No. 21-60766
Consolidated with No. 21-60800

In the United States Court of Appeals for the Fifth Circuit

WAGES AND WHITE LION INVESTMENTS, L.L.C., doing business as TRITON DISTRIBUTION, PETITIONER,

v.

FOOD & DRUG ADMINISTRATION, RESPONDENT.

ON PETITION FOR REVIEW OF A FINAL MARKETING DENIAL ORDER BY THE UNITED STATES FOOD AND DRUG ADMINISTRATION

UNOPPOSED BRIEF OF INDEPENDENT ACADEMIC AND PUBLIC HEALTH EXPERTS AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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STATEMENT OF INTERESTED PARTIES

No. 21-60766 Consolidated with No. 21-60800

The undersigned counsel of record certifies that the following listed persons and entities as described in the fourth sentence of Circuit Rule 28.2.1 have an interest in the outcome of this case. These representations are made in order that the judges of this court may evaluate possible disqualification or recusal.

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Clive D. Bates is the Director of Counterfactual, a London-based consultancy focused on a pragmatic approach to sustainability and public health. He has had a diverse career in the public, private, and not-for-profit sectors. From 1997-2003 Mr. Bates was Director of Action on Smoking and Health (UK), campaigning to reduce the harms caused by tobacco. He is the co- author of numerous science and policy submissions to the FDA related to ENDS and other reduced-risk products and recognizes the role that US policy plays in shaping international practice.

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SUMMARY OF ARGUMENT

This brief examines FDA's application of the public health standard ("Appropriate for the Protection of Public Health" or APPH) as set out in FDA's standardized Sample Decision Summary Technical Project Lead Report ("TPL Report").[1] This document is substantively identical to the TPL report that supported the marketing denial orders issued to Petitioners. *See* ROA. 21-60766.000115 and ROA.21-60800.000045.

In the TPL Report, FDA outlines the high-level reasoning for its determination of the APPH test in the case of Petitioners and thousands of other applications, as follows:

> These applications for flavored ENDS 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 that could justify that risk. Accordingly, in order to show that a flavored ENDS is APPH, the

[1] FDA, Sample Decision Summary: Technical Project Lead (TPL) Review of PMTAs. September 7, 2021 (accessed November 8, 2021) https://bit.ly/3wuPplI (PDF) accessible in context: https://bit.ly/3FbNcOW

> applicant must show that the benefit to adults switching from or reducing cigarettes outweighs the risk to youth.

In this statement, FDA presents applicants with a *balancing challenge*. Applicants are required to show "*robust evidence of potential benefits to adult smokers*" sufficient to justify the "*known and substantial risk of flavored ENDS with respect to youth appeal, uptake and use*." On one side of the balance—the potential benefits to adults—FDA has introduced new and extremely high evidentiary hurdles: […] 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) or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis. *See* ROA 21-60766.00514-005155.

Having established a new standard of evidence, FDA then applied a "fatal flaw" analysis and rejected thousands of PMTAs without further consideration because they do not provide randomized controlled trials, cohort studies, or other types of evidence to show non-tobacco flavored ENDS have greater smoking cessation efficacy than tobacco-flavored ENDS.

The focus of this brief is on (I) the operation of the APPH test; (II) on the *other side* of the balancing challenge that FDA has established, namely FDA's assertions about youth uptake and use of ENDS and the risks arising from flavored

ENDS; and (III) on the evidentiary hurdles that FDA is imposing on applicants for marketing orders of ENDS products.

ARGUMENT

A. FDA is Misapplying the APPH Test.

Under Section 910 of the Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act ("TCA"), FDA determines whether a new product is "appropriate for the protection of public health" (APPH). The APPH test is expressed in §910(c)(4) of the TCA.

> **Basis for Finding.** For purposes of this section, the finding as to whether the marketing of a tobacco product for which an application has been submitted is appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account—
>
> A. the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
>
> B. the increased or decreased likelihood that those who do not use tobacco products will start using such products.

There are four relevant considerations about the APPH test. First, no such test applies to combustible cigarettes; accordingly, the most dangerous products are easily accessible throughout the United States and their manufacturers do not face the threat of financial ruin from FDA's regulatory burdens and determinations. FDA's regime for evaluating ENDS amounts to a major barrier to entry for less harmful products than cigarettes and unjustified regulatory protection of the

incumbent combustible cigarette trade. FDA should be mindful of these barriers and lower them to the extent possible within the latitude allowed by the law. In practice, it has raised entry barriers to an extent that will exclude nearly all products that compete with combustible cigarettes.

Second, though Congress intended this test to apply to *pre-market* evaluation [TCA §910(a)(4)(A)], almost all the ENDS products under evaluation by FDA are already on the market. FDA's decision to grant or deny a marketing order is, therefore, essentially a decision about whether to withdraw a product already in use by consumers. The effect of FDA's determinations on public health will depend on how consumers respond to the withdrawal of a product they are already using. The behavioral response to a product withdrawal can be *damaging* to public health, for example, if it means relapse to smoking.

Third, the test applies to the "population as a whole." There is no distinction drawn between adolescents and adults in the Act. In some circumstances, ENDS use can be beneficial to adolescents who would otherwise smoke. As a matter of policy, FDA chooses to take no account of such benefits, but that approach is incompatible with the APPH test in §910(c)(4).

Fourth, the APPH test as applied by FDA primarily functions to filter out applications from small and medium-sized entities, regardless of the merits of their products. In applying the APPH test, FDA has chosen the most demanding possible

standards of evidence and intensified them over time. The effect of this in the first instance is *not* to test whether ENDS products already on the market are "appropriate for the protection of public health," but whether the firms involved, and expected revenue streams associated with each product under evaluation, are large enough to bear the costs of FDA's increasingly onerous regulatory demands. Companies, notably legacy tobacco companies, with strong balance sheets and a narrow range of high-volume and relatively simple ENDS products, are greatly advantaged in this regime. FDA's approach has the dual effect of protecting the cigarette trade from competition from diverse ENDS manufacturers and innovative products, while providing significant market-concentration in favor of larger corporate entities, including tobacco companies, operating in the ENDS market.

B. FDA's Approach Mischaracterizes Youth ENDS Use.

There are at least four deficiencies in the way that FDA applies the APPH test to flavored ENDS products in the reasoning provided in the TPL Report. These are briefly summarized in subsections 1. through 4. below and then elaborated upon in the following four sections.

1. FDA relies on a naïve view of the causes of tobacco and ENDS use. FDA assumes that ENDS flavors *cause* adolescent ENDS use, rather than simply reflecting user preferences once established as preferred products of ENDS users. In fact, the causes of tobacco use run far deeper and are not eliminated by removing

flavored products from the market. Without addressing the deeper drivers, the risk-taking drive to use tobacco, ENDS or other substances will find its expression in other risk behaviors, including smoking.

2. FDA ignores likely unintended consequences. FDA makes no assessment of the likely adolescent behavioral response to eliminating flavored products from the market and whether these may be harmful. FDA implicitly assumes that young people using flavored ENDS will cease using ENDS products if flavors are unavailable and these users will resort to healthier behaviors instead. However, this is only one of many possible responses, which include a relapse to smoking, uptake of smoking instead of ENDS, accessing unregulated black-market products, engaging in home mixing of e-liquids with attendant dangers, engaging in criminal supply chains, and accessing flavored synthetic nicotine products that fall outside FDA's jurisdiction.

3. FDA overlooks the benefits of diversion from smoking. FDA fails to recognize the plausible *benefits* to adolescent ENDS users who would otherwise smoke. The APPH standard applies to the "population as a whole" not just people over 18 or 21. There is increasingly persuasive evidence that ENDS function as a *diversion* from smoking for adolescents. *FDA has consistently refused to acknowledge this possible benefit.* If flavors are removed from the market, youth (including adolescents who secure flavored ENDS products illicitly) are more likely

to turn to combustible cigarettes, further perpetuating the harms of combustible tobacco use. However, nothing in the APPH standard allows FDA to ignore (or even *remotely suggests* that FDA should ignore) these real-world public health benefits, even if FDA's officials share our wish that young people do not use nicotine at all.

4. FDA's decision framework does not appropriately weigh risks and benefits arising from ENDS use. The risk to adult smokers from combustible tobacco use is severe and immediate while ENDS use risks to adolescents are more distant and speculative, not comparable in magnitude. FDA has provided no guidance on weighing respective risks and detriments to adults and adolescents; therefore providing no basis for operationalizing the APPH test. This is further complicated by FDA's failure to give weight to adverse behavioral responses to flavored ENDS restrictions (as described in paragraph 2. above) and plausible benefits to adolescent smokers who use flavored ENDS instead of smoking (as described in 3. above).

1. FDA Relies on a Naïve View of the Causes of Tobacco and ENDS Use.

In section 2.3.1 of the TPL Report, FDA discusses youth tobacco initiation and stresses the role of flavored ENDS products. But the causes of tobacco use run

deeper and have been well studied. For instance, Wellman et al. (2016)[2] published a systematic review of risk factors for smoking onset:

> Ninety-eight conceptually different potential predictors were identified in 53 studies. An increased risk of smoking onset was consistently (i.e., in four or more studies) associated with increased age/grade, lower SES [socio-economic status], poor academic performance, sensation-seeking or rebelliousness, intention to smoke in the future, receptivity to tobacco promotion efforts, susceptibility to smoking, family members' smoking, having friends who smoke, and exposure to films, whereas higher self-esteem and high parental monitoring/supervision of the child appeared to protect against smoking onset.

The drivers of tobacco use start with these psycho-social risk factors, not with characteristics of the products such as their flavorings.

In section 2.3.1.1 of the TPL Report, *Youth use of flavored ENDS,* FDA provides data showing non-tobacco flavors are widely used among adolescent ENDS users. But FDA leaps from showing that these flavors are commonly used to an assertion that they are a "primary reason" for use.

> 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.

All ENDS products are widely diverse and artificially flavored (including tobacco-flavored ENDS; unflavored e-liquid does not taste of tobacco). There is no

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[2] Wellman RJ, Dugas EN, Dutczak H, et al. Predictors of the Onset of Cigarette Smoking: A Systematic Review of Longitudinal Population-Based Studies in Youth. *Am. J. Prev. Med*. 2016 https://bit.ly/2YEndjC

reason why young people should have a default preference for tobacco flavor or any other flavor. The choice of flavors reflects preferences among young people already using ENDS, but it does not necessarily explain why they to decide to use ENDS in the first place. For that, FDA relies on studies that ask adolescent ENDS users why they use ENDS to establish the causal link between popularity of flavors and ENDS use (section 2.3.1.1. TPL Report):

> In addition, nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason. [15,16] In fact, among Wave 4 youth current ENDS users, 71% Reported using ENDS "because they come in flavors I like." [14]

Reference [15] in the TPL Report refers to Ambrose *et al.* (2015)[3]. But a reanalysis[4] of this data showed that when asked, young people stated motivations for vaping which mention flavors but also include various forms of harm reduction (*They might be less harmful to me than cigarettes* (79.1% of respondents), *They might be less harmful to people around me than cigarettes* (78.1%), *They help people to quit smoking cigarettes* (59.5%)). The first two harm reduction explanations, taken together, are the most significant reasons given.

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[3] Ambrose BK, Day HR, Rostron B, et al. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. *JAMA* 2015 https://bit.ly/3n960YW

[4] Shiffman S., Sembower MA, PATH Data: Harm Reduction is Teens' Top Reason for Using e-cigarettes. Poster SRNT 2017, Pinney Associates https://bit.ly/30k5hv1

Reference [16] in the TPL Report refers to Tsai *et al.* (2016)[5] which is a CDC analysis of the National Youth Tobacco Survey (NYTS) data. This source shows that most young people give reasons other than flavors for their ENDS use. However, it is surprising that FDA selected an analysis of 2016 data to describe the reasons given for ENDS use, when an equivalent (also from the CDC) using 2019 data is available, Wang *et al.* (2019)[6].

Abridged version of Table 6, Wang *et al.* 2019[7]		
Stated reasons for e-cigarette use (top five only)	**Use e-cigarettes only**	**Use e-cigarettes and other tobacco products**
I was curious about them	56.1%	38.4 %
Friend or family member used them	23.9%	22.2%
They are available in flavors, such as mint, candy, fruit, or chocolate	22.3%	26.6 %
I can use them to do tricks	22.0%	29.0%
They are less harmful than other forms of tobacco, such as cigarettes	17.2%	19.1%

[5] Tsai J, Walton K, Coleman BN, Sharapova SR, et al. Reasons for Electronic Cigarette Use Among Middle and High School Students — National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018. https://bit.ly/3H9VNDN

[6] Wang TW, Gentzke AS, Creamer MLR, Cullen KA, Holder-Hayes E, Sawdey MD, et al. Tobacco product use and associated factors among middle and high school students-United States, 2019. *MMWR Surveill Summ*. 2019 https://bit.ly/3Hf9Ese

[7] *Ibid*. Table 6. Reasons for e-cigarette use among middle and high school students who Reported using e-cigarettes and other tobacco products during the past 30 days — National Youth Tobacco Survey, United States, 2019 https://bit.ly/3n7XyJB

In the later, more relevant survey, the flavors explanation is a distant third behind 'curiosity' (not asked in the 2016 survey) and 'friend or family' influence.

Finally, FDA draws on reference [14] in the TPL Report, which refers to Rostron *et al.* (2020).[8] This is a 2020 study of 2016-17 PATH survey data. The problem with relying on this study is in the nature of the questioning: "*Participants Reporting product use were also asked a series of yes-no questions about whether various factors were a reason for their use*." ENDS users were asked to endorse or reject "*[e-liquids] come in flavors I like"* as a reason for use. But an affirmative answer would be an obvious default response, especially given that respondents could check any or all the options.

Reasons that young people choose to smoke or vape are more complicated than a single product characteristic; better, more recent sources exist than those selected by FDA. For example, Nicksic *et al*. (2019) examined reasons given for youth vaping.[9]

> This study found two overarching factors, "alternative to cigarettes" and "larger social environment", which combine sub-categories to explain main motivators of e-cigarette use.

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[8] Rostron BL, Cheng YC, Gardner LD, Ambrose BK. Prevalence and reasons for use of flavored cigars and ends among US youth and adults: Estimates from wave 4 of the PATH study, 2016-2017. *Am J Health Behav*. 2020. https://bit.ly/3C4x4Nu

[9] Nicksic NE, Snell LM, Barnes AJ. Reasons to use e-cigarettes among adults and youth in the Population Assessment of Tobacco and Health (PATH) study. *Addict Behav*. 2019 https://bit.ly/3CaX35J

Nicksic *et al.* listed thirteen factors influencing e-cigarette adoption, including a weak effect of flavor appeal but also several harm reduction motivations. Nicksic et al. (2019) Report:

> Items that loaded highly onto the "alternative to cigarettes" factor for youth and adults included using in places where cigarettes prohibited, less harmful to me and others, help quit smoking, no smell, and more acceptable. The "larger social environment" factor included people in the media use e-cigarettes, people who are important use them, enjoy socializing while using, and appealing advertising.

Finally, if ENDS flavors were a powerful cause of adolescent ENDS use then we would see a "youth vaping epidemic" everywhere that flavors are available, *e.g.,* UK and Europe, but this does not exist.

In conclusion, in this section we have discussed the multiple drivers of tobacco and ENDS use. These go far beyond the availability of flavored ENDS and removing flavored ENDS does not remove these drivers. For that reason, FDA cannot assume that removing flavored ENDS will cause a significant reduction in tobacco and nicotine use. It is more likely to adjust the pattern of tobacco and nicotine use, and not necessarily in ways that are beneficial for public health.

2. FDA Ignores Likely Unintended Consequences.

To make its case that flavors cause youth vaping, FDA relies on what young people say about their preferences (see Section II.A). In that case, FDA should also rely on what people say when asked how they would react if flavored ENDS were

withdrawn from the market. Posner et al. (2021)[10] asked 18–34-year-olds what they would do if non-tobacco flavors were banned (bold emphasis added):

> If restricted to tobacco flavors, 39.1% of e-cigarette users Reported being likely (very/somewhat) to continue using e-cigarettes (30.5% not at all likely); **33.2% were likely to switch to cigarettes** (45.5% not at all). Considering complete vape product sales restrictions, **equal numbers (~39%) were likely vs. not at all likely to switch to cigarettes.**

We are not aware of an equivalent study covering adolescents under 18-years, but this study provides at least a warning of possible adverse behavioral responses in young people.

Although five US states and hundreds of localities have implemented flavor bans in recent years, there has been little evaluation of these. Friedman (2021)[11] is one of the few studies that have evaluated nicotine use before and after a flavor ban. This research was supported the National Institutes of Health and the FDA Center for Tobacco Products. Friedman found *a significant increase in adolescent smoking*. The increase observed in San Francisco was not replicated in districts that had not

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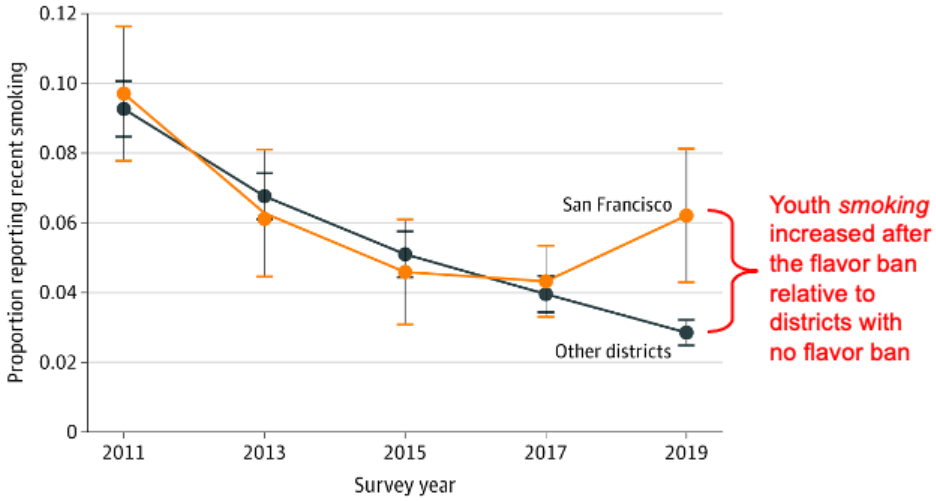
[10] Posner H, Romm KF, Henriksen L, Bernat D, Berg CJ. Reactions to Sales Restrictions on Flavored Vape Products or All Vape Products Among Young Adults in the United States. *Nicotine Tob Res*. 2021 https://bit.ly/30aAdOn

[11] Friedman AS. A Difference-in-Differences Analysis of Youth Smoking and a Ban on Sales of Flavored Tobacco Products in San Francisco, California. *JAMA Pediatr* 2021 https://bit.ly/3ktodyZ

imposed a flavor ban. The figure from Friedman 2021 is shown below with an annotation in red.



San Francisco's experience is an early assessment and not a definitive account of how behavioral transitions will play out. However, it raises questions about FDA's assumptions on young people's response to significant restrictions on the availability of flavored ENDS. One possibility is that they will simply stop vaping or never start. This is FDA's implicit assumption in Section 2.3. of the TPL Report. However, this is not the only possible outcome: a major contraction of the market for flavored ENDS may also cause:

- Increase in smoking, *e.g.,* San Francisco and as reported by young people when asked how they will respond - see Friedman (2021) and Posner (2021) above, respectively.

- Switching from products no longer legally available (most flavored ENDS) to products with granted marketing orders, such as tobacco or menthol flavored ENDS products, with no change in risk to young people.
- Cross-border illicit trade in products not having marketing orders in the United States but are legally manufactured and available in other jurisdictions.
- Increase in home mixing and 'garage' production of e-liquids with informal distribution among family, school-friends, and neighbors. Poorly controlled and insanitary informal production presents significant health and safety risks.
- Formation of a black market in illicitly produced or counterfeit flavored products. These may increase harms compared to lawfully manufactured products (see Omaiye et al. (2021):[12] "*Restriction of JUUL flavours may have inadvertently caused a migration of users to a potentially more harmful product"*).

[12] The restrictions on Juul flavored products have led to a rise in illicit and counterfeit pod products. A recent analysis showed one of these to be potentially more harmful than the Juul equivalents. Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. Flavour chemicals, synthetic coolants and pulegone in popular mint-flavoured and menthol-flavoured e-cigarettes. *Tob Control* 2021 https://bit.ly/3ojRvB2

- Increased contact between young people and criminal supply networks, with adolescents engaged both as customers and as low-level vendors. Multiple adverse consequences flow from such interactions.

- Accelerated development of flavored synthetic nicotine products falling outside FDA's jurisdiction could fill the gap in the flavored ENDS market with unregulated products.

Gravely *et al.* (2021)[13] examined possible responses to flavor restrictions in the United States, Canada, and England. The authors found:

> Predicted behavioral responses were: 28.8% would continue vaping an available flavor, 28.3% would find a way to get their banned flavor(s), 17.1% would stop vaping and smoke instead, 12.9% said that they would stop vaping and not smoke, and 12.9% do not know what they would do.

There is no discussion of behavioral responses or adverse consequences in FDA's TPL Report, which essentially ignores these risks or renders them irrelevant. Yet understanding the behavioral response of users and non-users, including adolescents, is the key challenge in the APPH test.

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[13] Gravely S, Smith DM, Liber AC, Cummings KM, East KA, Hammond D, et al. Responses to potential nicotine vaping product flavor restrictions among regular vapers using non-tobacco flavors: Findings from the 2020 ITC Smoking and Vaping Survey in Canada, England, and the United States. *Addict Beh*av 2021 https://bit.ly/3oRuSo3

3. FDA Overlooks the Benefits to Adolescents.

Conspicuously absent from FDA's discussion of youth vaping in section 2.3.1 is any recognition that ENDS use may be beneficial to young people. For policy purposes, it should be assumed there is a large difference in risk between smoking and ENDS use. According to a major assessment by the National Academies of Science, Engineering and Medicine[14] "*While e-cigarettes are not without health risks, they are likely to be far less harmful than combustible tobacco cigarettes*". Many other assessments concur. Though all parties would prefer young people not to use nicotine, there is a clear public health benefit if they emerge from adolescence as ENDS users rather than smokers.

Since 2016, researchers have insisted that to understand youth ENDS use, it is necessary to segment adolescent use by intensity or frequency of use (number of days used in the past 30 days) and by tobacco use history. Villanti et al (2016)[15] highlighted the interactions between ENDS use and tobacco use.

> Prevalence estimates for a single product mask the complex patterns of frequency, temporality, and poly-use in youth. Two-thirds of past

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[14] National Academies of Sciences, Engineering, and Medicine; Review of the Health Effects of Electronic Nicotine Delivery Systems; Eaton DL, Kwan LY, Stratton K, eds. *Public Health Consequences of E-Cigarettes*. National Academies Press; 2018 https://bit.ly/3qzJLhf

[15] Villanti AC, Pearson JL, Glasser AM, Johnson AL, Collins LK, Niaura RS, et al. Frequency of youth e-cigarette and tobacco use patterns in the U.S.: Measurement precision is critical to inform public health. *Nicotine Tob Res*. 2016. https://bit.ly/3n4rhmO

> 30-day exclusive e-cigarette users have ever used tobacco. Poly-use is the dominant pattern of tobacco and e-cigarette use among US middle and high school students.

This means, at that time, frequent ENDS use was highly concentrated in adolescents with a propensity for tobacco use, and therefore there is a likelihood that they would otherwise be smokers. For these users, *ENDS use may be beneficial*.

In the update to this paper, Collins et al. (2016)[16] emphasized that more intensive ENDS use was at extremely low levels among those who had not previously used tobacco:

> It remained rare in 2015 for tobacco naïve youth to have Reported using e-cigarettes on 10 or more days in the past month (less than 0.1%).

Analysis of 2018 data by Glasser et al. (2021)[17] reached similar conclusions: the frequent vapers were mainly past tobacco users and frequent vaping was rare among tobacco naïve users:

> Results underscore the importance of including the full context of use patterns. The majority of vapers (60.0%–88.9% by use frequency) were concurrent [past-30-day] or ever tobacco users. About 4% of students were tobacco naïve and vaped in the [past 30 days], but few (0.4%) vaped regularly on 20 or more days. Reporting youth vaping data with frequency and tobacco product co-use will give public health decision-makers the best possible information to protect public health.

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[16] Collins LK, Villanti AC, Pearson JL, Glasser AM, Johnson AL, Niaura RS, et al. Frequency of Youth E-Cigarette, Tobacco, and Poly-Use in the United States, 2015: Update to Villanti et al. […] *Nicotine Tob Res*. 2017 https://bit.ly/3wCKY8k7

[17] Glasser AM, Johnson AL, Niaura RS, Abrams DB, Pearson JL. Youth Vaping and Tobacco Use in Context in the United States: Results From the 2018 National Youth Tobacco Survey. *Nicotine Tob Res* 2021https://bit.ly/3F9yuYP

While there was a substantial increase in adolescent e-cigarette use between 2017 and 2019, it is important to be clear that most adolescent use was *infrequent*, and *frequent* use was highly concentrated in young people who had a prior history of tobacco use. Jarvis et al (2020)[18] concluded:

> While use of e-cigarettes in US high-school students increased sharply between 2017 and 2019, frequent use and signs of e-cigarette dependence remained rare in students who had only ever used e-cigarettes and never any other tobacco product.

Recent analysis strengthens the argument that ENDS create a *diversion* away from adolescent smoking. Selya & Foxon (2021)[19] quantified a possible diversion effect:

> A simulation model shows that a substantial diversion effect is needed to explain observed nicotine use trends among US adolescents, and it must be larger than any possible opposing catalyst effect, if present.

Sokol & Feldman (2021)[20] concluded that high school seniors who used e-cigarettes may have otherwise been cigarette smokers:

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[18] Jarvis M, Jackson S, West R, Brown J. Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA? *Qeios* 2020 https://bit.ly/3oDts0j

[19] Selya AS, Foxon F. Trends in electronic cigarette use and conventional smoking: quantifying a possible 'diversion' effect among US adolescents. *Addiction* 2021 https://bit.ly/3C9ZxBg

[20] Sokol N, Feldman J. High school seniors who used e-cigarettes may have otherwise been cigarette smokers: evidence from Monitoring the Future (United States, 2009-2018). *Nicotine Tob Res* 2021 https://bit.ly/30d68Oe

> E-cigarette use is largely concentrated among youth who share characteristics with smokers of the pre-vaping era, suggesting e-cigarettes may have replaced cigarette smoking.

This is consistent with observed US adolescent population trends, which have seen a sharp decline in smoking as ENDS use has risen. Levy et al. (2019)[21] examined trends in youth ENDS use and smoking to find:

> There was a substantial increase in youth vaping prevalence beginning in about 2014. Time trend analyses showed that the decline in past 30-day smoking prevalence accelerated by two to four times after 2014. Indicators of more established smoking rates, including the proportion of daily smokers among past 30-day smokers, also decreased more rapidly as vaping became more prevalent.

FDA as a matter of policy does not recognize these benefits arising from youth ENDS use and they are not discussed in the TPL Report. However, there is no basis for excluding such benefits from an APPH assessment, which must apply to *the whole population*. In fact, former FDA Commissioner, Scott Gottlieb MD, made the policy of denying the benefits of ENDS to adolescent would-be smokers explicit (bold emphasis added).[22]

> No child should use any tobacco product. We've seen cigarette use decline among kids, while e-cig use has grown sharply. This is happening even as overall rates of tobacco use among kids has declined, according to recent data. This is still not acceptable, even if the trends

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[21] Levy DT, Warner KE, Cummings KM, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. *Tob Control* 2019 https://bit.ly/3DfPlc8

[22] FDA Scott Gottlieb, FDA's Nicotine and Tobacco Regulation and the Key Role of Regulatory Science, 18 June 2018 https://bit.ly/3F7qdof

> are moving in a more positive direction of reduced overall use of tobacco products. **Even if kids are using ENDS instead of cigarettes —and that migration in part accounts for the decline in youth cigarette use—that's still not an acceptable trade.**

While we may all wish that young people would not use nicotine or have any vices, regrettably they do. A switch to a less harmful form of nicotine is a real-word effect that cannot be excluded from an APPH assessment. Ignoring such effects will cause FDA to be indifferent to increased adolescent smoking and, therefore, to related harms that arise from regulatory determinations that favor cigarettes at the expense of ENDS.

4. FDA Has Engaged in an Inappropriate Risk to Benefit Analysis.

FDA retrospectively imposed a new evidentiary test for flavored ENDS, but has not shown how this test could be operationalized. A missing element is the relative weight FDA gives to adult smoking cessation compared to youth ENDS uptake. A dependent adult smoker faces significant, rising and near term-risks of serious disease (cancer, cardiovascular, respiratory etc.). Smoking is responsible for 480,000 deaths per year in the United States and smoking cessation provides a significant public health dividend, by whatever means achieved. CDC showed ENDS became the most popular quitting aid by 2016[23]:

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[23] Caraballo RS, Shafer PR, Patel D, Davis KC, McAfee TA. Quit methods used by us adult cigarette smokers, 2014-2016. *Prev Chronic Dis*. 2017. https://bit.ly/3228mAX

> Substituting some cigarettes with e-cigarettes was used by a greater percentage of smokers than the nicotine patch, nicotine gum, or other cessation aids approved by the US Food and Drug Administration.

In contrast, teenage ENDS use causes net detriment only in those who would never have used nicotine. Among such users, ENDS use could be infrequent, transitory, their habit never leading to dependence. In rare cases, it could lead to more intensive use or to a lifetime of ENDS use, but even this would be substantially less detrimental than a lifetime of smoking.

The question remains: How should the risks to adolescent ENDS users be compared to the risks to adult smokers? FDA has provided no insight or guidance into how qualitatively different detriments should be compared, yet risks are at the heart of an APPH assessment, FDA's new balancing test, and the comparative efficacy standard the FDA now imposes on manufacturers of flavored ENDS.

FDA has presented PMTA applicants with a balancing challenge—showing benefits to adults from flavored ENDS use outweigh detriments to youth. But the balance of public health is more complex than this recognizes. To be credible, a balancing calculation must include:

- Detriments to adolescents who become ENDS users but would otherwise never use nicotine. These are exceedingly difficult to assess without knowing if or how ENDS use would progress through one's life.

- Adolescent benefits arising from ENDS use versus smoking. These benefits concentrate in youth populations at greatest risk from tobacco dependence and long-term harms.

- Adolescent detriments arising from adverse behavioral responses to restrictions on flavored ENDS products via its regulatory determinations including increased smoking or black-market engagement.

- Adult health benefits arising from smoking cessation.

The simple framework FDA has outlined in its standardized sample TPL Report is insufficient to meet the APPH requirements of §910(c)(4).

C. FDA's Proposed Evidence Hurdles Are Unrealistic for Nearly All Companies and Products.

In its TPL Report, FDA elaborates the evidentiary hurdle it requires for flavored ENDS products.

> 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) or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis.

Exceedingly burdensome, these tests will not provide results that will credibly inform the APPH determination for most products. Relevance of RCTs and cohort studies are discussed below.

1. Randomized Controlled Trials

Randomized controlled trials (RCTs) are essential and long-established for isolating the effect of drugs or other 'interventions'. But they have considerable limitations when applied to consumer products, where users' preferences and motivations, vendors' marketing practices, and wider environment play an important role in determining whether users choose a product in the first place and then switch from smoking to ENDS.

The main way ENDS users benefit from flavors is choosing what flavor works for them personally, something that is a continuous process of discovery and in which *variety* is part of the appeal (just as it would be with preferences for food/ drink). In RCT, volunteers are randomly assigned to use product under assessment (a flavored ENDS) or a control (e.g., a tobacco flavored ENDS). Their preferences for using a range of products and their evolving preferences over time are deliberately eliminated from the trial. It is unlikely, therefore, that RCTs will be able to capture the beneficial effect of flavored ENDS.

RCTs are also expensive, though cost varies considerably. Nevens *et al*. (2019)[24] provide an estimate for a standard *non-commercial* RCT of $1.7 million

[24] Nevens H, Harrison J, Vrijens F, Verleye L, Stocquart N, Marynen E, et al. Budgeting of non-commercial clinical trials: Development of a budget tool by a public funding agency. *Trials* [Internet]. 2019 https://bit.ly/30oCVjG. See Table 2: https://bit.ly/3qvQ2dL

excluding taxes. For small/medium-sized companies with diverse flavored product range, such costs for each product variant are untenable.

2. Cohort Studies

Cohort studies are impractical for all but a few very large companies with very narrow product ranges and customers they can track. In fact, a cohort study may not be practical even for these companies. Real ENDS users do not behave in a way that allows for a product-specific cohort study. Users of flavored ENDS will use a range of flavors, made by a variety of manufacturers, and their pattern of use will evolve over time. Part of the experience of vaping is to try new flavors and to experiment with new flavors. Even if an ENDS manufacturer could assemble a cohort through a complex network of vape shops, it would not be able to produce *product-specific* findings for nearly all flavored products because most users do not make exclusive and prolonged use of a single product.

3. FDA Ignores the Potential Effectiveness of Post-Market Surveillance Reporting.

RCTs and cohort studies are exceedingly expensive and, as discussed above, may not provide the necessary insights to inform a determination of the APPH test. *Amici*, with others, wrote to the Secretary of Health and Human Service and FDA

in 2019[25] arguing that the current approach to regulation would result in a "crisis" and suggesting seven options for simplification to meet FDA's commitment to make its authorization regime more "more efficient, transparent, and predictable." One of these proposals was to place greater reliance on post-market surveillance to assess behavioral and population aspects of the impact of new products.

> FDA could rely more heavily on post-market surveillance and corrective action. It would make far more sense to have a relatively straightforward and transparent compliance regime for access to the market (the approach taken by the European Union), and to address problems with retrospective action if problems arise. Companies will have to submit extensive plans for post-market surveillance. This is a better use of limited financial and personnel resources than extensive pre-market burdens, as it will allow FDA to assess what is going on in the market after a product is introduced. If there are signs that a product is inappropriate for the protection of public health, FDA has the power to revoke or qualify the marketing order, a far more targeted regulatory action.

A post-market surveillance plan gathers post-market data for use in risk analysis and could be included in any marketing order granted. In fact, inclusion of a post-market surveillance plan is currently a requirement of a PMTA submission for any ENDS product. It is a matter of regret that FDA did not adopt this approach or the other six suggestions for improved efficiency, predictability, and transparency. A crisis is now unfolding.

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[25] Attorney General Tom Miller (Iowa) *et al*., letter to Alex H. Azar II, Secretary of Health and Human Service, copied to FDA. *Regulation of vaping products – a crisis in 2020*. July 24, 2019. https://bit.ly/3C7zWcj See sections 4.2 and 4.3 of this communication.

CONCLUSION

The decision-making framework presented in FDA's TPL Report does not provide a reliable basis for weighing the range of benefits and detriments to adults and adolescents and is not a credible basis for assessing the APPH test. The evidentiary hurdles are impossible for all but a few of the largest companies and a few high-volume commodity products. The requirement to balance benefits to adults against detriments to youth is simplistic: it ignores the benefits of ENDS to the youth most at risk of tobacco use and fails to recognize that a regulator's interventions can have perverse unintended consequences.

FDA should reconsider its approach to the APPH test. FDA could make scientific findings at the level of the whole ENDS category and focus its evaluation resources on the responsible marketing and branding plans of ENDS companies. It should not try to micromanage youth risk behaviors by denying adults (and some adolescents) access to products that are working well as alternatives to smoking..

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This document complies with the word limit of FED. R. APP. P. 29(a)(5) because, excluding the parts of the document exempted by FED. R. APP. P. 32(f), this document contains 6,496 words.

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CERTIFICATE OF CONFERENCE AND RULE 29(A)(4)(E) STATEMENT

I hereby certify Pursuant to FED. R. APP. P. 29(a)(5), counsel for *Amici Curiae* state that Petitioner and Respondent have all articulated their consent to the filing of the subject brief. Pursuant to FED. R. APP. P. 29(a)(4)(E), counsel for *Amici Curiae* state that no counsel for any party authored this brief in whole or in part and that no party nor their counsel made a monetary contribution toward its preparation.

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CERTIFICATE OF SERVICE

Pursuant to FED. R. APP. P. 15(c), I hereby certify that on November 17, 2021, true and correct copies of the foregoing Unopposed Brief of Independent Academic and Public Health Experts as *Amici Curiae* in Support of Petitioner was filed with the Clerk's Office for the United States Court of Appeals for the Fifth Circuit using the CM/ECF system and was served by electronic mail upon the following persons:

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