No. 21-71302

In the United States Court of Appeals for the Ninth Circuit

MY VAPE ORDER, INC.,

Petitioner,

v.

UNITED STATES FOOD & DRUG ADMINISTRATION,

Respondent.

On Petition for Review of a Final Marketing Denial Order by the United States Food & Drug Administration

UNOPPOSED BRIEF OF DR. DAVID B. ABRAMS, CLIVE D. BATES, AND DAVID T. SWEANOR, J.D. AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

[Filed with Consent of All Parties Pursuant to Federal Rule of Appellate Procedure 29(a)]

Mary G. Bielaska
ZANICORN LEGAL, PLLC
845 Third Avenue, 6th Floor
New York, NY 10022
(858) 761-2197
mary.bielaska@zanicorn.com

Jodi K. Swick
MCDOWELL HETHERINGTON LLP
1 Kaiser Plaza, Suite 340
Oakland, CA 94612
(510) 628-2145
jodi.swick@mhllp.com

Attorneys for Amici Curiae Dr. David B. Abrams, Clive D. Bates, and David T. Sweanor, J.D.

CORPORATE DISCLOSURE STATEMENT

Pursuant to Fed. R. App. P. 26.1 and 29(a)(4)(A), the undersigned counsel for *Amici Curiae* hereby certifies that the following *Amici Curiae* are individual persons:

Dr. David B. Abrams

Clive T. Bates

David T. Sweanor, J.D.

Accordingly, there are no parent corporations or any publicly held corporation which owns 10% or more of relevant corporate stock required to be disclosed pursuant to the Federal and Local Rules.

Dated: November 24, 2021

/s/ *Mary G. Bielaska*
Mary G. Bielaska

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Statutes **Page(s)**

Other Authorities

INTEREST OF AMICI CURIAE[1]

The *Amici Curiae* are public health experts with extensive experience related to tobacco and public health policy. **Dr. David B. Abrams** is Professor, Department of Social and Behavioral Science New York University School of Global Public Health. Dr. Abrams is director of the Office of Behavioral and Social Sciences Research, National Institutes of Health, founding director of the Schroeder National Institute of Tobacco Research and Policy Studies and Professor, Health Behavior and Society, Bloomberg School of Public Health, The Johns Hopkins University. He has published over 300 peer-reviewed articles and authored the award-winning *The Tobacco Dependence Treatment Handbook: A Guide to Best Practices*.

Clive D. Bates is the Director of Counterfactual, a London-based consultancy focused on a pragmatic approach to sustainability and public health. 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.

---

[1] Pursuant to Fed. R. App. P. 29(a)(4)(E), *Amici* certify that no counsel for a party authored this brief in whole or in part, and no person other than *amici* or their counsel made a monetary contribution intended to fund the preparation or submission of this brief. The parties have consented to its filing under Fed. R. App. 29(a)(2).

David T. Sweanor J.D., is Adjunct Professor of Law and Chair of the Advisory Board of the Centre for Health Law, Policy and Ethics at the University of Ottawa. Professor Sweanor has worked on global tobacco and health issues for 40 years, helping set many global precedents in Canada.

INTRODUCTION

Section 910 of the Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act ("TCA"), sets out the review process for a Pre-Market Tobacco Product Application ("PMTA"). In its review, FDA determines whether a new applicant product is "appropriate for the protection of public health" (APPH) through a comprehensive assessment of evidence including but not limited to toxicology and individual risk, smoking cessation effects, risk perceptions, youth uptake and marketing controls. 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.

This brief examines FDA's application of the APPH standard as set out in FDA's standardized Sample Decision Summary Technical Project Lead Report

("TPL Report").[2] This document is substantively identical to the TPL report that supported the marketing denial orders issued to Petitioner.

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

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

This sets up a novel balancing challenge: to show that the incremental adult smoking cessation value of non-tobacco flavored ENDS compared to tobacco-flavored ENDS outweighs "known and substantial" risks to youth from flavored ENDS. On one side of this balancing challenge—the potential incremental 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.

---

[2] 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

Having established an onerous new standard of evidence, FDA then used a "fatal flaw" checklist to deny over one million PMTAs without further consideration because they do not provide randomized controlled trials, cohort studies, or other types of (unspecified) evidence that FDA had retrospectively deemed necessary.

SUMMARY OF ARGUMENT

This brief concentrates on three aspects of the decision-making framework that FDA used to deny over one million PMTAs.

First, *amici* highlight how FDA's approach *in aggregate* functions as *de facto* standard-setting (with the effect of prohibiting or severely restricting flavored ENDS) but without the disciplines of formal rulemaking required under the Tobacco Control Act. Had such disciplines been followed, FDA would have to account for adverse effects arising from the distortion of the consumer nicotine market in favor of cigarettes, unintended perverse consequences of withdrawing ENDS products already in use by millions of consumers, and to recognize the benefits of ENDS to adolescents who would otherwise be smoking.

Second, *amici* argue FDA's assertion that there is "*known and substantial risk to youth of flavored ENDS*" is simplistic and highlight the likely negative public health consequences for youth of FDA denying nearly all flavored ENDS applications. *Amici* show that the psychosocial causes of tobacco and ENDS use run deeper than merely the availability of flavored products and, therefore, that a *de facto*

ban on flavored products could lead to perverse unintended consequences such as a return to smoking or accessing black markets rather than FDA's desired goal of youth abstinence from ENDS use. *Amici* also show that FDA purposefully ignores important *benefits* of ENDS use among adolescents who would otherwise smoke and has not appropriately weighed the respective harms of youth vaping and adult or adolescent smoking.

Third, *amici* suggest FDA's new requirements for randomized controlled trials or cohort studies are excessive and are, in any case, unlikely to be informative for an APPH test for a single product. *Amici* previously proposed that FDA should rely on post-market surveillance to identify adverse public health effects at the population level. It could then use its powers to rescind marketing orders when and if problem products or sub-categories emerge, rather than trying to second guess future trends and micromanage youth risk behaviors with arbitrary bans.

ARGUMENT

A. The APPH Test as Applied by FDA Will Function as a Near Complete Ban on Flavored ENDS Products That Amounts to De Facto Rulemaking with Perverse Consequences for the Whole Market That Are Beyond the Scope of Individual Product Applications.

The evidentiary test set by FDA will be impossible for almost all (and possibly all) manufacturers to meet for flavored ENDS products. It has already led to the vast majority having their applications denied. It will, therefore, *change the*

market as a whole and have effects on public health that would be beyond the scope of any individual applicant to assess. This is because the adverse population effects arise from the *aggregate* results of FDA's application of its evidentiary standard to over one million applications.

The new standard (or its result – the likely removal of nearly all flavored products from the market) amounts to *de facto* informal rulemaking by FDA. In 2018, FDA published Advanced Notice of Proposed Rulemaking (ANPRM) to assess options to prohibit or restrict flavored ENDS products.[3] The Tobacco Control Act provides safeguards against FDA rulemaking that would cause net population harm. Under Section 907 (Tobacco Product Standards) of the Tobacco Control Act, FDA itself is required to meet an APPH standard in setting standards *See* TCA §907(a)(3).

> **In General**. The Secretary may adopt tobacco product standards in addition to those in paragraph (1) if the Secretary finds that a tobacco product standard is appropriate for the protection of the public health.

In a 2018 response to this ANPRM, *amici,* with others, argued many of the points set out in this brief, summarized in the quote below.[4]

---

[3] Regulation of Flavors in Tobacco Products: A Proposed Rule by the Food and Drug Administration, March 21, 2021. 83 FR 12294. https://bit.ly/3FFEY21

[4] Miller T, Bates C, Abrams D, Niaura R, Sweanor D. Regulation of Flavors in Tobacco Products: A Proposed Rule by the Food and Drug Administration. July 19, 2018 https://bit.ly/3wGDq4v

> To summarize, the chain of reasoning required to justify rulemaking to prohibit particular flavors, flavor categories or flavor descriptors in non-combustible products is extremely challenging, with the real possibility that FDA intervention could cause harm both to adults and young people if it makes misjudgments about the (1) effects of vaping on health, and (2) the effect of flavors on vaping. FDA would need to show that vaping itself is a source of net harm (this is unlikely) and show that particular flavors or descriptors were increasing uptake and contributing to harm (this is difficult). Finally, it would need to show its proposed intervention would be proportionate and effective, and not prone to excessive unintended consequences (for this, there is no credible evidence). The FDA does not have a reliable case at any point in this chain of reasoning.

There are four reasons to doubt that FDA would meet the APPH test in TCA §907 had it proposed a ban on flavored ENDS products through rulemaking.

First, the PMTA process and APPH test do not apply to combustible cigarettes, which have a much less onerous path to market; 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. The harms arising from adult and adolescent cigarette smoking far outweigh the harms arising from youth use of ENDS.

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 deny a marketing order is, therefore, a decision to *withdraw* a product already in use by consumers. The effect of FDA's determinations on public health will depend on how millions of consumers respond in total to the withdrawal of thousands of products 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, home mixing, or accessing the black market.

Third, the APPH 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 to youth, but that approach is incompatible with the APPH test in either the PMTA pre-market review process TCA §910(c)(4) or in rulemaking for setting product standards §907(a)(3).

Fourth, the APPH test, as applied by FDA, primarily functions to eliminate applications from small and medium-sized entities, regardless of the merits of their products. 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. In Asserting There is a "Known and Substantial Risk to Youth of Flavored ENDS" FDA 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.

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) [5] 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 [socioeconomic status], poor academic performance, sensation-seeking or rebelliousness, intention to

[5] 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

> 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 psychosocial 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 artificially flavored, including tobacco-flavored ENDS (unflavored e-liquid does not taste of tobacco). There is no 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 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 the 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) [6]. But a reanalysis[7] 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 reason given.

Reference [16] in the TPL Report refers to Tsai *et al.* (2016)[8] , 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

---

[6] 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

[7] 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

[8] 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

reasons given for ENDS use, when an equivalent (also from the CDC) using 2019 data is available, Wang *et al.* (2019).[9]

Abridged version of Table 6, Wang *et al.* 2019[10]		
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%

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).[11] This is a 2020 study of 2016-17 survey data. The problem

---

[9] 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

[10] *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

[11] 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

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. [12]

> 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.

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

---

[12] 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

> 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.,* the UK and Europe, but this does not exist.

In conclusion, we have discussed the multiple drivers of tobacco and ENDS use. These go far beyond the availability of flavored ENDS. 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 of Removing All or Nearly All Flavored ENDS Products from the Market.

To make its case that flavors cause youth vaping, FDA relies on what young people say about their preferences. 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)[13] asked 18–34-year-olds what they would do if non-tobacco flavors were banned (bold emphasis added):

---

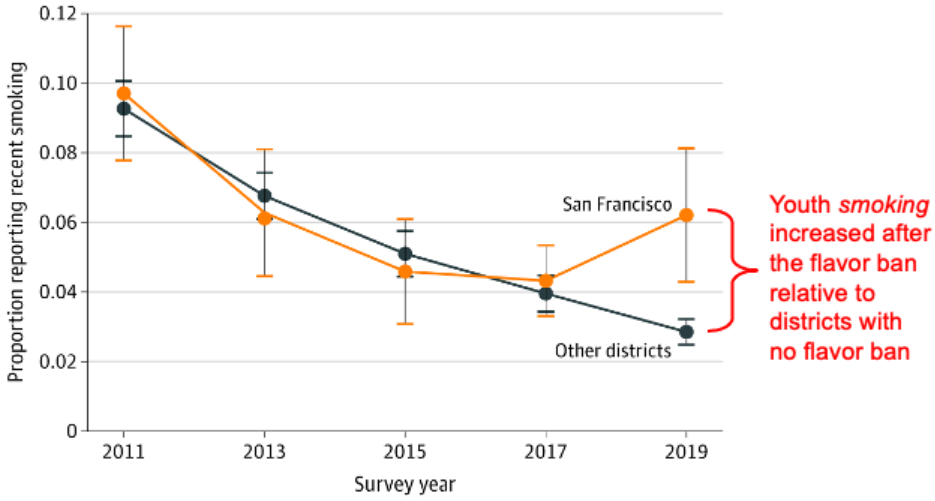
[13] Posner H, Romm KF, Henriksen L, Bernat D, Berg CJ. Reactions to Sales Restrictions on Flavored Vape Products or All Vape Products Among Young Adults in the United States. *Nicotine Tob Res*. 2021 https://bit.ly/30aAdOn

> 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.

Friedman (2021)[14] is one of the few studies that has evaluated nicotine use before and after a flavor ban. This research was supported by 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 imposed a flavor ban. The figure from Friedman 2021 is shown below with an annotation in red.

[14] 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



San Francisco's experience 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 lead to:

- Initiation or relapse to 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 to tobacco flavored ENDS products, with no change in risk to young people.
- Accessing cross-border illicit trade in products that are legally manufactured and available in other jurisdictions.

- Increasing home mixing and 'garage' production of e-liquids with informal distribution among family, school-friends, and neighbors.
- Formation of a black market in illicitly produced or counterfeit flavored products.
- Increased contact between young people and criminal supply networks, with adolescents engaged both as customers and as low-level vendors.
- Accelerated development of flavored synthetic nicotine products falling outside FDA's jurisdiction.

Gravely *et al.* (2021)[15] examined possible responses to flavor restrictions in the United States, Canada, and England.

> 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.

The authors found a mixture of expected behavioral responses, with only one in eight saying they would cease tobacco and ENDS use altogether. A *majority* of those declaring their intent would make an adverse behavioral response.

---

[15] 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 Behav.* 2021 https://bit.ly/3oRuSo3

Yet, there is no discussion of behavioral responses or adverse consequences in FDA's TPL Report, which essentially ignores these risks.

3. FDA Overlooks the Benefits of ENDS Use to Adolescents.

Conspicuously absent from FDA's discussion of youth vaping in section 2.3.1 of its TPL Report 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,[16] "*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 and to focus public health concerns on the frequent users as they have the greatest risk of forming dependency.

---

[16] 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

Villanti *et al*. (2016)[17] and a follow-up by Collins *et al*. (2017)[18] concluded frequent ENDS use was highly concentrated in adolescents with an existing propensity for tobacco use and remained rare for tobacco naïve youth. For the ENDS users who would otherwise be smoking, *ENDS use may be beneficial*.

Analysis of 2018 data by Glasser et al. (2021)[19] 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.

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*,

---

[17] 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

[18] 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

[19] 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

and *frequent* use was highly concentrated in young people who had a prior history of tobacco use. Jarvis *et al*. (2020)[20] 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)[21] 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) [22] concluded that high school seniors who used e-cigarettes may have otherwise been cigarette smokers:

> 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.

---

[20] 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

[21] 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

[22] 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

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)[23] 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 the possible benefits arising from youth ENDS use, and they are not discussed in the TPL Report. In fact, former FDA Commissioner, Scott Gottlieb MD, made the policy of denying the benefits of ENDS to would-be adolescent smokers explicit (bold emphasis added).[24]

> 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 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.**

---

[23] 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

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

While all responsible adults wish that young people would not use nicotine, regrettably, many do. A switch to a less harmful form of nicotine is a real-world public health effect that cannot be excluded from an APPH assessment. Ignoring such effects will cause FDA to be indifferent to increased adolescent smoking that arises from regulatory determinations that favor cigarettes at the expense of ENDS.

4. FDA Has Provided No Basis for Comparing Risks of Adolescents Flavored ENDS use to Risks of Smoking.

FDA has not shown how the APPH test could be operationalized. A crucial 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, whatever method is used to achieve it. CDC showed ENDS became the most popular quitting aid by 2016[25]:

> 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.

---

[25] 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

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 and their habit transitory, 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? Individual applicants could only guess at these weightings, and they would depend on information about future use decades ahead that is, by definition, not yet available.

FDA has presented PMTA applicants with a balancing challenge—showing benefits to adults from flavored ENDS outweigh detriments to youth. But the balance of public health is more complex than this recognizes. It should compare benefits and detriments to both adults and adolescents and apply appropriate weighting to different forms of detriment and benefit. If it took this approach, its assessment of APPH would be dominated by changes in the *smoking* status of both adults and adolescents caused by ENDS use.

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.

Though exceedingly burdensome, these tests will not provide results that will credibly inform the APPH determination for most products. The relevance of RCTs and cohort studies is discussed below.

1. Randomized Controlled Trials Are Expensive but Do Not Capture the Reasons Why a Smoker Chooses an ENDS Product to Start with Including Flavor Choices.

Randomized controlled trials (RCTs) are essential and long-established for isolating the effect of drugs or other medical interventions. But they have considerable limitations when applied to consumer products, where users' preferences and motivations, vendors' marketing practices, and the 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 the 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 the cost varies considerably. Nevens *et al*. (2019)[26] provide an estimate for a standard *non-commercial* RCT of $1.7 million excluding taxes. For small/medium-sized companies with diverse flavored product ranges, such costs *for each product variant* are untenable.

2. Cohort Studies Will Not Work for a Specific Product Because Most ENDS Users Use a Variety of Products and Vary Their Preferred Product Over Time.

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, often made by a variety of manufacturers, and their pattern

---

[26] 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

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 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. Also, they cannot be used to assess benefits and detriments to youth. *Amici*, with others, wrote to the Secretary of Health and Human Service and FDA in 2019[27] arguing that the current approach to regulation would result in a "crisis" and suggesting seven options for simplification to meet FDA's commitment to making 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

---

[27] 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.

> 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, the 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.

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.

November 24, 2021

Respectfully submitted,

MARY G. BIELASKA

/s/ Mary G. Bielaska
MARY G. BIELASKA*
ZANICORN LEGAL, PLLC
845 Third Avenue
6th Floor
New York, NY 10022
(858) 761-2197
mary.bielaska@zanicorn.com
*Admission Pending

JODI K. SWICK

/s/ Jodi K. Swick
Jodi K. Swick
McDowell Hetherington LLP
1 Kaiser Plaza, Suite 340
Oakland, CA 94612
(510) 628-2194
jodi.swick@mhllp.com

Attorneys for Amici Curiae Dr. David B. Abrams, Clive D. Bates, and David T. Sweanor, J.D.

CERTIFICATE OF COMPLIANCE

I hereby certify as follows:

1. The foregoing **UNOPPOSED BRIEF OF DR. DAVID B. ABRAMS, CLIVE D. BATES, AND DAVID T. SWEANOR, J.D. AS *AMICI CURIAE* IN SUPPORT OF PETITIONER** complies with the word limitation requirements contained in Fed. R. App. P. 29(a)(5) and Ninth Circuit Rule 32-1(a). The brief contains 6,529 words according to the word count of the word-processing system used to prepare the brief (excluding the parts of the brief exempted by Fed. R. App. P. 32(f)).

2. The foregoing **UNOPPOSED BRIEF OF DR. DAVID B. ABRAMS, CLIVE D. BATES, AND DAVID T. SWEANOR, J.D. AS *AMICI CURIAE* IN SUPPORT OF PETITIONER** likewise complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and with the type style requirements of Fed. R. App. P. 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point Times New Roman font.

November 24, 2021

/s/ Mary G. Bielaska
Mary G. Bielaska

Attorney for Amici Curiae

CERTIFICATE OF CONFERENCE

I hereby certify pursuant to FED. R. APP. P. 29(a)(2), counsel for *Amici Curiae* state that Petitioner and Respondent have all articulated their consent to the filing of the subject brief.

November 24, 2021

/s/ Mary G. Bielaska
Mary G. Bielaska

Attorney for Amici Curiae

CERTIFICATE OF SERVICE

I hereby certify that on November 24, 2021, the foregoing **UNOPPOSED BRIEF OF DR. DAVID B. ABRAMS, CLIVE D. BATES, AND DAVID T. SWEANOR, J.D. AS *AMICI CURIAE* IN SUPPORT OF PETITIONER** was filed November 24, 2021, I electronically filed the foregoing **BRIEF OF *AMICI CURIAE* INDEPENDENT ACADEMIC AND PUBLIC HEALTH EXPERTS IN SUPPORT OF PETITIONER** with the Clerk of the Court of the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF system. All participants in the case are registered CM/ECF users and service on the below parties will be accomplished by e-mail by operation of the Court's CM/ECF system:

Eric Heyer
THOMPSON HINE LLP
1919 M Street NW, Suite 700
Washington, DC 20036-1600
(202) 263-4128
eric.heyer@thompsonhine.com

Counsel for Petitioner
MY VAPE ORDER, INC.

Alisa Beth Klein
U.S. DEPARTMENT OF JUSTICE
950 Pennsylvania Ave. NW
Washington, DC 20530
alisa.klein@usdoj.gov

Counsel for Respondent
U.S. FOOD AND DRUG ADMIN.

Kate Talmor
U.S. DEPARTMENT OF JUSTICE
1100 L Street NW
Washington, DC 20530
(202) 616-8351
kate.talmor@usdoj.gov

Counsel for Respondent
U.S. FOOD AND DRUG ADMIN.

Eric B. Beckenhauer
U.S. DEPARTMENT OF JUSTICE
1100 L Street NW
Washington, DC 20530
(202) 514-3338
eric.beckenhauer@usdoj.gov

Counsel for Respondent
U.S. FOOD AND DRUG ADMIN.

Lindsey Powell
U.S. DEPARTMENT OF JUSTICE
950 Pennsylvania Ave. NW
Washington, DC 20530
lindsey.e.powell@usdoj.gov

Counsel for Respondent
U.S. FOOD AND DRUG ADMIN.

J. Gregory Troutman
TROUTMAN LAW OFFICE, PLLC
4205 Springhurst Blvd., Suite 201
Louisville, KY 40241
(502) 412-9190
jgtatty@yahoo.com

Counsel for Amicus Curiae
37 NATIONAL AND STATE ELECTR. NICOTINE DELIVERY SYSTEM PRODUCT ADVOCACY ASSOCIATIONS

November 24, 2021

/s/ Mary G. Bielaska
Mary G. Bielaska

Attorney for Amici Curiae