed the second flaw in holding that FDA must consider the health benefits which flavored ENDS products confer upon both adult ***and youth*** smokers. Reply App. at 11a. FDA's marketing denial order, Pet. App. 16a - 20a, and accompanying Technical Project Lead document, Pet. App. 21a – 45a, clearly evidence a failure to consider that a flavored ENDS product could ever confer health benefits upon youths who smoke or use them in lieu thereof. FDA's internal report clearly apprised it of such benefits, and the Fifth Circuit correctly analyzed this point.

Third, FDA errs in arguing a difference between this case and *Bidi Vapor LLC v. FDA*, 47 F.4th 1191 (11th Cir. 2022). *Bidi* found that FDA acted arbitrarily by failing to consider the manufacturers' marketing plans given its acknowledgement of the lower risks of youths using flavored open-system E-Liquids.[24] Granted, Gripum's PMTA lacked a marketing plan because its business model does not involve the marketing or retail sale of E-Liquids. *Bidi*, however, does not apply solely to marketing plans as FDA did not premise its 2020 flavor guidance upon the relationship between the low likelihood of youth use and a PMTA applicant's marketing plans.

Bidi found that FDA ignored its own internal knowledge regarding the low risk of youths using

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[24] 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).

flavored open-system E-Liquids when lumping all flavored E-Liquids into the same basket. FDA did the same with respect to Gripum as evidenced by its marketing denial order and Technical Project Lead document. Review is warranted given the circuit split between *Bidi* and the Seventh Circuit.

CONCLUSION

This case is a microcosm of everything that ails the federal bureaucracy. Congress did more than just write a basic regulatory outline and then have FDA fill in the blanks. Instead, Congress allowed FDA to choose the products which it would regulate in the face of *Brown & Williamson, supra*. FDA's arbitrary regulation of flavored open-system ENDS products became a moving target which violated both the TCA's notice-and-comment rulemaking requirements and the APA's due process concepts. This upsets the constitutional equilibrium in a way inconsistent with the Framers' intentions.

The Court should grant Gripum's petition for a writ of certiorari for the reasons both set forth above and therein.

Respectfully submitted,

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APPENDIX A
Opinion of Fifth Circuit Court of Appeals
[Filed March 23, 2023]

United States Court of Appeals for the Fifth Circuit

No. 23-60037

R.J. Reynolds Vapor Company; RJR Vapor Company, L.L.C.; Avail Vapor Texas, L.L.C.; Mississippi Petroleum Marketers and Convenience Stores Association,

Petitioners,

Versus

Food & Drug Administration; Robert Califf, *in his official capacity as Commissioner of the United States Food & Drug Administration*; United States Department of Health and Human Services; Xavier Becerra, *in his official capacity as Secretary of the United States Department of Health and Human Services*,

Respondents,

consolidated with

No. 23-60128

R.J. Reynolds Vapor Company; RJR Vapor Company, L.L.C.; Avail Vapor Texas, L.L.C.; Mississippi Petroleum Marketers and Convenience Stores Association,

Petitioners,

Versus

United States Food & Drug Administration; Robert M. Califf, *Commissioner of Food and Drugs*; United States Department of Health and Human Services; Xavier Becerra, *Secretary, U.S. Department of Health and Human Services*,

Respondents.

Appeal from the Food & Drug Administration
Agency Nos. PM0000637, PM0000713,
PM0000554, PM0000561

Before King, Jones, and Smith, *Circuit Judges*.

Edith H. Jones, *Circuit Judge*:

The Food and Drug Administration denied petitioners' application to market menthol-flavored e-cigarettes. Petitioners seek a stay pending review of the denial order on the merits. We grant the stay.

I. Background

This court has become quite familiar with the legal and regulatory framework underpinning this case. *See Big Time Vapes, Inc. v. FDA*, 963 F.3d 436, 437 (5th Cir. 2020); *Wages & White Lion Invs. v. FDA*, 16 F.4th 1130 5th Cir. 2021) (stay order); *Wages & White Lion Invs. v. FDA*, 41 F.4th 427 (5th Cir. 2022) (merits decision), *vacated* 58 F.4th 233 (5th Cir. 2023). And the material facts resemble those in *Wages & White Lion*, with some notable differences.

The Food and Drug Administration ("FDA") has been regulating tobacco products since 2009 under the Family Smoking Prevention and Tobacco Control Act ("TCA"). Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified at 21 U.S.C. § 387, *et seq.*).

And since 2016, the FDA has been in the business of regulating e-cigarettes,[1] including those containing no tobacco flavoring. *See* 81 Fed. Reg. 28,974, 28,976 (May 10, 2016). In order to continue marketing e-cigarettes, manufacturers must submit to the FDA a premarket tobacco product application ("PMTA"). 21 U.S.C. § 387j.

In June 2019, the FDA issued a "how-to" guide for submitting e-cigarette PMTAs. FDA, *Guidance for Industry, Premarket Tobacco Applications for Electronic Nicotine Delivery Systems* (June 2019) ("PMTA Guidance"), https://bit.ly/2R5TyYj. In it, the agency stated that it "does not expect that applicants will need to conduct long-term studies to support an application." *Id.* at 13. The Proposed and Final Rules repeated this expectation. *See* Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. 55,300, 55,387 (October 4, 2021); 84 Fed. Reg. 50,566, 50,619 (Sept. 25, 2019). The FDA also recommended that applicants use "products that consumers are most likely to consider[] interchangeable" when submitting "comparative health risk data." PMTA Guidance at 13.

With this guidance in mind, Petitioner R.J. Reynolds Vapor Company ("RJRV") submitted a PMTA for its menthol-flavored Vuse Vibe e-cigarette on March 31, 2020,[2] well ahead of the

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[1] Known more technically as electronic nicotine delivery systems ("ENDS").

[2] Vuse Vibe is a cartridge-based, closed system e-cigarette, which is distinct from "open system" and disposable e-cigarettes. In contrast, the products at issue in *Wages & White Lion* are flavored liquids used in "open system" e-cigarettes. 41 F.4th at 443 n.1 (Jones, J., dissenting).

September 9, 2020, deadline. *See* 21 U.S.C. § 387j; *Wages*, 16 F.4th at 1135. On December 18, 2020, the FDA sent RJRV a deficiency letter regarding several other pending PMTAs for RJRV's flavored ENDS. The FDA instructed RJRV to "provide evidence to demonstrate that the use of these flavored products (*other than menthol*) increases the likelihood of complete switching among adult smokers relative to tobacco or menthol-flavored products." (emphasis added). Because this advice expressly excluded its menthol-flavored products, RJRV did not supplement its menthol Vuse Vibe PMTA.[3]

Over two years later, on January 24, 2023, the FDA denied RJRV's PMTA in a marketing denial order ("Denial Order"). A stated basis for the denial was that RJRV's long-term studies "were not brand- or product specific," and, as such, "did not demonstrate that [RJRV's] menthol flavored new products are more likely to promote complete switching or significant cigarette reduction compared to tobacco-flavored products." Additionally, the FDA stated that the "marketing restrictions and other mitigation measures that [RJRV] proposed cannot mitigate . . . risks to youth sufficiently." RJRV petitioned the FDA for a stay, which was denied. RJRV and three other companies then petitioned this court for review and moved to stay the Denial Order.[4] We granted an administrative stay, and now we enter a full

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[3] RJRV's application for Vuse Vibe already spanned over 150,000 pages.

[4] The FDA also denied a PMTA for menthol Vuse Ciro. Petitioners no longer sell that product, and so do not seek a stay as to the denial of its marketing application.

stay pending resolution of RJRV's petition on the merits.

II. Discussion

As a preliminary matter, venue is proper in this circuit because a petitioner has its "principal place of business" here.[5] 21 U.S.C. § 387l(a)(1)(B). Also, because it is undisputed that "at least one" petitioner—namely, RJRV—has standing, Article III's case-or-controversy requirement is satisfied. *Town of Chester v. Laroe Estates, Inc.*, 581 U.S. 433, 439, 137 S. Ct. 1645, 1651 (2017). 556 U.S. 418, 433, 129 S. Ct. 1749, 1760 (2009). Our judgment is "guided by sound legal principles" that "have been distilled into consideration of four factors: (1) whether the stay applicant has made a strong showing that he is likely to succeed on the merits; (2) whether the applicant will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies." *Id.* at 434, 129 S. Ct. at 1761 (internal quotation marks omitted). "The first two factors . . . are the most critical." *Id.*

RJRV has made the strong showing of its likely success on the merits, irreparable injury, and the balance of harms and public interest weigh in favor of granting the stay. Thus, RJRV has met its "burden of showing that the circumstances justify an exercise of [our] discretion." *Id.*

A. Likelihood of success

The FDA's order is reviewed under the Administrative Procedure Act's ("APA") "arbitrary

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[5] Petitioner Mississippi Petroleum Marketers and Convenience Stores Association is incorporated in and has its principal place of business in Mississippi.

and capricious" standard, 5 U.S.C. § 706(2)(A), and will pass muster so long as it is "reasonable and reasonably explained." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). To begin with, this means an "agency must defend its actions based on the reasons it gave when it acted"; we will not let the agency cut corners by entertaining *post hoc* rationalizations. *DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020). Further, when an agency changes course, it must take into account "serious reliance interests" its "longstanding policies may have engendered" along with "alternatives that are within the ambit of the existing policy." *Id.* at 1913 (internal quotation marks omitted and alterations adopted).[6] Additionally, failure to consider "relevant factors" will render "an agency's decreed result" unlawful. *Michigan v. EPA*, 576 U.S. 743, 750, 135 S. Ct. 2699, 2706 (2015). The above requirements ensure that an agency has engaged in "reasoned decisionmaking." *Id.*

Specifically, RJRV demonstrates that the FDA failed to reasonably consider the company's legitimate reliance interests concerning the need for longitudinal studies and marketing plans; failed to consider relevant evidence, *inter alia*, that youthful users do not like menthol-flavored e-cigarettes; and has created a *de facto* rule banning all non-tobacco-flavored e-cigarettes without following APA notice and comment requirements.

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[6] Colloquially, this is known as the "surprise switcheroo" doctrine. *Azar v. Allina Health Servs.*, 139 S. Ct. 1804, 1810 (2019); *Env't Integrity Project v. EPA*, 425 F.3d 992, 996 (D.C. Cir. 2005).

1. Legitimate reliance interests

The FDA did not reasonably consider RJRV's legitimate reliance interests before changing its position on the types of comparative studies and marketing plans critical to a compliant and complete PMTA. Dealing with administrative agencies is all too often a complicated and expensive game, and players like RJRV "are entitled to know the rules." *Alaska Prof'l Hunters Ass'n v. FFA*, 177 F.3d 1030, 1035 (D.C. Cir. 1999), *abrogated on other grounds by Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 135 S. Ct. 1199 (2015). To keep things fair, agencies must give notice of conduct the agency "prohibits or requires" and cannot "surprise" a party by penalizing it for "good-faith reliance" on the agency's prior positions. *Christopher v. Smithkline Beecham Corp.*, 567 U.S. 142, 156–57, 132 S. Ct. 2156, 2167–68 (2012). At a bare minimum, "[w]hen an agency changes its existing position, it . . . must at least display awareness that it is changing position and show that there are good reasons for the new policy." *Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 136 S. Ct. 2117, 2125–26 (2016). It follows that "unexplained inconsistency in agency policy is a reason for holding an [action] to be an arbitrary and capricious change from agency practice." *Id.* at 2126 (internal quotation marks omitted).

The FDA inexplicably switched its position on menthol-flavored e-cigarettes in at least two crucial ways. First, before the application deadline, the FDA represented that long-term studies were likely unnecessary and that applicants had discretion to use "products that consumers are most likely to consider[] interchangeable" when submitting "comparative health risk data." PMTA Guidance at 13. The FDA

then notified RJRV directly that for its "flavored products (*other than menthol*)," it should submit evidence that those products "increase[d] the likelihood of complete switching among adult smokers relative to tobacco or menthol flavored products." (emphasis added) The FDA never told RJRV that similar evidence would be required for its menthol Vuse Vibe PMTA. RJRV relied upon these representations when crafting its PMTAs and supplemental filings.

Despite its representations, the FDA's subsequent Denial Order stated that RJRV's "studies were not brand- or product-specific, and thus did not demonstrate that [RJRV's] menthol-flavored new products are more likely to promote complete switching or significant cigarette reduction compared to tobacco-flavored products." In the same vein, the accompanying Technical Project Lead ("TPL") faulted RJRV's studies for failing to "assess the impact of menthol-flavored ENDS . . . on cigarette smoking switching behavior" or "complete switching or significant cigarette reduction *over time*." (emphasis added) And again, nearly parroting FDA's earlier instruction, the TPL stated that RJRV "did not submit evidence from a [randomized controlled trial] or cohort study showing that its menthol-flavored ENDS provide an added benefit to adult smokers in terms of complete switching or significant cigarette reduction over tobacco-flavored ENDS." In other words, the FDA's prior representations were that RJRV need not submit long-term studies showing that its menthol-flavored ecigarette was more likely than a tobacco-flavored e-cigarette to cause smokers to quit. Yet the lack of that evidence became the very basis on which the FDA denied RJRV's application.

The FDA's second unexplained switch was from the policy on marketing plans it announced in its April 2020 Final Guidance ("2020 Guidance").[7] The 2020 Guidance enumerated "adequate measures" manufactures could take "to prevent minors' access" to ENDS products. FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (Revised): Guidance for Industry*, 21–22, https://bit.ly/3ZPRkPx. These included: (1) age-verification barriers for retail websites; (2) enforcement monitoring programs with retailers; (3) a limit on the number of ENDS that can be purchased at once or over a period of time; and (4) a mystery shopper program. *Id.* at 22. The guidance also listed common ways manufacturers improperly target minors, such as advertising with "social media influencers," "popular children's characters," and kid-friendly "cartoon or animated characters." *Id.* at 26–27. RJRV's proposed marketing plan accounted specifically for these and many more measures.

The FDA changed positions on this front as well, cursorily stating in its Denial Order that RJRV's "marketing restrictions and other mitigation measures" were insufficient. Remarkably, the TPL recounted the same "restrictions on advertising and promotion" and "restrictions on sales access" that the FDA had

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[7] *See* 85 Fed. Reg. ¶ 23,973 (Apr. 30, 2020). The 2020 Guidance revised an earlier edition, published in January 2020, in which the FDA first described the marketing restrictions manufacturers could implement to restrict youth use. *Enforcement Priorities for Electronic Nicotine Delivery Systems: Guidance for Industry*, 85 Fed. Reg. ¶ 720 (Jan. 7, 2020).

earlier hailed as "adequate measures," but concluded that none of them actually worked to a sufficient degree. In fact, the only measures described as potentially effective were "age-gating technologies that require user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product or geo-fencing technologies." These extreme measures were not listed in the 2020 Guidance. The TPL concluded that "only the most stringent mitigation measures could provide sufficient assurance" against the risks to youth from flavored ENDS.

The FDA's Denial Order wholly failed to explain both of these "about face" maneuvers. Of course, the FDA could have *formally* changed its requirements, but it did not. *Regents*, 140 S. Ct. at 1914 ("Making that difficult decision was the agency's job, but the agency failed to do it."). These "unexplained" and "inconsistent" positions are likely arbitrary and capricious. *See Encino Motorcars*, 579 U.S. at 222, 136 S. Ct. at 2126.

The FDA's disregard for the principles of fair notice and consideration of reliance interests is exacerbated by its failure to consider alternatives to denial. When an agency changes course, as the FDA did here, it must take into account "alternatives that are within the ambit of the existing policy." *Regents*, 140 S. Ct. at 1913 (internal quotation marks omitted and alterations adopted). For example, the FDA could have invited RJRV to submit supplemental filings to shore up its menthol Vuse Vibe application, as it had done for RJRV's non-tobacco-flavored e-cigarette PMTAs. Apparently, the FDA accepted as many as 13 amendments for RJRV's other applications. FDA, *TPL Review of PMTA, PM0000491, PM0000492* 11–14 (Dec. 4, 2018),

https://tinyurl.com/2p83ymvb. The FDA gave RJRV no such opportunity for its menthol PMTA.

2. Failure to consider relevant factors

The FDA did not adequately address RJRV's evidence that substantial health benefits would accrue to adult and youth cigarette smokers alike who switched to menthol Vuse, while popularity among youth would remain low overall. For example, RJRV's application contained studies that "switching from smoking to use of menthol Vuse Vibe substantially reduces toxicant exposure in a manner similar to smoking abstinence." RJRV also submitted evidence of low popularity among youth relative to other flavored ENDS.

This evidence was overlooked even though it comports with the FDA's own findings published at the time RJRV filed its PMTA. In its 2020 Guidance, in response to the concern over a growing level of youth vaping, the FDA cited evidence that "youth use of menthol-flavored products is not as high as that for mint- and fruit-flavored products," *id.* at 15, and that "youth overwhelmingly prefer certain flavors . . . such as fruit, mint, and candy," *id.* at 24. Specifically, a survey of 8th, 10th, and 12th graders found that mango, mint, and fruit were the most popular flavors, together accounting for 75% of responses, while menthol and tobacco ranked among the least popular with between 2% and 6% each. *Id.* Further, the guidance noted menthol's unique status as "the only characterizing flavor available in cigarettes." *Id.* at 23.

This is where the plot thickens. Internal memoranda circulated among the FDA's Center for Tobacco Products ("CTP") and CTP's Office of Science ("OS") emerged in December 2022. *See*

Alex Norcia, *Memos Show FDA Overruled Science-Office Call to OK Menthol Vapes*, Filter Magazine (Dec. 14, 2022) ("Norcia"), https://bit.ly/3JjjcVi. These reveal that OS, well into reviewing a PMTA for a menthol-flavored e-cigarette, recommended in late 2021 that the PMTA be granted because benefits to smokers likely outweighed the "known risks to youth from the marketing of the products." Then in July 2022, a new CTP director appeared on the scene and told OS that "the approach to menthol-flavored ENDS should be the same as for other flavored ENDS, i.e., the products could be found [appropriate for the protection of the public health] only if the evidence showed that the benefits of the menthol-flavored ENDS were greater than tobacco-flavored ENDS, which pose lower risk to youth." OS then changed its position. These memoranda are strong evidence that CTP developed and internally circulated new criteria for evaluating PMTAs for menthol-flavored ENDS in Summer 2022, long after RJRV had filed its application.

When rejecting RJRV's evidence in the Denial Order, the FDA brushed over its prior statements about the low popularity of menthol flavored e-cigarettes among youth and substantial benefits for cigarette smokers who make the switch. Because its "new policy rest[ed] upon factual findings that contradict those which underlay its prior policy," the FDA had to provide "a more detailed justification." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515, 129 S. Ct. 1800, 1811 (2009). It did not do so. This sudden turnabout further reinforces that the Order is likely arbitrary, capricious, or otherwise unlawful.

3. "Tobacco product standard"

RJRV has adduced evidence that the FDA has effectively banned all non-tobacco-flavored e-cigarettes, pursuant to its new and secret heightened evidentiary standard, without affording affected persons any notice or the opportunity for public comment. There is no dispute that the TCA requires the FDA to abide by notice-and-comment rulemaking procedures before establishing a "tobacco product standard."[8] 21 U.S.C. § 387g(c)–(d). Similarly, it is clear that a ban on all but tobacco-flavored e-cigarettes would constitute a "tobacco product standard." *See id.* § 387g(a)(1)(A); *id.* § 387g(a)(2); *id.* § 387g(a)(3). The FDA admits that it "has yet to grant" a single application to market non-tobacco-flavored e-cigarettes. This means it has denied over 355,000 such applications, which amount to 99% of all timely-filed PMTAs. FDA, Press Release, *FDA Denies Marketing to Two Vuse Menthol E-Cigarette Products* (Jan. 24, 2023), https://bit.ly/3YRYWzB; Jim McDonald, *FDA Denies PMTAs for 300,000 More Flavored E-Liquids*, Vaping 360 (Sept. 3, 2021), https://bit.ly/3Fu08SS. *Cf.* FDA, *Premarket Tobacco Product Marketing Granted Orders* (Feb. 7, 2023), https://bit.ly/3lbNEIV. The only question, then, is whether the FDA has instituted a *de facto*

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[8] Some argue Congress impermissibly delegated authority to the FDA in violation of the "major questions" doctrine by permitting the agency to determine what constitutes a new "tobacco product." *See, e.g.*, En Banc Brief for 38 Nat'l and State Elec. Nicotine Delivery Sys. Prod. Advoc. Ass'ns as Amici Curiae Supporting Petitioners, *Wages & White Lion Invs. v. FDA* (No. 21-60766) at 20–24. We do not consider that argument here.

ban on non-tobacco-flavored e-cigarettes. If so, then it has violated the APA by failing to provide those regulated with notice or an opportunity for public comment.

The alleged ban stems in part from the "Fatal Flaw" memorandum. It is common knowledge that by Summer 2021, the FDA unexpectedly found itself inundated with millions of PMTAs. To speed up application processing, the agency circulated an internal memorandum providing a new "standard of evidence" for some PMTAs for flavored e-cigarettes. The standard should sound familiar: PMTAs now require evidence from a randomized controlled trial or long-term study, along with "strong evidence that the flavored products have an added benefit relative to that of tobacco flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking."[9] FDA, *PMTA Review: Evidence to Demonstrate Benefit of Flavored ENDS to Adult Smokers* (Aug. 17, 2021); *see also* Timothy Donahue, *Lawsuits Focus on FDA's 'Fatal Flaw' Review for PMTAs*, Vapor Voice (Nov. 19, 2021), https://bit.ly/3lil0Wt (linking to "fatal flaw" memoranda); Alex Norcia, *FDA Memos Reveals Its*

[9] The dissenting judge in the now-vacated *Wages & White Lion* merits opinion noted that although the Fatal Flaw memo was rescinded at the end of August 2021, "its approach appears to have been followed in a check-box 'scientific review' form that indicated only whether a PMTA included a randomized controlled trial or longitudinal cohort study." *Wages*, 41 F.4th at 444 (Jones, J. dissenting). The deficiency letter FDA sent RJRV in 2021 and the internal memoranda between CTP and OS are additional evidence that this standard remained in full effect for all non-tobacco-flavored e-cigarette PMTAs.

"Fatal Flaw" Rejection plan for Flavored Vapes, Filter (Nov. 3, 2021), https://bit.ly/3mY6T9m. Every PMTA that did not include the requisite new evidence was denied. The result: not a single PMTA for non-tobacco flavored e-cigarettes has been granted.[10]

We thus must consider whether this heightened evidentiary standard may avoid the APA's notice-and-comment requirements because the Fatal Flaw memo and its progeny were general statements of policy rather than substantive rules. This question "turns on whether an agency intends to bind *itself* to a particular legal position." *Texas v. EEOC*, 933 F.3d 433, 441 (5th Cir. 2019) (quoting *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 94 (D.C. Cir. 1997)). An action is binding "if it appears on its face to be binding," "is applied by the agency in a way that indicates it is binding," or "retracts an agency's discretion to adopt a different view of the law." *Id.* at 441–42 (internal quotation marks omitted and alteration adopted). Further, a substantive rule "affects the rights of broad classes of unspecified individuals." *City of Arlington v. FCC*, 668 F.3d 229, 242 (5th Cir. 2012); *see also id.* (citing *MacLean v. DHS*, 543 F.3d 1145, 1161 (9th Cir. 2008) (agency action constituting "de facto rulemaking" "may require a notice and comment period")); *Gen. Elec. Co. v. EPA*, 290 F.3d 377, 381–85 (D.C. Cir. 2002 (an EPA guidance document

[10] It is worth noting that when this standard was expanded to menthol-flavored ecigarette PMTAs, OS employees expressed their concern to CTP that the standard would "result in the removal of all ENDS from the U.S. market except for tobacco-flavored ENDS." *See* memo attached in Norcia at 3. n.3 (FDA-LOGICTECHNOLOGY-000171). They had good foresight.

was a legislative rule that should have been issued following notice and an opportunity for public comment).

We conclude that the Fatal Flaw memo's heightened evidentiary standard "bears all the" of a substantive rule. *City of Arlington*, 668 F.3d at 242. First, the memo is binding on its face by mandating that applications contain "the *necessary* type of studies." Second, it has been applied in a way that indicates it is binding; indeed, the subsequent, myriad Denial Orders refer to the same deficiencies identified as "fatal" in the memo. Third, it took away the FDA reviewers' former discretion to consider individual PMTAs solely on their merits and instead requires a cursory, boxchecking review. Finally, it affected the rights of literally hundreds of thousands of applicants whose PMTAs were denied. This is not a close call. *See Iowa League of Cities v. EPA*, 711 F.3d 844, 872–76 (8th Cir. 2013) (vacating two letters sent by the EPA to Senator Charles Grassley as containing new legislative rules without satisfying notice and comment procedures); *Safari Club Int'l v. Zinke*, 878 F.3d 316, 333–34 (D.C. Cir. 2017) (setting aside a press release issued by the U.S. Fish and Wildlife Service for creating an industry ban without going through notice and comment); *Batterton v. Marshall*, 648 F.2d 694, 710 (D.C. Cir. 1980) (holding unlawful a new methodology for collecting and computing unemployment statistics never published or announced by the Department of Labor).

In sum, the FDA has articulated reasons to be concerned about youth vaping. But "[r]egardless of how serious the problem an administrative agency seeks to address, . . . it may not exercise its

authority 'in a manner that is inconsistent with the administrative structure that Congress enacted into law.'" *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125, 120 S. Ct. 1291, 1297 (2000) (holding that Congress had not yet empowered the FDA to regulate tobacco products). Here, RJRV is likely to show that the FDA has instituted a *de facto* ban on non-tobacco-flavored e-cigarettes without going through notice-and-comment. Such action would be held unlawful and set aside as promulgated "without observance of procedures required by law." 5 U.S.C. § 706(2)(D).[11]

B. Irreparable injury

RJRV submits allegations, unchallenged by FDA, that because of the Order, it will incur substantial financial losses in annual revenue as well as reputational harm. It will also have to pay a hefty sum to remove the product from the market and subsequently dispose of it. "[S]ubstantial

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[11] The Seventh and Eleventh Circuits granted motions to stay FDA Denial Orders for other non-tobacco flavored e-cigarette PMTAs. *See Gripum LLC v. FDA*, No. 21-2840, 2021 WL 8874972 (7th Cir. Nov. 4, 2021); *Bidi Vapor LLC v. FDA*, 47 F.4th 1191 (11th Cir. 2022). The Sixth Circuit has denied a motion to stay. *Breeze Smoke, LLC v. FDA*, 18 F.4th 499 (6th Cir. 2021). And this court granted a motion to stay in *Wages*, 16 F.4th 1130.

Ruling on the merits, court decisions have denied e-cigarette manufacturers' petitions for review. *See Avail Vapor, LLC v. FDA*, 55 F.4th 409 (4th Cir. 2022); *Liquid Labs LLC v. FDA*, 52 F.4th 533 (3d Cir. 2022); *Gripum, LLC v. FDA*, 47 F.4th 553 (7th Cir. 2022); *Prohibition Juice Co. v. FDA*, 45 F.4th 8 (D.C. Cir. 2022). Those decisions are unpersuasive on the facts before us.

financial injury" may be "sufficient to show irreparable injury," especially when there is "no guarantee of eventual recovery." *Texas v. EPA*, 829 F.3d 405, 433 (5th Cir. 2016); *Alabama Ass'n of Realtors v. HHS*, 141 S. Ct. 2485, 2489 (2015). Further, "complying with a regulation later held invalid almost *always* produces irreparable harm of nonrecoverable compliance costs." *Texas v. EPA*, 829 F.3d at 433. There is no suggestion, for instance, that RJRV could overcome the FDA's sovereign immunity to recover costs. *See Wages*, 16 F.4th at 1142. Given RJRV's uncontested allegations and legal arguments, we conclude that it has met its burden of showing irreparable harm if denied a stay pending appeal. "Thus, the two most critical factors favor granting a stay." *Id.* at 1143.

C. Balance of harms and public interest

"[T]he maintenance of the status quo is an important consideration in granting a stay." *Barber v. Bryant*, 833 F.3d 510, 511 (5th Cir. 2016). Here, RJRV's menthol Vuse Vibe has been lawfully sold for almost seven years, three of which the FDA spent reviewing its application. RJRV contends that a "a small delay of this one denial order will not harm FDA." The FDA does not argue otherwise. "Given the great likelihood that [RJRV] will ultimately succeed on the merits," we agree that this factor favors a stay. *Texas Democratic Party v. Abbott*, 961 F.3d 389, 412 (5th Cir. 2020).

It is of highest public importance that federal agencies follow the law. *See Texas v. Biden*, 10 F.4th 538, 559 (5th Cir. 2021) (per curiam). The FDA argues that we should defer to "Congress's policy choice" "that it is in the public interest to prohibit the marketing of a new tobacco product until FDA finds that it will produce, on balance, a

benefit to the public health." This argument is obviously colored by the FDA's view of the merits. "But our system does not permit agencies to act unlawfully even in pursuit of desirable ends." *Alabama Ass'n of Realtors*, 141 S. Ct. at 2490. In sum, "there is generally no public interest in the perpetuation of unlawful agency action," *Texas v. Biden*, 10 F.4th at 560. And there is no evidence that "Congress's policy choice" included an exemption from mandatory federal administrative procedures.

III. Conclusion

All four factors favor granting a stay pending appeal. RJRV has easily met its burden. For the foregoing reasons, RJRV's motion for a stay pending review of its petition is GRANTED.

APPENDIX B
FDA Memorandum (Excerpt)
[Prepared July 9, 2021]

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

From: Anne Radway, M.S.
Associate Director
Division of Regulatory Project Management
Office of Science, CTP
Digitally signed by Rosanna Beltre-S
Date: 2021.07.09 11:28:49 -04'00'

Through: Matthew Holman, Ph.D.
Director
Office of Science, CTP
Digitally signed by Matthew R. Holman -5
Date: 2021.07.09 11:33:09 -04'00'

Subject: ENDS Containing Non-Tobacco Flavored E-Liquid: Approach to PMTAs not in Substantive Scientific Review (Phase III)

Background

As of September 9, 2020, FDA commenced review of premarket applications for electronic nicotine delivery systems (ENDS) products on the market as of August 8, 2016; applicants were required by a court order to submit applications to FDA by this date. The majority of these applications are for non-tobacco flavored ENDS products. To date, OS has implemented its plan to review a subset of these applications in this first year: the PMTAs selected for review were identified using a plan described in the Premarket Application Review Prioritization Plan memorandum, signed August

31, 2020. Office of Science has been tasked with developing a new plan to effectively manage the remaining non-tobacco flavored ENDS PMTAs not in Phase III, substantive scientific review. This task has been assigned by the Acting Commissioner given the likely impact on the marketplace on September 10, 2021 (the end of the enforcement discretion period for deemed tobacco products) and in order to take final action on as many applications as possible by September 10, 2021. The objective is to address these applications by applying a standard for evidence necessary to demonstrate an incremental benefit to adult smokers of non-tobacco flavored ENDS products.

Discussion

As described in Section 910 of the FD&C Act, to receive marketing authorization under the PMTA pathway, FDA must conclude that the marketing of the product is appropriate for the protection of public health (APPH), including both tobacco users and nonusers. Based on the information available to date, FDA has determined this evaluation requires evidence that can demonstrate whether an applicant's new non-tobacco flavored product(s) will provide an incremental benefit to adult smokers relative to the applicant's tobacco-flavored product(s). In particular, the evidence necessary for this evaluation would be provided by either a randomized controlled trial (RCT) or a longitudinal cohort study. The absence of these types of studies is considered a fatal flaw, meaning any application lacking this evidence will likely receive a marketing denial order (MOO).

Considering the large number of applications that remain to be reviewed by the September 9, 2021 deadline, OS will conduct a Fatal Flaw review of PMTAs not in Phase III for non-tobacco flavored

ENDS products. The Fatal Flaw review is a simple review in which the reviewer examines the submission to identify whether or not it contains the necessary type of studies. The Fatal Flaw review will be limited to determining presence or absence of such studies; it will not evaluate the merits of the studies. To decrease the number of PMTAs without final action by September 9, 2021, OS used a database query to identify the top twelve manufacturers with the largest number of pending PMTAs not in Phase III for non-tobacco flavored e-liquid products. These applications were pulled out of their respective place in the PMTA priority list, and Phase II Filing was initiated (see Appendix A) [omitted]. Following completion of filing those applications that are filed will immediately initiate Fatal Flaw review.

For the remaining PMTAs not in Phase III for non-tobacco flavored e-liquid products, FDA will send an General Correspondence letter requesting the applicant to confirm if their PMTA contains such evidence and, if so, to direct FDA to the location in the application where the studies can be found. Manufacturers eligible for this process, OS is identifying open PMTAs submitted from April 1, 2020 to September 9, 2020 that have been Received, Accepted and/or Filed and have not entered Phase III. Additionally, PMTAs were filtered based on product characterizing flavor (non-tobacco flavors), product type (i.e., open or closed e-liquid or closed e-cigarette), and category/subcategory (i.e., Other/Other). General Correspondence letters will be issued to companies listed in Appendix B [omitted]. If later FDA discovers a manufacturer was not issued a General Correspondence letter when they should have been, the applications will be evaluated on a case-by-case basis.

* * *

Note: Remainder of text, footnotes and endnotes omitted.