VAPOR TECHNOLOGY ASSOCIATION

Via Electronic Submission

July 19, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Docket No. FDA-2017-N-6565: Regulation of Flavors in Tobacco Products

Dear Sir or Madam:

The Vapor Technology Association ("VTA") respectfully submits the attached comments to the United States Food and Drug Administration ("FDA") in response to the Advance Notice of Proposed Rulemaking published on March 21, 2018, entitled "Regulation of Flavors in Tobacco Products."

VTA is submitting the comments electronically through the portal at Regulations.gov.

Respectfully submitted,

Tony Abboud
Executive Director
Vapor Technology Association

The Vapor Technology Association's Comments in Response to FDA's Advance Notice of Proposed Rulemaking: Regulation of Flavors in Tobacco Products

Docket No. FDA-2017-N-6565

July 19, 2018

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I. INTRODUCTION

As the voice of the vapor products industry, the Vapor Technology Association is grateful for the opportunity to present data and information to FDA regarding the Electronic Nicotine Delivery System ("ENDS") product category and the role of flavors therein.

A. The Vapor Technology Association

The Vapor Technology Association is the national non-profit industry trade association whose more than 600 members are dedicated to developing and selling high quality vapor products that provide adult consumers with a safer alternative to traditional combustible cigarettes. Our trade association includes the leading manufacturers of aerosolizing apparatuses – commonly known as vapor devices or e-cigarettes – manufacturers of e-liquids, flavorings, and components, as well as wholesalers, importers, and brick-and-mortar vape shop retailers.

As is the case with the vapor industry in general, many of the VTA's members are small businesses that have created significant employment opportunities in their local communities and that contribute substantially to local and state economies. Specifically, the VTA is proud to claim as its members 22 independent state vapor trade associations and their member companies, the majority of which are small businesses and retailers who have implemented strict standards to prevent youth access to vapor products. The state vapor associations that are working directly with VTA on developing sound policy, implementing marketing standards, and preventing youth access to vapor products include the following:

Arizona Smoke Free Business Alliance
Arkansas Vape Advocacy Alliance
Breathe Easier Alliance of Alabama
California Smoke Free Organization
Florida Smoke Free Association
Georgia Smoke Free Association
Indiana Smoke Free Alliance
Iowans For Alternatives to Smoking Tobacco
Kentucky Smoke Free Association
Louisiana Vaping Association
Maryland Vapor Alliance
Montana Smoke Free Association
Nevada Vaping Association
Ohio Vapor Trade Association
Oregon Vapor Trade Association
Pink Lung Brigade
Smoke Free Alternatives Coalition of Illinois
South Dakota Smoke Free Association

Tennessee Smoke Free Association
Texas Vapor Coalition
Utah Smoke Free Association
Virginia Smoke Free Association

The VTA has been at the forefront of the most critical issues confronting the vapor industry and has specifically attacked the issue of ensuring that vapor products are properly marketed towards adults only. To that end, the Board of Directors of the VTA has been speaking publicly on the issue of ending youth access to ENDS products and has developed the industry's first comprehensive set of marketing standards, the VTA Marketing Standards for Membership, a copy of which is attached hereto as Appendix 1.

B. Summary of Considerations

ENDS products occupy a singularly unique place among the range of products legally defined as "tobacco products" under the Tobacco Control Act. ENDS products are more than 95% safer than combustible cigarettes and so sit at the extreme opposite end of the "tobacco products" risk continuum. Uniquely among all tobacco products, all ENDS flavors, including tobacco flavors, are artificial. The existing science strongly suggests that ENDS products, and particularly non-tobacco flavors in ENDS products, are a beneficial aid to smokers' harm reduction and smoking cessation efforts. In contrast, non-tobacco flavors have not been definitively linked to initiation of ENDS use among non-smokers, including youth, and, even if they could be, there is no scientific evidence of a so-called "gateway effect" to more harmful combustible cigarettes. In light of the predictable harms that would result to former, current, and future smokers if access to non-tobacco flavored ENDS were restricted, FDA should demand of itself the highest level of scientific evidence before considering potentially restricting access to ENDS products. As outlined in the comments and answers to questions posed by FDA in the ANPRM below, such evidence does not exist as regards flavors in ENDS products.

Based on the science developed to date, the substantial public health benefits that non-tobacco flavored ENDS provide to smokers far outweigh the potential physiological and public health risks. There is no valid scientific basis that would justify FDA adopting a product standard that would restrict access to non-tobacco-flavored ENDS products. Rather, to the extent that FDA is concerned about youth access to ENDS products, FDA should more strictly enforce the restrictions against sales to minors that are already within FDA's enforcement powers and also consider whether it might be appropriate to adopt marketing and advertising restrictions to further limit youth exposure to such messaging. If FDA elects to pursue the latter, VTA's self-imposed Marketing Standards for Membership provide a reasonable template.

VTA's specific responses to the questions set forth in the ANPRM are attached hereto as Appendix 2 and scientific references are attached as Appendix 3.

II. BECAUSE ENDS PRODUCTS OCCUPY A UNIQUE PLACE ON THE RISK CONTINUUM, FDA WOULD BE ILL ADVISED TO REGULATE ENDS FLAVORS WITHOUT THE HIGHEST DEGREE OF SCIENTIFIC CERTAINTY.

Because ENDS products are unlike any other product that may be regulated pursuant to this ANPRM, the FDA must consider the very unique aspects of ENDS products, the position that they occupy on the risk continuum, and the enormous promise for tobacco harm reduction that they uniquely represent. Specifically, because the proven health risks associated with ENDS products are so low and the potential benefits of such products are so high, FDA should demand of itself the most rigorous scientific standard of certainty before considering any product standard or other restriction on the sale of flavored ENDS products. This is especially true where FDA is considering whether to regulate one specific aspect of ENDS products and the science simply cannot support any restriction, as is the case with flavors here.

A. Section 907 of the FDCA Requires FDA to Have a Valid Scientific Basis Before It Can Regulate Flavors.

Based on VTA's review of the peer-reviewed research on the role of tobacco and non-tobacco flavors in ENDS, FDA does not have a sound scientific basis upon which to issue a product standard or otherwise restrict the sale or distribution of any ENDS flavor. Section 907 of the federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 387g, provides that, in order to adopt a tobacco product standard, FDA must have a scientific basis for determining that the standard is "appropriate for the protection of the public health." 21 U.S.C. § 387g(a)(3)(A). To make such a determination, FDA must consider scientific evidence concerning:

- the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard;
- the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- the increased or decreased likelihood that those who do not use tobacco products will start using such products.

21 U.S.C. § 387g(a)(3)(B)(i). FDA is also required to consider "all other information submitted in connection with a proposed standard, including information concerning the countervailing effects of the tobacco product standard on the health of adolescent tobacco users, adult tobacco users, or nontobacco users, such as the creation of a significant demand for contraband or other tobacco products that do not meet the requirements of this chapter and the significance of such demand." 21 U.S.C. § 387g(b)(2). Given that the current state of research in connection with ENDS products (as set forth in Sections III – VI, below) does not provide a sound scientific basis for doing so, VTA respectfully submits that

FDA should take no action to restrict the manufacture, sale, or distribution of any ENDS flavor.[1]

What follows is a detailed explanation of the numerous reasons that, for the sake of both individual and public health, FDA must examine the role of flavors in ENDS products differently than any other product under consideration and why FDA should impose on itself the highest standard of scientific certainty before it acts to regulate or limit ENDS flavors in any way at this time. Never has a technological innovation in the form of a widely accessible consumer product emerged to compete so aggressively with the combustible cigarette which, even today, kills nearly half a million Americans every year. For that reason alone, FDA should be very circumspect about any regulation that might in any way impair or limit the ability of addicted adult smokers to take up ENDS products.

B. As a Category, ENDS Products Are At Least 95% Safer than Combustible Cigarettes and Save Lives.

FDA is aware of the significant literature review and evaluations undertaken by the internationally recognized and esteemed Royal College of Physicians in 2014, 2015, and 2016 – evaluations which concluded unequivocally that the potential hazard to health arising from long-term use of ENDS products is five percent (5%), and probably substantially less than that, of the comparable harm resulting from the use of traditional combustible products. (Royal College Report, 2016.) This year-over-year conclusion is also shared by the United Kingdom's Department of Health – Public Health England – which reached an identical conclusion after conducting its independent review of the peer reviewed literature in 2015 and 2016. (McNeill A, et al., 2018.)

Similarly, U.S. researchers recently published a study in *Tobacco Control* concluding that switching from traditional cigarettes to e-cigarettes would annually prevent between 1.6 million and 6.6 million premature deaths in the United States. (Levy, et al., 2017.) This conclusion was further bolstered by the rigorous analysis of the National Academies of Sciences, Engineering, and Medicine ("NASEM") which, in January 2018, published the following material findings regarding e-cigarettes:

- "There is ***conclusive evidence*** that completely substituting e-cigarettes for combustible tobacco cigarettes **reduces users' exposure to numerous toxicants and carcinogens** present in combustible tobacco cigarettes." (NASEM Report at 604.)

[1] Importantly, the absence of a sound scientific or legal basis for restricting flavors in ENDS products does not mean that VTA does not endorse continuing the discussions that it has already commenced with FDA to achieve a rational regulatory scheme, as well as the implementation of agreed product standards pertaining to the manufacture and distribution of ENDS and/or e-liquids.

- "There is ***substantial evidence*** that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in **reduced short-term adverse health outcomes in several organ systems**." (NASEM Report at 617.)

- "The evidence about harm reduction suggests that **across a range of studies and outcomes, e-cigarettes pose less risk to an individual than combustible tobacco cigarettes**." (NASEM Report at 11, 487.)

It is important to note that all of the foregoing pronouncements included ENDS products of varying flavors, meaning that, on balance, the existence or inclusion of flavors in ENDS products was factored into all of these conclusions that e-cigarettes are overwhelmingly safer than smoking.

Fortunately, adult smokers have been availing themselves of the harm reduction opportunity presented by ENDS products *en masse*. The Centers for Disease Control reports that the number of smokers as a percentage of the U.S. population has dropped dramatically from 20.6% in 2009,[2] when ENDS products first gained traction in the United States, to only 15.5% as of 2016.[3] Unless FDA can prove that such remarkable advances in the reduction of cigarette smoking have been achieved notwithstanding the dramatic growth and availability of ENDS products to addicted adult smokers, FDA should not take any steps that could reverse this substantial decline in smoking.

C. ENDS Products Sit at the Opposite End of the Risk Continuum From Combustible Products.

In addition to taking into account the accepted scientific conclusions that vapor products are demonstrably safer than combustible cigarettes, FDA also must take into account the place that ENDS products occupy on the opposite end of the risk continuum from combustible cigarettes – a place occupied by the products that deliver nicotine without combustion and in the absence of any tobacco. As the foregoing reflects, the ENDS product category presents a substantially less harmful alternative to traditional combustible cigarettes and provides a significant opportunity to advance the public health goals of smoking cessation and harm reduction by enabling existing smokers to move down the risk continuum from combustible cigarettes to less harmful ENDS products.

Indeed, FDA itself has repeatedly acknowledged this unique feature of the ENDS category. As recently as April 24, 2018, Commissioner Gottlieb stated that FDA "see[s] the possibility for ENDS products . . . to provide a potentially less harmful alternative for

[2] CDC, Trends in Current Cigarette Smoking Among High School Students and Adults, United States, 1965–2014, available at:
https://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/index.htm.

[3] CDC Press Release, Smoking is down, almost 38 million American adults still smoke (Jan. 18, 2018).

currently addicted individual adult smokers who still want to get access to satisfying levels of nicotine without many of the harmful effects that come with the combustion of tobacco" and that e-cigarettes "may offer a potentially lower risk alternative for individual adult smokers." (FDA Statement, April 24, 2018.)

Moreover, on June 11, 2018, in a dramatic and important statement, the American Cancer Society ("ACS") recognized that e-cigarettes occupy a place on the risk continuum that is much closer to nicotine replacement therapies than to the combustible tobacco products with which ENDS are routinely and inaccurately associated:

> Tobacco products are designed and intended to deliver nicotine to the user, but the toxicity associated with these products varies widely. At one end is the conventional cigarette, which, when burned and inhaled, delivers more than 7000 chemicals to the user, including at least 70 carcinogens, and is designed to cause and sustain addiction to nicotine while killing one-half of all long-term users. At the other end are medicinal nicotine products, which pose minimal risk and have been approved by FDA as safe and effective for tobacco cessation. Along the spectrum— and closer to nicotine-replacement therapies than to combustible tobacco products—are current-generation ENDS, which are likely to be much less harmful than combustible tobacco products. (Douglas, et al., 2018.)

Thus, FDA must temper any desire to broadly limit flavors in all "tobacco products" by recognizing the end of the risk continuum at which ENDS products are being experienced by adult smokers.

D. The Unique Attributes of ENDS Products Require that They Be Examined and Treated Differently Than Any Combustible Tobacco Product.

Although ENDS are encompassed in the Tobacco Control Act's broad legal definition of "tobacco products," they differ markedly from virtually every other product covered by that definition in multiple meaningful ways and so must also be treated differently as a matter of FDA policy. FDA must resist the temptation to lump together ENDS products with combusted tobacco products since doing so serves no meaningful scientific or policy objective when evaluating completely different types of products – one, an organic agricultural product that is combusted, and the other a consumer electronic that delivers a vapor which contains zero tobacco – the only common attribute of which is nicotine.

The distinctions between ENDS and combustible tobacco products are clearly made by the American Cancer Society, which pointed out that our primary public health mission must be focused on ending the use of combustible cigarettes. We agree. In explaining the evolution of their position regarding ENDS products, the American Cancer Society recognized the uniqueness of ENDS products and underscored the fact that there is no real comparison between the ENDS category and deadly cigarettes:

> Although many ENDS deliver nicotine, flavor additives, and other chemicals, they do not burn tobacco, a process that yields an estimated 7000 chemicals, including at least 70 carcinogens. Thus, public misunderstanding underscores the urgent need for consumer education about the absolute and relative risks posed by different tobacco products and to reinvigorate smokers' understanding of the importance of quitting combustible tobacco. Whereas complete information on all the potential risks and benefits of ENDS is not yet available, there is sufficient information to allow ACS to act now with a clear focus on the primary goal of ending deadly combustible tobacco use, which is responsible for approximately a one-half million deaths per year and 30% of all cancer deaths in the United States. (Douglas, et al., 2018.)

To be clear, even in the absence of "complete information," the American Cancer Society has recognized that there is "sufficient information" to focus more forcefully on the combustible products that kill while spreading truthful information about the harm reduction potential of ENDS products.

Based on similar rationale, it is vital that FDA recognize another fundamentally unique attribute of ENDS products: unlike any "tobacco product" being examined, ENDS products have no base "tobacco" flavor. The ANPRM is replete with references to and questions about "non-tobacco" flavors, apparently attempting to draw the distinction between the naturally occurring flavor of combustible tobacco products and any "characterizing flavors" that may be added to change the natural tobacco flavor. If nothing else underscores the fundamental difference between ENDS products and tobacco products, it is the fact that the naturally occurring flavor of e-liquids *prior to the introduction of flavorings* is NOT tobacco because ENDS e-liquids do not contain tobacco. Rather, the only naturally occurring e-liquid flavor would be that resulting from the combination of the primary ingredients of propylene glycol, vegetable glycerin, and nicotine.

This distinction is important because many of the presumptions that FDA may have in connection with why flavors are added to combustible products do not apply to ENDS products. Unlike any combustible tobacco product, without the introduction of flavors, the vaporization of totally unflavored e-liquids would be so unpalatable that they would not be consumed. Thus, in making any decision to regulate flavors in ENDS, FDA must recognize that artificially permitting the use of "tobacco" flavor to the exclusion of all other flavors would do nothing but promote relapse by ENDS users that are current and former smokers back to combustible cigarettes. In other words, the dialectic of examining whether, as with cigarettes, flavors should be eliminated in favor of naturally occurring tobacco does not exist with respect to e-liquids.

Finally, FDA cannot overlook the fact that, unlike any of the other "tobacco products" subject to this ANPRM, only ENDS products offer the adult smoker the option

and ability to reduce the amount of nicotine being consumed in an absolute way, rather than simply based on consumption. As noted in various studies, and as is obvious from a cursory review of the marketplace, there is a wide selection of ENDS products on the market with varying levels of nicotine. This empowers the ENDS user with the ability to choose the amount of nicotine at which they start and, most importantly, choose lower levels of nicotine – including zero nicotine – as they mature in their use of ENDS. This fact makes ENDS products entirely unique from all of the other products subject to this ANPRM and again requires FDA to be circumspect about limiting its availability.

As importantly, the varying levels of nicotine available in ENDS products also demonstrates that ENDS are much closer on the nicotine continuum to NRTs – which are the other readily available nicotine-containing products on the market with different levels of nicotine. But, in stark contrast, only ENDS products offer the lowest levels of nicotine and, most importantly, offer ZERO nicotine options to their users. In that regard, ENDS products occupy a more advantageous spot on the nicotine continuum – zero – below NRTs. In other words, unlike NRTs, which can only offer flavored nicotine options to their customers trying to quit, only ENDS products give the quitting smoker the most important option – the option to continue using the product without nicotine. Hence, while FDA only has authority to regulate tobacco-derived nicotine containing ENDS products, an incorrect limitation on flavors in nicotine-containing ENDS products would severely hamper the ability of adult smokers to titrate down to zero.

E. The Role that Flavors Play in ENDS Products and in Cessation Demands That FDA Treat Them Differently.

Today, non-tobacco flavors play a crucial role in the ENDS product category. The ability of millions of adult consumers to reduce their reliance on and, indeed, quit smoking combustible cigarettes altogether, depends in large part on continued, reliable access to non-tobacco-flavored ENDS products. By way of introduction to the role of non-tobacco flavors in the ENDS category today and why they cannot be viewed through the same policy prism as other tobacco products, VTA believes at it is helpful to juxtapose the current situation with that of characterizing flavors in cigarettes at the time of passage of the Tobacco Control Act in 2009.

1. The Role of Non-Tobacco Flavors in the ENDS Category Today Differs Substantially from that of Characterizing Flavors in Cigarettes Prior to their Ban Under the Tobacco Control Act.

The role of non-tobacco flavors in the ENDS category today differs markedly from that of so-called "characterizing flavors" under the Tobacco Control Act in 2009. Section 907 of the FDCA was enacted pursuant to the Tobacco Control Act. Section 907(a)(1)(A), which applies only to cigarettes, distinguishes between tobacco and menthol-flavored cigarettes and those containing other so-called "characterizing" flavors, including "strawberry, grape, orange, clove, cinnamon, pineapple, vanilla, coconut, licorice, cocoa,

chocolate, cherry, and coffee." 21 U.S.C. § 387g(a)(1)(a). Section 907 prohibits the use of characterizing flavors in cigarettes. *Id*.

As part of the rationale for establishing the ban on characterizing flavors for cigarettes, the House Report prepared in conjunction with passage of the Tobacco Control Act noted that the ban on characterizing flavors in Section 907(a)(1) was intended to deter youth initiation of such products. H.R. Rep. No. 111-58, at 37 (2009). However, the House Report also justified the characterizing flavor ban on the basis that no negative public health effects were expected as a result of the ban. *Id*. at 38. Such was the case because there was "low overall use" of such products by adult smokers and "none of the cigarettes covered by the ban—including those with the characterizing flavors of fruit, chocolate, and clove—is used regularly by a large number of addicted adult smokers." *Id*. The House Report went on to observe:

> . . . . Instead, these cigarettes tend to be used only occasionally, either by regular users of other products, by individuals who are experimenting with tobacco use, or by those who smoke only in certain social settings. Given that few adult smokers ever use the flavored cigarettes that will be banned and that most adult smokers name other products as their regular brand, it is likely that regular use of these products by heavily addicted adult smokers is negligible.
>
> All of these factors—irregular, experimental, and social setting use and low overall use within the U.S. population—support the Committee's conclusion that precipitous removal of these products from the market will not result in a large number of heavily addicted smokers facing the sudden withdrawal of the products to which they are addicted, with unknown consequences for the health of the individual users or the overall population. The Committee notes that prohibition of a product that is used regularly by a large number of heavily addicted adult users would pose different questions of public health than those posed by the ban in section 907(a)(1). For example, the health care system might not be capable of handling the sudden increased demand for cessation assistance in the case of a more broadly used product, leaving millions of smokers without medical support. In addition, the sudden removal of a legal source for such a product without the type of consideration and review that FDA will be able to conduct might unnecessarily increase the illegal black market risk, which could also pose a health hazard to users.

Id.

In stark contrast to the state of facts existing with respect to flavored cigarettes at the time of passage of the Tobacco Control Act in 2009, as of 2014, some 10.2 million U.S. adults had used non-tobacco-flavored ENDS products in the past 30 days (Bonhomme, et al., 2016). Today, that number is likely much higher and, as explained further in the

following sections of these comments, many of these individuals are former smokers who rely heavily on the wide variety of non-tobacco flavors found in nicotine-containing e-liquids.

Again, different from cigarettes and, indeed, uniquely among legally-defined "tobacco products," *all* ENDS products have a "characterizing" flavor, as even tobacco flavors are artificially added to the propylene glycol or vegetable glycerin and nicotine "base" solution. Further, far from being "irregular" and "experimental", as was the case with characterizing flavors in cigarettes, the use of non-tobacco flavors in e-liquids by adult consumers of ENDS is pervasive and, in many cases, critical to their personal efforts at smoking cessation. As the House Report anticipated, and as is discussed further below, a product standard prohibiting non-tobacco flavors in ENDS products would likely have a substantially counterproductive impact on public health and force many adult users of ENDS either back to combustible cigarettes or to other illicit black market or do-it-yourself alternatives that can pose substantial safety risks.

2. Only ENDS Products Can Claim, With Accumulating Scientific Support, That Flavors Play a Role in Smoking Cessation.

As will be explained in greater detail below, a strong trend in the scientific literature supports the proposition that the availability of a wide variety of non-tobacco flavors in nicotine-containing e-liquids used in ENDS products further bolsters smoking cessation and promotes larger numbers of smokers to permanently transition to less harmful ENDS products. Rather than merely help sell more products, the availability of non-tobacco flavors in ENDS products actually advances the public health goals of reducing reliance on harmful combustible cigarettes and improving smoking cessation rates. Given the growing body of scientific literature suggesting an important role for non-tobacco flavors in ENDS as a harm reduction tool, it would be premature for FDA to consider limiting the availability of these flavors to adult consumers of ENDS products. Flavored ENDS products are filling the gap left by the failure of nicotine replacement therapies to ease smokers' transitions from combustible cigarettes to complete smoking cessation.

Indeed, flavored ENDS products are unique in that they are the only tobacco product that allows the user to titrate down his or her level of nicotine intake over time. Rather than inflict collateral damage on current and former adult smokers who rely on e-liquids with non-tobacco flavors to lessen or break entirely their dependency on combustible cigarettes, FDA should more forcefully utilize the enforcement tools that it already has to discourage manufacturers and retailers from engaging in marketing practices that can be enticing to youth and consider establishing strict tobacco product marketing standards similar to the voluntary marketing standards adopted by the VTA to combat youth initiation of tobacco products, including ENDS.

For all of these reasons, it is clear that ENDS products cannot be viewed through the same policy prism as characterizing flavors in other tobacco products, including cigarettes. The myriad unique attributes of vapor products require FDA to implement a strict standard

of scientific certainty before it even considers regulating flavors in ENDS products. As explained below, existing science simply does not support any action by FDA at this time.

III. EXISTING PEER REVIEWED SCIENTIFIC RESEARCH DOES NOT SUPPORT LIMITING FLAVORS IN ENDS PRODUCTS BUT, RATHER, SUPPORTS PRESERVING THE POTENTIAL FOR CONTINUED RELIANCE ON FLAVORS TO AID WITH SMOKING CESSATION.

As explained in detail below, the existing peer reviewed scientific research regarding the role of flavors in ENDS products does not provide a sound basis for limiting access to any flavors—including non-tobacco flavors—in ENDS. Rather, the existing science supports continuing to allow adult consumers, including current and former smokers, full access to such flavors to support their efforts at smoking cessation.

A. Adult Consumers Use and Rely Upon A Wide Variety of Non-Tobacco-Flavored ENDS Products.

In order to fully understand the beneficial impact of flavors in ENDS products, it is important to recognize that a wide diversity of flavors are popular with adult consumers of nicotine products. Unlike the limited product range and market for flavored cigarettes prior to 2009, today there is a broad selection of non-tobacco-flavored e-liquids available to and popular with adult consumers of all ages. One recent study (Hsu, et al., 2018) that analyzed the websites of online e-liquid retailers in 2016 and 2017 identified more than 15,000 distinct flavors of e-liquids available to adult consumers. Some studies have suggested that older vapers are less likely to use a variety of different flavors than younger adult vapers (Ashford, et al., 2017; Cataldo, et al., 2015); tobacco flavored e-liquids are most likely to be used by current and former smokers (Berg, 2016; Bunch, et al., 2018). It is scientifically unacceptable to suggest that flavors are solely intended to attract or appeal to youth when the evidence suggests that adults of all ages like many categories of flavors – including fruits, sweets, and cool flavors – and tend to dislike harsh and bitter flavors (Zare, et al., 2018; Harrell, et al., 2017b). These findings are borne out in surveys (Bonhomme, et al., 2016; Berg, 2016; Bowler, et al., 2017; and Krishan-Sarin, et al., 2014), experimental studies (Goldenson, et al., 2016; Kim, et al., 2016; Garrison, et al., 2018), and focus groups (Soule, et al., 2016; Kim, et al., 2017).

Studies have reached contradictory conclusions as to whether flavored ENDS use varies by sex, with some researchers suggesting that males are more likely to prefer tobacco flavors (Dawkins, et al., 2013; Bunch, et al., 2018) while females report preferring non-tobacco, sweet, and fruit flavors (Pineiro, et al., 2016; Dawkins, et al., 2013; Bunch, et al., 2017), while others have found that trends in flavor use did not vary by sex (i.e., Harrell, et al., 2017b; Bowler, et al., 2017; Kim, et al., 2016.) Similarly, some studies have found no demonstrable differences in ENDS flavor preferences between people of different races (i.e., Harrell, et al., 2017b; Ashford, et al., 2017; Kim, et al., 2016), while others have suggested that African Americans prefer menthol flavor (Bowler, et al., 2017; Bonhomme,

et al., 2016) and Caucasians prefer fruit and candy flavors (Bonhomme, et al., 2016.) What is certain, however, is that adults enjoy and use a wide variety of ENDS flavors.

Most germane to the ANPRM, as examined in greater detail in Section III.B., below, both anecdotal evidence and a growing body of literature suggest that, as smokers transition from combustible cigarettes to use of ENDS products, they first tend to use tobacco and menthol-flavored e-liquids, but eventually transition to non-tobacco flavors as their dependency on combustible cigarettes decreases. In part, this trend may be due to the fact that many ENDS products sold as kits include tobacco-flavored e-liquids, so it is thus probable that an existing smoker's first exposure to an ENDS product is more likely to involve a tobacco-flavored e-liquid. However, as also discussed below, the existing literature also lends support to the hypothesis that, as smokers wean themselves off of cigarettes, they tend to gravitate toward non-tobacco flavors to avoid the taste sensations associated with tobacco flavors that they believe may cause them to relapse into smoking. The continued availability of non-tobacco flavors is thus critical to encourage cessation in existing smokers, to prevent relapse into combustible cigarettes, and to increase harm reduction as a matter of public health policy.

B. The Existing Reliable Literature Strongly Supports the Role of Non-Tobacco ENDS Flavors as Valuable Smoking Cessation Tools.

The existing reliable scientific literature on flavors and ENDS products—including longitudinal analyses, survey data, and experimental studies—trends strongly in favor of the conclusion that access to a wide variety of flavors—and particularly non-tobacco flavors—plays a critical role in encouraging cessation among existing smokers and preventing relapse. Thus, any move by FDA to restrict access to such flavors has the potential to significantly impede smoking cessation efforts for millions of current and former smokers and consign them to the adverse health effects that accompany continued smoker status.

1. Two Longitudinal Studies Based on PATH Study Data Found Users of Non-Tobacco-Flavored ENDS Are More Likely to Reduce Cigarette Use or Quit Altogether.

To date, two reliable longitudinal analyses of data from the Population Assessment of Tobacco and Health (PATH) Study have studied the role of non-tobacco flavors in e-liquids and determined that users of such flavors were more likely to have reduced their cigarette consumption or have quit smoking altogether.

One longitudinal study analysis by Chen (2018) found that users of e-cigarettes with one or more non-tobacco / non-menthol flavors were *significantly more likely* to have reduced or quit smoking over time than non-e-cigarette users, thus suggesting that the continued availability of such flavors is important to support smoking cessation efforts. The data collected between Wave 1 and Wave 2 indicated that "*25.9% of respondents either reduced or quit smoking,"* with 6.7% currently using e-cigarettes with tobacco / menthol

flavors and 11.5% currently using e-cigarettes with one or multiple non-tobacco flavors. In that analysis, the author examined longitudinal data from the PATH Study to examine differences in smoking reduction / cessation among young adult smokers (age 18-34) who: (1) did not use e-cigarettes; (2) used e-cigarettes with tobacco and/or menthol flavors; and (3) used e-cigarettes with other flavors. Of the 4,645 smokers in Wave 1 who responded to the e-cigarette flavor questions in Wave 2, 844 were current e-cigarette users, approximately one-third of whom used tobacco and/or menthol flavors and approximately two-thirds of whom used other flavors. Adjusted logistic regression showed that subjects who used e-cigarettes at Wave 2 with either one "other" flavor (AOR = 2.5, $p<0.001$) or multiple "other" flavors (AOR = 3.0, $p<0.001$) were significantly more likely to have reduced or quit smoking in the past year than non-e-cigarette users. The study also demonstrates that proper understanding and access to flavors is important to those reducing smoking or quitting. With respect to their reasons for using e-cigarettes, subjects who reported that e-cigarettes "help people quit smoking" (OR = 2.3, $p<0.001$) and "come in flavors I like" (OR = 2.1, $p = 0.007$) were more than twice as likely to have reduced or quit smoking in the past year compared to those who did not endorse those reasons.

A second important longitudinal analysis by Buu, et al., (2018) demonstrated the harm reduction potential of access to a variety of non-tobacco flavors by finding use of non-tobacco flavored e-cigarettes to be positively associated with a lower quantity of combustible cigarette use over time. In this analysis, 2,727 subjects who reported at Wave 1 of the PATH Study that they were exclusively smokers (i.e., had smoked more than 100 cigarettes in their lifetime and had smoked in the last 12 months) and had not used an e-cigarette in the past 12 months were re-examined at Wave 2 to determine if e-cigarette use was associated with changes in smoking behavior. Users of e-cigarettes at Wave 2 were defined as subjects who used e-cigarettes some days or every day in the last 30 days. The use of flavoring was measured by the subjects' responses to the question: "In the past 30 days, was any of the e-cigarettes / e-cigarette cartridges / e-liquid you used flavored to taste like menthol, mint, clove, spice, fruit, chocolate, alcohol drinks, candy, or other sweets?" Notably, the use of non-tobacco flavored e-cigarettes (i.e., a positive response to the foregoing question) was positively associated with a lower quantity of combustible cigarette use at Wave 2 ($p<0.05$).

2. Survey Data Also Strongly Correlate Use of Non-Tobacco Flavors in ENDS Products With Successful Cigarette Quit Attempts.

In addition to the two longitudinal studies noted above, an extensive body of survey data also reflects statistically significant associations between the use of non-tobacco flavors in ENDS products and successful attempts to quit smoking combustible cigarettes. The literature recognizes that dual use of cigarettes and e-cigarettes among existing smokers is common and is often a necessary step toward total "switching" and complete smoking cessation.

Beginning this trend in the literature, an early internet survey study by Farsalinos, et al., (2013b) found that of 4,618 e-cigarette users, 91.9% of the participants were former

smokers. The survey found that the remaining participants reporting smoker status had, on average, reduced their consumption of combustible cigarettes from 20 per day to 4 per day. The respondents reported using an average of three different flavors of e-liquids on a regular basis, with former smokers switching between flavors more frequently than current smokers, with over 69% of former smokers doing so on at least a daily basis. More than 50% of the participants reported that the taste of an e-liquid gets "blunt" with long-term use of the same flavor. Fruit and sweet flavors were found to be more popular among former smokers, while tobacco flavors were more popular at the time of initiation of electronic cigarette use.

Importantly, the Farsalinos survey suggested that restricting the availability of flavors would have a negative effect on reducing smoking or quitting altogether. Significantly, 48.5% of the survey respondents reported that restricting the availability of non-tobacco flavors would increase their cravings for combustible cigarettes, while 39.7% reported that they would have been less likely to reduce or quit smoking if non-tobacco flavors were not available to them. Binary logistic regression analysis showed that a greater number of flavors regularly used was independently associated ($B = 0.089$, $p = 0.038$) with complete smoking abstinence in the survey population of dedicated, long-term vapers. Flavor availability was rated as "very important" (4 on a scale of 1 to 5) with respect to reducing or quitting combustible cigarettes. These results led the study authors to conclude that variability in flavors both resulted in reduced cigarette cravings and promoted smoking cessation in the population of smokers studied. Moreover, they hypothesized that the switch away from tobacco flavors over time may have reflected a desire by users to reduce their cravings for combustible cigarettes.

The increasing popularity of non-tobacco flavors among adult smokers for harm reduction and smoking cessation efforts is also supported by very recent survey results. In a survey conducted by Russell, et al., (2018) of 20,836 adult e-cigarette users that had used an e-cigarette on at least 20 out of the last 30 days, 15,807, or *76.4%, had completely substituted e-cigarettes for conventional cigarettes*. The researchers found that the number of smokers who had used a non-tobacco flavor as their first ENDS flavor increased substantially over time. Among the survey participants that were either "switchers," dual users, or former smokers, the percentage who had first used a tobacco flavor with their first ENDS product decreased from 46.0% prior to 2011 to 24.0% between 2015 and 2016. Meanwhile, first purchases of fruit-flavored e-liquids increased from 17.8% to 33.5% during that same time. Among these current and former smokers, tobacco and menthol flavors, which were the two most popular flavors for initiating e-cigarette use prior to 2013, are now the fifth and sixth most popular currently used flavors, behind (1) fruit / fruit beverage, (2) dessert/pastry, and (3) candy/chocolate/sweets.

The researchers concluded that "[a]ccess to a variety of non-tobacco flavored e-liquid may be important for encouraging and assisting adults to use e-cigarettes in place of conventional cigarettes" and that "[r]estricting access to non-tobacco e-cigarette flavors may discourage smokers from attempting to switch to e-cigarettes." To be sure, this conclusion is bolstered by an earlier online survey conducted by Russell, et al. (2017). In

that survey, 4,192 ENDS users who were former smokers that quit by using e-cigarettes were asked what advice they would provide to smokers who are considering using ENDS to quit smoking. One of the primary themes was that such smokers should "find a combination of vaping device, flavors of e-liquids, and nicotine strength that works for you."

Several other survey studies have also demonstrated that smokers tend to begin e-cigarette use with the tobacco and menthol flavors that most closely resemble the cigarette flavors to which they are accustomed and that they then transition to other flavors over time—particularly as they cease use of combustible cigarettes altogether. An online survey (Truman, et al., 2018) of 218 vapers in New Zealand found that 23% both vaped and smoked. The results of the survey were consistent with a progression from initially both vaping and smoking using less effective electronic cigarette types, then moving to more powerful devices, and moving away from tobacco and menthol flavors (which 42% of respondents reported having used at one time) to experiment with other flavors (as only 10% of respondents were still using tobacco and menthol flavors at the time of the survey). The authors concluded that smokers' experimentation with non-tobacco flavors was consistent with reducing or stopping combustible tobacco use.

Another online survey (Adriaens, et al., 2017) of 215 vapers that were both smokers and ex-smokers found that while 19% were dual users, 81% had completely switched to vaping. Both groups had been vaping for an average of 22 months and used flavors other than tobacco. In contrast, at the time of e-cigarette initiation, tobacco was the flavor primarily used by the respondents. Similarly, a focus group study of electronic e-cigarettes users by Simmons, et al. (2016) also concluded that it is plausible that e-cigarette users may use tobacco and menthol flavors to ease the transition to e-cigarettes and then switch to a contrasting flavor to prevent the tobacco flavor from serving as a cue to resume combustible cigarettes.

Still other surveys have similarly found statistically significant associations between cessation and the preference for non-tobacco flavors in electronic cigarettes. A study authored by Tackett, et al., (2015) that analyzed data collected in-person from 215 vape shop customers found that the respondents had, on average, used ENDS for seven months, that two-thirds (66%) had quit smoking altogether (a finding that was biochemically verified through exhaled CO readings) and that those who continued to smoke had reduced their daily cigarette usage from a mean of 22.1 to a mean of 7.5 ($p<0.001$), an overall average decline of almost 15 cigarettes per day. The study also found that 72% of the subjects used non-tobacco / non-menthol flavors and that subjects who used these flavors were significantly more likely ($p=0.035$) to quit smoking entirely than those who relied on tobacco or menthol flavors. In fact, quitting was two and a half times more likely among respondents using fruity, candy, or bakery-flavored e-liquids than those using tobacco or menthol-flavored e-liquids. The study authors concluded that "regulators should carefully examine the cost-benefit of banning flavors," as "the current available science would not support a decision to do so."

More descriptive surveys also support the conclusion that the availability and desirability of non-tobacco flavors supports smoking cessation efforts. An early online survey conducted in 2011-2012 of 1,347 vapers from 33 countries found that 1,123 – 83.3% - of them had stopped smoking and that, while tobacco was the most popular flavor identified, when allowed to choose more than one "preferred" flavor, significant proportions of ex-smokers selected "fruit," "chocolate / sweet flavor," "coffee," and "vanilla" flavors in addition to tobacco and mint/menthol flavors. (Dawkins, et al., 2013.) Similarly, a very early survey by Etter (2010) found that of 81 electronic cigarette users, 63% were former smokers. The positive feature of electronic cigarettes most frequently identified by the respondents was the *taste and variety of flavors*.

3. An Experimental Study Demonstrates the Harm Reduction Potential of Flavored ENDS, Even Absent Any Subjective Intent to Quit Smoking.

An experimental study reported by Litt, et al., (2016) also powerfully underscores the potential for flavored ENDS to reduce reliance on cigarettes, even in the absence of subjective intent to quit smoking. In that study, 88 current smokers were asked to adopt e-cigarettes for a period of six weeks. To minimize the confounder effect that a desire to quit smoking might result in reduced use of all tobacco products, the study authors recruited only participants that reported no subjective intent to quit using combustible cigarettes. Study participants were allowed to taste and smell e-liquids flavored with tobacco, menthol, cherry, and chocolate and were provided with an ENDS product with either their preferred flavor or a randomly assigned control flavor.

Significantly, during the six-week period, cigarette smoking rates dropped from an average of approximately 16 cigarettes per day to 7 cigarettes per day. The largest drop in smoking rates (to 4.0 cigarettes per day) occurred among those participants using menthol e-cigarettes, while the smallest reduction (to 9.8 cigarettes per day) occurred among those using chocolate-flavored e-liquids, thus reinforcing the notion that menthol flavor plays an important role in early smoking cessation efforts involving ENDS products. Interestingly, smokers assigned the menthol e-cigarette tended to reduce their use of both the e-cigarette and combustible cigarettes. What is remarkable about this study is that, even in the absence of any desire or intent to quit, the use of flavored e-liquids resulted in a dramatic reduction in cigarette smoking.

4. The Only Potentially Counter-Indicative Studies Suffer from Methodological Weaknesses and, Therefore, are Entitled to No Weight.

In contrast to the foregoing studies demonstrating that the availability of a wide variety of non-tobacco flavors plays an important role in smoking cessation, one study, by Dai and Hao (2016) purports to suggest that use of flavored e-cigarettes is associated with lower odds of intention to quit tobacco use among youth. A second study, by Weaver, et al., (2018) purports to suggest that flavored ENDS do not significantly influence cigarette quit

rates. For the reasons described below, both studies suffer from methodological weaknesses and are entitled to no weight.

The Dai and Hao study is based on the Centers for Disease Control's National Youth Tobacco Survey ("NYTS") cross-sectional data and suggests that using flavored e-cigarettes is associated with lower odds of intention to quit tobacco use among current-smoking 6th to 12th graders (aOR = 0.6; p = 0.006). The study's analysis, however, suffers from several fatal flaws stemming both from the authors' overly constricted interpretation of the survey instrument itself and their faulty methodological assumptions.

As an initial matter, the NYTS study purports to examine intent to smoke and intent to quit, as opposed to actual empirical data on the initiation, use, or cessation of e-cigarettes or combustible cigarettes. Only 11 of the 81 questions purport to address e-cigarettes at all, and of these, no survey question is structured so as to elicit empirical data on the initiation, use, or cessation of e-cigarettes. The subjects of NYTS were also students in 6th through 12th grades—a broad cohort with a wide range of potential psychological maturity levels that is not typically considered for serious analyses of cessation because of the absence of goal-oriented activity due to the subjects' young ages.

As the basis for their categorization of the NYTS respondents, the authors categorize as flavored e-cigarette "users" those students who answered that they had used a flavored e-cigarette at least once during the last 30 days, regardless of whether such use was a one-time-only event of experimentation, as opposed to regular use. Respondents were categorized as "never smokers," "former smokers," or "current smokers" based not on whether they had actually smoked 100 cigarettes in their lives, but exclusively on their answers to two questions: (1) "Have you ever tried cigarette smoking, even one or two puffs?" and (2) During the past 30 days, on how many days did you smoke cigarettes?" Thus, it is quite possible (and, indeed, likely, given the respondents' age range), that a respondent may have puffed on a cigarette only one time in his or her life in the past 30 days and that the respondent would be labeled a "current smoker."

The authors of the study also use a questionable reference group for purposes of evaluating intention to quit and reaching speculative conclusions regarding the role of flavors in that decision. Instead of comparing the results reported by "nonflavored" (i.e., tobacco-flavored) e-cigarette users to those reported by "flavored" (i.e., menthol and other flavored) e-cigarette users with respect to intention to quit, flavored e-cigarette users are compared to "never" e-cigarette users. This apples-to-oranges comparison provides no valuable insight into the role of menthol and other non-tobacco flavors themselves in youth users' decisions regarding cessation.[4]

[4] VTA recognizes that, on its face, the Dai and Hao study (and also the Weaver study described below) appear to be similar to the Chen study insomuch as the comparison group to non-tobacco-flavored ENDS users is non-ENDS users. However, the statistical methodologies used by Dai and Hao and Weaver, on the one hand, and Chen, on the other, render these comparator groups problematic for Dai and Hao and Weaver, but not for

Finally, the authors' statistical methodology is highly questionable, as the authors fail to test for heterogeneity when comparing two adjusted odds ratios for e-cigarette use with flavor and e-cigarette use with no flavor in Table 2 of their paper. Absent a test for heterogeneity, the statistics upon which the authors rely to support their conclusion that their study "confirmed that current youth smokers who reported use of [non-tobacco] flavored e-cigarettes had a significantly lower intention to quit tobacco use in the next 12 months (aOR = 0.6; p = 0.006) compared with those who reported not using e-cigarettes" is meaningless and should be given no weight by FDA in considering the state of the literature on the role of flavors in smoking cessation.

Similarly, a study published very recently by Weaver, et al., purported to examine the effect of "real-world" e-cigarette use on smoking quit rates among 821 adult smokers. While described as a prospective study, the subjects were only followed for 12 months. The study attempted to measure the effects of many variables, including number of quit attempts, smoking abstinence for at least 30 days, as well as frequency and duration of use, device type, e-liquid flavor, and reasons for use. The authors concluded that "there was limited evidence that e-liquid flavor might influence quitting rates." As with the Dai and Hao study, significant methodological weaknesses undermine the authors' purported conclusion of no significant relationship between flavored ENDS use and smoking cessation.

First, the study was not a conventional cohort study, in which a population is defined in terms of its exposure at baseline and then followed for a significant period of

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Chen. Chen validated her relevant population samples using a Goodness of Fit test and then applied a methodologically appropriate Chi Square test. The resulting *p* value was not affected by the fact that two different variables (ENDS user vs non-ENDS user and tobacco-flavored ENDS vs. non-tobacco-flavored ENDS) were at issue because both population samples were appropriately representative under the Goodness of Fit test. In short, the *p* values reported by Chen were thus reliable.

In contrast, the Dai and Hao and Weaver studies did not rely on Goodness of Fit and Chi Square tests, but instead relied on weighted logistic regression analysis using estimated sample weights. Neither paper reports the distribution occurring among each relevant sample population, but, as a general rule, weighted logistic regression analysis is not appropriately used when more than one variable distinguishes the two populations that are the subject of the comparison. For a successful weight correction in weighted logistic regression analysis, the samples must exhibit homogenous characteristics so as to focus the weighting appropriately on the single variable at issue (here, flavor-based effects). Because Dai and Hao and Weaver used non-ENDS users as the control group for non-tobacco-flavored ENDS users, this homogeneity requirement was not met in either study. Instead, the presence of two variables (ENDS user vs non-ENDS user and tobacco-flavored ENDS vs. non-tobacco-flavored ENDS) likely confounded the results, rendering the *p* values reported by Dai and Hao and Weaver wholly unreliable.

time. Importantly, some participants used ENDS at baseline, whereas others only started using ENDS as of the time of the follow-up survey 12 months later. Almost 60% of the subjects (n=486) never used ENDS. There were 335 subjects who used ENDS, and it is not even clear how many of these were users at baseline.

Second, the ENDS users in the group were heterogeneous, with a mix of both regular and longer-term users and less regular and/or shorter-term users. Only a small proportion (13% - 21%, depending on whether the baseline or follow-up survey is considered) were daily users of ENDS, meaning that at least 79% of respondents reporting ENDS use were not daily ENDS users. Nevertheless, the authors merely present the association of ENDS use with the likelihood of quitting by categorizing respondents into two groups of "any ENDS use" and "daily ENDS use" without providing any further breakdown on frequency of use (i.e., 0, 1-2 days/week, 3-4 days/week, 5-6 days/week, etc.).

Third, the results reported by the authors appear to be anomalous insomuch as they find a stronger and statistically significant association between non-daily ENDS use and successful quitting of cigarettes, but not between daily ENDS use and successful quitting.

Finally and most importantly, given the explanation provided in the footnote above, as regards flavors specifically, the authors examine flavors using "non-ENDS users" as the reference group, instead of the more appropriate, but miniscule "tobacco/unflavored" group of ENDS users. The numbers in the analysis of flavors are very small: among the 27 subjects who had not smoked for at least 30 days at follow-up, 3 used tobacco/unflavored ENDS, 7 used menthol/wintergreen/mint ENDS, and 17 used "other" flavored ENDS. Because the reference group is not one that is valuable as regards the role of flavors in quit attempts, the paper provides no useful information regarding the association of flavors with the likelihood of quitting and should be given no weight by FDA.

C. The FDA's Articulated Concern About Dual Use Impeding or Delaying Cessation is Misplaced and Inconsistent With Existing FDA Policy.

FDA has often raised the potential concern of "dual use" of ENDS products and combustible cigarettes, suggesting that ENDS are being used as a crutch to extend the time that a person continues to smoke. This assertion has been used by some to question and by others to undercut the role that ENDS play in cessation efforts. In examining the appropriate policy with respect to ENDS products, the United Kingdom's Department of Public Health clearly explained why the dual use concern is illogical:

> It has been suggested that there is a risk of sustained dual use among smokers who might otherwise have quit smoking completely, representing missed opportunities to achieve complete cessation. This concern clearly applies equally to NRT, which is licensed for what is in effect dual use and recommended on the grounds that dual use is likely to increase quit attempts. The concern is therefore inconsistent; if dual use is good as a pathway to quitting, that surely applies to dual use involving either NRT or electronic cigarettes. (Britton and Bogdanovica, 2014.)

In addition to the fact that there is simply no evidence to support such a concern for either adults or youth, FDA already has declared that continuing to use non-combustible nicotine products, *even if* one continues to smoke cigarettes, is appropriate. To be sure, five years ago (and prior to first raising "dual use" concerns in the proposed Deeming Regulation), FDA recognized the inherent contradiction between arguing against dual use and for public health, and amended its policy pertaining to the dual or poly-use of nicotine replacement products and tobacco products. *See* Modifications to Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use, 78 Fed. Reg. 19,718 (Apr. 2, 2013).

Despite the hyperbolic claims that we hear from some today regarding the "addictiveness" and the "dangers" of nicotine, the FDA reported to Congress in 2013 that, "[w]e also note that although any nicotine-containing product has the potential to be addicting, based on the available evidence, currently marketed OTC NRT products do not appear to have significant potential for abuse or dependence." *Id*. at 19,720.

Interestingly, FDA made this statement because it was asked to change the warning labels in 2013 on over-the-counter nicotine replacement therapies ("NRTs"), including fruit, mint, cinnamon, and other flavored NRTs. At that time, NRTs included a stark dual use warning to smokers instructing them never to dual use:

> "**Do not use** if you continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products."
>
> "Stop smoking completely when you begin using the [NRT product]."

Id. at 19,719.

But, FDA abandoned the dual use warnings altogether, removing the "Stop use" warning, removing the requirement that the user "quit" first, and even permitting new instructions to continue ingesting nicotine *even after* the end of the recommended period without having to speak to a physician. Thus, based solely on the "safety" of continually ingesting the pharmaceutical grade nicotine, FDA had no concerns about any adverse implications toward continued cigarette use or, for that matter, the continued poly-use of any other tobacco products.

In so doing, FDA expressly encouraged dual use. Given that e-cigarettes contain the same or lower levels of nicotine that most NRTs, and given the fact that FDA lifted the dual use restriction for other nicotine-containing products that contain no tobacco, the FDA has acknowledged that alternative nicotine consumption, even if it involves continued cigarette smoking, is preferable to individuals no longer using those alternatives.

Going forward, policies adopted by FDA in connection with ENDS should advance the potential for encouraging and enabling smokers to reduce consumption or quit

altogether. FDA already has recognized that it should not discourage individuals trying to quit smoking using alternative nicotine products by instructing them that dual use is wrong. Hence, that consideration is equally true for ENDS, including flavored ENDS.

D. Conclusion.

While further study of the linkages between the availability of non-tobacco flavors and cessation continues to be warranted, the clear prevailing trend in the existing reliable scientific literature supports the conclusion that such flavors are particularly helpful as an aid to smokers' cessation and relapse prevention efforts. As a result, unlike the case with combustible cigarettes almost a decade ago, any product standard that would limit the availability of non-tobacco flavors to adult ENDS users creates the possibility of significantly impeding the cessation efforts of millions of current and future smokers and condemning them to adverse health effects that can be avoided if access to the full range of flavored ENDS products is maintained.

IV. THE CONTINUING DECLINES IN YOUTH SMOKING AND YOUTH VAPING MAKE CLEAR THAT ANY SUPPOSED "GATEWAY" CONCERN IS MISINFORMED AND THE SCIENCE ON INITIATION, PARTICULARLY AMONG YOUTH AND YOUNG ADULTS, DOES NOT SUPPORT FDA IMPLEMENTING ANY RESTRICTIONS ON ENDS FLAVORS.

In light of the current state of the literature and the fact that ENDS use by youth has dropped significantly in recent years, any regulatory action by FDA that would restrict access to non-tobacco flavors on the basis that they are a significant factor in attracting youth to ENDS would be premature and any such action undertaken on the theory that such flavors promote a gateway effect to combustible cigarettes would be entirely without any scientific basis.

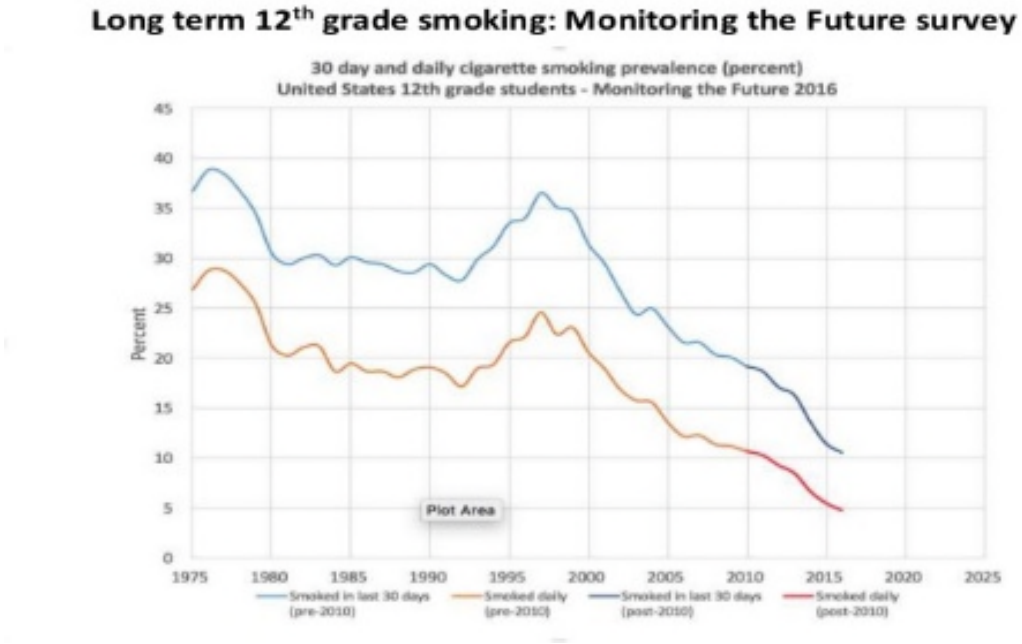
A. Fears of An E-Cigarette "Gateway" Evaporate As Youth Cigarette Smoking and Vaping Continue to Plummet.

If it were true that e-cigarettes, or any product for that matter, were a "gateway" to cigarette smoking, one would expect to see that cigarette smoking is increasing. Such simply is not the case, however, as both the smoking rate and vaping rate among youth continue to plummet.

It is well-established that the youth smoking rate in the United States is at the lowest rate ever and *falling* at the fastest rate ever. In 2016, U.S. Centers for Disease Control (CDC) data from its Youth Risk Behavior Survey on tobacco use showed that cigarette smoking (past 30 days) fell 47% among middle school students and 41% among high school students between 2011-2015, the years when the vapor products industry grew exponentially. (Singh T, et al., 2016.) Importantly, just last month, the CDC announced that past-30 day use of cigarettes has fallen to 7.6% amongst high school students and 2.1% amongst middle school students. (Wang, et al., 2018.) Moreover, the

CDC again announced the continuing decrease in the use by youth of *any* tobacco product (which by their definition include e-cigarettes), which is now down to 19.6% among high schoolers and 5.6% among middle-schoolers. (Wang, et al., 2018.)

This trend is not new. In December 2016, the University of Michigan's *Monitoring the Future*[5] study reported, "Cigarette smoking among teens in grades 12, 10 and 8 continued a decades-long decline in 2016 and reached the lowest levels recorded since annual tracking began 42 years ago."[6]



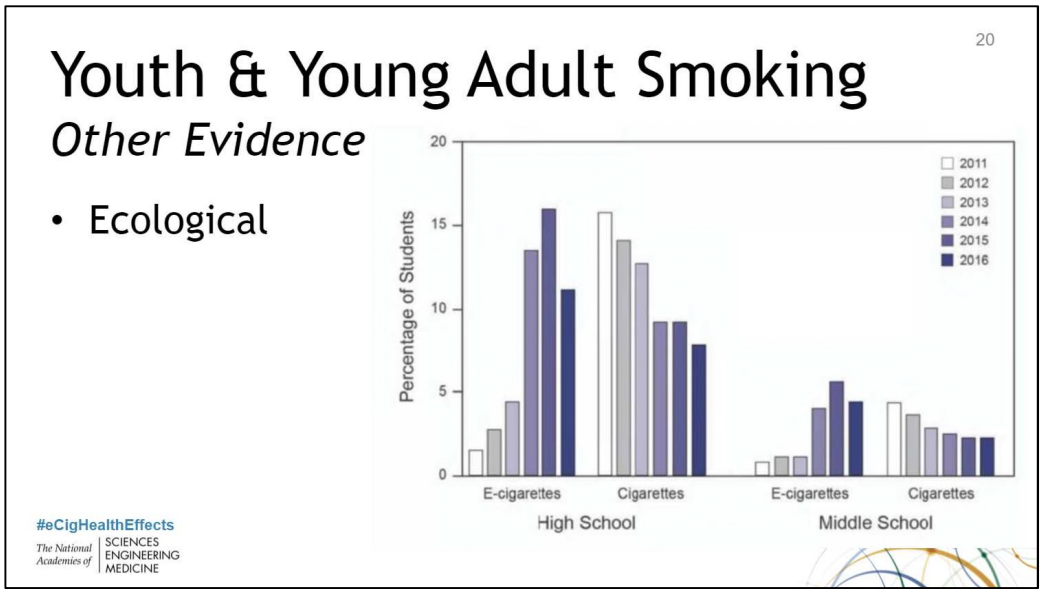
As importantly, the media hysteria about an alleged epidemic of ENDS use among youth is also belied by the actual data. The CDC's annual reports on youth and tobacco found that during the 2015-2017 period, the rate of reported use of ENDS products among high school students dropped from 16% to 11.7%, and the rate among middle school students dropped from 5.3% to 3.3%. (Jamal A., et al., 2017; Wang, et al., 2018.) What this

[5] Monitoring the Future ("MTF") is an ongoing study of the behaviors, attitudes, and values of American secondary school students, college students, and young adults. Each year, a total of approximately 50,000 8th, 10th and 12th grade students are surveyed (12th graders since 1975, and 8th and 10th graders since 1991). The Monitoring the Future Study has been funded by the National Institute on Drug Abuse, a part of the National Institutes of Health. MTF is conducted at the Survey Research Center in the Institute for Social Research at the University of Michigan.

[6] Press Release, University of Michigan, *Teen cigarette smoking drops to historic low in 2015,* December 16, 2015, available at:
http://monitoringthefuture.org/pressreleases/15cigpr_complete.pdf.

means is that, *for the second year in a row, overall youth use of e-cigarettes is once again dramatically down from its peak in 2015.*

Even before the updated CDC declining youth numbers were reported, Dr. Nancy Rigotti presented the following data summarizing the findings of the NASEM report at the E-Cig Summit in Washington, D.C.[7] Importantly, while addressing the science involving whether ENDS products may cause youth to try smoking at some point, Dr. Rigotti put up the following slide and explained as follows:



> "However, against that is the enormous amount of ecological data that shows – this is just an example that many of you are familiar with, you've probably seen it already today – that at the same time that e-cigarette use went up very rapidly among adolescents in the U.S. that cigarette use was falling. Hard to argue that there is a gateway there."

In summarizing the NASEM conclusions on youth e-cigarette use leading to ever-use of cigarettes, which she noted were "carefully worded," Dr. Rigotti explained: "So, what we are not actually saying here is that it leads to young youth smoking, something that has been sometimes lost in translation."

Nonetheless, despite nearly a million fewer youth tobacco users and declining smoking, others in the public health community continue to engage in hyperbole, claiming that the problem is something other than what the data proves. What once was a dramatic

[7] Rigotti, N. Presentation. U.S. National Academies of Sciences, Engineering & Medicine Report: Summary and Relevance to Clinicians: Slideshow available at: https://www.e-cigarette-summit.us.com/files/2018/05/Nancy-Rigotti.pdf. Video of presentation available at: https://vimeo.com/album/5155140.

increase in e-cigarette use between 2011 and 2015 has dropped dramatically in what CDC calls a "non-linear decrease." The CDC's statistics demonstrate once again that e-cigarette curiosity amongst youth peaked in 2015 and now remains at a statistically significant reduced level in 2017, having dropped two years in a row.

There is no reliable literature that concludes that the availability of non-tobacco flavors in ENDS products makes more likely any gateway effect of progression from ENDS to cigarettes. In the end, as Dr. Rigotti clarified from the NASEM Report, the "enormous amount of ecological data" makes it "hard to argue that there is a gateway there."

B. The Current Research on Youth Initiation of ENDS Suffers from Methodological Weaknesses.

Stated simply, the science on initiation and an alleged "gateway" effect, particularly among youth and young adults, does not support restricting access to non-tobacco flavored ENDS products. In the ANPRM itself, FDA engages in an unjustified assumption regarding flavors and ENDS insomuch as it requests information on "how" flavors attract youth, as opposed to "*whether* and how" flavors attract youth.[8] In fact, the existing literature suggests only that, at most, non-tobacco flavors may be one factor among several that may lead youth to initiate use of ENDS products. The current state of the science does not provide reliable answers to the question of whether flavors in e-cigarettes are significantly associated with the likelihood of initiation by youth or young adults.

It bears emphasizing that, when it comes to youth, significant methodological weaknesses are pervasive in many studies that attempt to address initiation and flavored ENDS products. To the extent that these studies attempt to tie the availability of non-tobacco-flavored ENDS products to *actual* youth initiation, these weaknesses significantly lessen the studies' empirical value and undermine the conclusions that the researchers draw.

Ideally, longitudinal studies would enroll large numbers of youth before use of any tobacco product was begun and the subjects would be studied for multiple years. There are also potential confounders present in any survey involving youth that are not present in those involving adults. For example, given the illicit nature of tobacco products for those under the legal age and the fact that the surveys are often taken in a classroom setting, it is not always clear whether the subjects answer the surveys honestly. Researchers (Fan, et al., 2006; Tourangeau and Yan, 2007) have identified these issues as a source of potential error in similar, non-tobacco-related surveys. Further, to the extent that survey data are relied upon to determine "choices" by users of particular tobacco products, given the illicit nature of tobacco products for youth, there are real questions about whether a respondent really "chooses" to use a particular tobacco product or merely does so because that was the product that was available because, for example, a friend offered it to the respondent or a parent left that particular tobacco product lying around the house.

[8] Regulation of Flavors in Tobacco Products, 83 Fed. Reg. 12294, 12294 (Mar. 21, 2018).

As a result, instead of asking about *actual* use, many surveys ask merely about *intent to use* as a stand-in for evaluating initiation. Actual examples of the types of methodologically questionable inquiries that have been posed in survey instruments purporting to address the relationship between ENDS products and initiation include the following:

- "For what reasons might you use e-cigarettes?" [posed to non-users of ENDS] (Berg, 2016.)

- "If one of your best friends were to offer you an e-cigarette or other vaping device with [flavor condition], would you use it?" (Pepper, et al., 2016.)

- "How interested would you be in using a [flavor] product?" (Shiffman, et al., 2015.)

Experimental studies are also not immune to these methodological deficiencies. By way of example, multiple experimental studies have offered subjects choices between two different hypothetical ENDS products and asked them which they would choose or rather try, even though there is no actual use by the study participants. (i.e., Czoli, et al., 2016; Shang, et al., 2017.) It is, at the very least, highly debatable whether these hypothetical, "stand-in" approaches are scientifically justified or provide a sound basis for regulatory action. Because virtually all of the studies that purport to link the availability of ENDS flavors to youth initiation suffer from at least one of these methodological weaknesses, they should be given little weight by FDA.

C. The Existing Research Cannot Properly Evaluate the Role that Flavors Actually Play in ENDS Initiation and Only Suggests that Flavors May Be One of Several Relevant Factors in ENDS Use Among Youth and Young Adults.

With the understanding that the "enormous amount of ecological data" proves there is no gateway effect, we turn to the consideration of the scientific studies on potential initiation. The existing research—largely consisting of cross-sectional surveys and focus groups that explore the reasons for vaping— cannot properly evaluate the role that flavors actually play in initiating use of ENDS products and, *at best*, only suggests that flavors may be one factor among several for ENDS use among youth and young adults.

The only reliable longitudinal study on the use of flavors and initiation demonstrates that the availability of "good flavors" is *not* a reliable predictor of continued or more frequent use of e-cigarettes over time, and so suggests that simply avoiding youth initiation is not a solid basis on which to regulate flavored ENDS. In the study, conducted by Bold, et al., (2016), 340 middle and high school students were surveyed in the fall of 2013 (Wave 1) and the spring of 2014 (Wave 2). Each of the students had already ever used an e-cigarette at Wave 1. The students were asked to endorse as many of 11 possible

reasons for first trying e-cigarettes as were applicable. The most common reported reason was "curiosity" (reported by 57.1% of respondents). The second most-reported reason was "good flavors" (reported by 41.8% of respondents). The reported reasons for trying e-cigarettes at Wave 1 were then examined as predictors of continued e-cigarette use at Wave 2. The "good flavors" response was *not* a significant predictor of either continued use or more frequent use of e-cigarettes at Wave 2. Rather, using e-cigarettes to quit smoking was the most robust predictor of continued e-cigarette use at Wave 2.

Other, non-longitudinal surveys suggest that while flavors are one reason why youth and young adults use e-cigarettes, other reasons are often equally or even more frequently cited. Further, several reported surveys, Villanti, et al., (2017), Kinouani, et al., (2017), Berg (2016), and Kong, et al., (2014), do not even rank flavors at the top of the list of reasons why youth may initiate ENDS use. Villanti, et al., (2017) performed a cross-sectional analysis of the Wave 1 PATH study data, but included 45,971 youth and adults. The response of "comes in flavors I like" did not appear in the top three reasons for using e-cigarettes among past 30-day users in the 18-24 year-old age bracket. Rather, the top three reasons given for this age bracket were: (i) less harmful to me than cigarettes; (ii) less harmful to other people than cigarettes; and (iii) can use where you can't smoke.

Berg (2016) conducted an online survey of 1,567 young adults (ages 18-34, of which 56% were current smokers and 53% were current e-cigarette users). Among e-cigarette non-users, "they come in appealing flavors" and "I like experimenting with flavors" were only the third and fourth most common reasons given by nonusers as to why they might try e-cigarettes. Among current e-cigarette users, the two reasons relating to flavors were the fifth and sixth most common reasons for use. For both groups, more popular reasons were: "they don't smell" and "they might be less harmful than cigarettes."

In a cross-sectional analysis of data collected from a study of 1,086 French university students that had ever tried an e-cigarette, Kinouani, et al., (2017) concluded that the top two reasons for trying an e-cigarette were curiosity (ranging from 66.3% among former smokers to 86% among never-smokers) and someone offering one to try (ranging from 60% among former smokers to 64.9% among current smokers). The attractiveness of e-liquid flavors came in a distant third at 17.8% among never-smokers and 28.6% among former smokers.

Similarly, a survey of 1,157 young people from middle school to college who had ever used an e-cigarette by Kong, et al., (2014) found that the top three reasons for experimentation with e-cigarettes were curiosity (54.4%), appealing flavors (43.8%), and peer influences (31.6%). These studies thus also do not support singling out flavors as a way to curb youth initiation of ENDS.

Moreover, Ambrose, et al., (2015) performed a cross-sectional analysis of data on flavored tobacco use among 13,651 youth (ages 12-17) in Wave 1 of the 2013-14 PATH study. Of these, 3.1% had used an e-cigarette within the last 30 days. Among that 3.1% of e-cigarette users, the top three reasons for use were endorsed by similar percentages of

respondents: (i) comes in flavors I like (81.5%); (ii) might be less harmful to me than cigarettes (79.1%); and (iii) might be less harmful to people around me than cigarettes (78.1%). This conclusion only supports the notion that there are several equally popular reasons other than flavors for why youth may try ENDS products.

Further, multiple surveys have also found overall interest in trying e-cigarettes to be low among non-smoking youth in general and that the presence of non-tobacco flavors does not dramatically affect interest in trying e-cigarettes. These surveys thus also support the conclusion that limiting flavor availability will not materially reduce use of ENDS products in non-smoking youth. Shiffman, et al., (2015) conducted a survey of 216 non-smoking teens and 432 adult smokers. Respondents were asked to indicate their interest on a scale from 1 to 10 in e-cigarettes characterized by 15 different flavor descriptors, including tobacco, menthol, bubble gum, cotton candy, gummy bear, and fruit. Non-smoking teens showed a very low level of interest (0.41 ± 0.14 on a 0-10 scale) and teen interest did not vary by flavor. Adult smokers' interest was modest (1.73 ± 0.10 on a 0-10 scale), but still significantly higher than that of the non-smoking teens. Pepper, et al., (2016) conducted a national survey of 1,125 adolescents between 13 and 17 years of age in 2014 and 2015. Participants were randomly assigned to respond to survey items about 1 of 5 e-cigarette flavors (menthol, candy, fruit, tobacco, or alcohol). The results showed that only 3.3% of never e-cigarette users were interested in trying e-cigarettes, and only 2.0% of never e-cigarette users were interested in trying them if a particular flavor was offered by a friend. Pepper, et al., (2013) had previously conducted a cross-sectional online survey of 228 adolescent males aged 11-19 in 2011 and found that only 2 participants (less than 1% of the survey group), both of whom were cigarette smokers, had ever tried an ENDS product. Participants' willingness to try "plain"-flavored (assumed to be tobacco flavored) versus chocolate, mint, or apple-flavored e-cigarettes did not differ.

An experimental study also supports the conclusion that the presence of non-tobacco flavors does not significantly impact the appeal, or lack thereof, of e-cigarettes or combustible cigarettes among youth. A study conducted by Vasiljevic, et al., (2016) with 471 children aged 11-16 who had never smoked or used an e-cigarette showed participants one of three advertisements (for candy-flavored e-cigarettes, non-flavored e-cigarettes, or no advertisement). Exposure to either set of advertisements did not increase the appeal of smoking combustible cigarettes or the appeal of using e-cigarettes, nor did it reduce the perceived harm of smoking, which was high.

As the forgoing reflects, the present state of the literature only suggests that flavors may be one factor among several reasons for ENDS use among youth and young adults and cannot tie the availability of desirable flavors to continued or more frequent use of ENDS products over time. Especially when considered in light of the limitations in studies involving youth highlighted in the previous section, an insufficient scientific basis exists for FDA to consider restricting access to non-tobacco-flavored ENDS based on their alleged attractiveness to youth.

D. There is No Reliable Science for the Proposed "Gateway Theory" as Relates to ENDS and Combustible Cigarettes.

Again, the clear government data demonstrates a continuing year over year decline in cigarette smoking among youth, notwithstanding the widespread availability of ENDS products on the market. Much like the absence of information supporting youth initiation, there is no reliable literature to support the "gateway theory" hypothesis that the availability of flavors in ENDS products somehow supports progression from e-cigarette use to smoking cigarettes. In fact, the only study that purports to support such a theory is Dai and Hao (2016), which concludes that the use of flavored e-cigarettes is associated with significantly higher odds of intention to initiate cigarette use among never-smoking youth. But, the Dai and Hao study is fundamentally flawed in several respects and so is not reliable or entitled to any weight by FDA. As noted under the cessation section, above, the study was based on a cross-sectional analysis of data reported by 6th through 12th graders in the 2014 National Youth Tobacco Survey. Logistic regression was used to determine whether flavored e-cigarette use was associated with intention to start smoking among never-smoking youth. Of the respondents, 2,017 reported using e-cigarettes in the last 30 days, of whom 1,228, or 60.9%, reported using flavored e-cigarettes. Among never-smoking youth, 288, or 55.6% of current e-cigarette users reported using flavored e-cigarettes. Compared with not using e-cigarettes in the past 30 days, using flavored e-cigarettes was associated with higher odds of intention to initiate cigarette use among never-smoking youth (aOR = 5.7; $p<0.0001$), leading the authors to conclude that flavored e-cigarette use is associated with an increased risk of smoking among youth.

As with their conclusions on cessation, however, the authors' conclusions on initiation are fatally flawed by the paper's methodological weaknesses. First, the NYTS study purports to examine intention to smoke, as opposed to actual empirical data on initiation of combustible cigarettes. Second, as the basis for their categorization of the NYTS respondents, the authors categorize as flavored e-cigarette "users" those students who answered that they had used a flavored e-cigarette at least once during the last 30 days, regardless of whether such use was a one-time-only event of experimentation, as opposed to regular use. The authors similarly only categorized NYTS "never smoking" respondents' intention to initiate cigarette use as "no intention to initiate cigarette smoking" if respondents selected "definitely not" to *both* the question: (1) "Do you think you will smoke a cigarette in the next year?"; and (2) "Do you think you will try a cigarette soon?" Even if a respondent answered "probably not" to either or both of these questions, the respondent was still classified into the group labeled as "intention to initiate cigarette smoking." Thus, 15 of the 16 possible response combinations to the two questions would lead to the respondent being categorized as "intention to initiate cigarette smoking." Third, as was also the case with their cessation analysis (as discussed above) the authors also use a questionable reference group for purposes of evaluating intention to initiate smoking. Instead of comparing the results reported by "nonflavored" (i.e., tobacco-flavored) e-cigarette users to those reported by "flavored" (i.e., menthol and other non-tobacco-flavored) e-cigarette users with respect to intention to initiate smoking, flavored e-cigarette users are compared to e-cigarette non-users. This apples-to-oranges comparison

provides no valuable insight into the role of menthol and other non-tobacco flavors themselves in youth users' decisions regarding initiation. Finally, as with their cessation analysis. the statistical methodology on initiation is suspect. The authors report adjusted odds ratios but fail to specify for what variables the odds ratios were adjusted. The authors also fail to test for heterogeneity when comparing two adjusted odds ratios to determine if they are significantly different from each other.

In light of these severe deficiencies, the paper's conclusion that youth use of flavored e-cigarettes is associated with a significantly higher likelihood of intention to initiate cigarette use among never-smoking youth is unreliable and entitled to no weight by FDA. Enacting a product standard on the basis that non-tobacco flavors support progression from ENDS use to that of combustible cigarettes among youth would run the risk of violating the requirement under the Administrative Procedure Act that an agency not act merely on the basis of an "unsupported assumption." *National Gypsum Co. v. EPA*, 968 F.2d 40, 43-44 (D.C. Cir. 1992).

E. Conclusion.

The science on initiation and an alleged "gateway" effect related to ENDS flavors, particularly among youth and young adults, does not support restricting access to non-tobacco flavored ENDS products. Recent data showing declining initiation and use of both cigarettes and ENDS products by youth belie the notion that ENDS somehow act as a "gateway" to combustible cigarettes. There is also no reliable literature that suggests that the availability of non-tobacco flavors in ENDS products makes more likely any progression from use of ENDS to combustible cigarettes. The existing research on initiation, particularly among youth, cannot properly evaluate the role that flavors actually play in ENDS initiation and, at best, only suggests that flavors may be one among several relevant factors. The single reliable longitudinal survey on the use of flavors and initiation demonstrates that the availability of "good flavors" is not a reliable predictor of continued or more frequent use of e-cigarettes by youth over time. Any regulatory action that would restrict access to non-tobacco flavors on the basis that they attract youth to ENDS would be premature and any such action undertaken on the theory that such flavors promote a gateway effect to combustible cigarettes would be entirely without any scientific basis.

V. THE PREDICTABLE ADVERSE PUBLIC HEALTH EFFECTS OF LIMITING ACCESS TO NON-TOBACCO-FLAVORED ENDS PRODUCTS WOULD FAR OUTWEIGH ANY SPECULATIVE PUBLIC HEALTH BENEFIT.

The predictable adverse public health effects of limiting access to non-tobacco-flavored ENDS products would far outweigh any speculative public health benefit. Consideration of the health effects associated with flavors in ENDS products also weighs against any product standard that would limit access to such products. As discussed below, as regards toxicity, non-tobacco-flavored ENDS are far less harmful than cigarettes and, unlike cigarettes, have not been shown to lead to substantial adverse health effects in humans. Restricting access to non-tobacco flavored ENDS could also have unintended

negative public health consequences, including higher cigarette relapse rates among current ENDS users, the creation of an illicit and unregulated market for flavored ENDS products, and growth of the substantial market for DIY flavored ENDS products that already exists, along with increased risks of adverse events to both users and non-users, including children.

A. Non-Tobacco-Flavored ENDS are Far Less Harmful than Cigarettes and, Unlike Cigarettes, Have Not Been Shown to Lead to Substantial Adverse Health Effects in Humans.

As a category, non-tobacco-flavored ENDS are far less harmful than cigarettes and, unlike cigarettes, have not been shown to lead to substantial adverse health effects in humans. Prior to addressing potential concerns regarding toxicity and flavors in ENDS, it bears reiterating that ENDS, as a category, reside on the far opposite end of the tobacco product continuum of risk from combustible cigarettes and that, as discussed with respect to cessation, above, ENDS were conceived and are marketed as an alternative to smoking.

The NASEM Report underscores the significantly different human health concerns between ENDS and combustible cigarettes by finding substantial evidence that, except for nicotine, exposure to potentially toxic substances in e-cigarettes is substantially lower than from cigarettes and thus poses less risk. (NASEM Report at 6, 598.) As NASEM notes:

> Laboratory tests of e-cigarette ingredients, in vitro toxicological tests, and short-term human studies suggest that e-cigarettes are likely to be far less harmful that combustible tobacco cigarettes. However, the absolute risks of the products cannot be unambiguously determined at this time. Long-term health effects, of particular concern for youth who become dependent on such products, are not yet clear. (NASEM Report at 1.)

NASEM thus concluded that there is "conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes." (NASEM Report at 11, 604.)

As FDA is aware, e-liquids are typically composed of a carrier liquid (propylene glycol and/or vegetable glycerin), water, nicotine, and flavoring compounds. The science regarding flavored e-liquids—especially as regards physiological effects in humans—is not yet sufficiently developed to identify which, *if any*, toxicological concerns are associated specifically with flavors in ENDS products. To date, there has been a large number of toxicology studies performed on flavored e-liquids and aerosols through laboratory analyses, cell culture studies, and three limited animal studies. However, there is very little information on the actual physiological effects of aerosolized ENDS flavorings in humans.

1. Laboratory Analyses Are Variable, Non-Standardized, and Inconclusive.

While generalized laboratory analyses involving e-liquid toxicity exist, few studies have isolated flavorings as the source of any potentially concerning aerosol constituents. Of the approximately twenty-seven laboratory studies that VTA has reviewed, approximately one-third evaluated flavored e-liquids*, but not the aerosols that they generate*. Those studies are thus not relevant to assessing potential human health effects arising from the inhalation of aerosolized *flavoring* ingredients. Moreover, of the approximately 18 studies that did evaluate e-liquid aerosols, only four studies utilized an appropriate unflavored "base" formulation as a control so as to isolate any toxicity concerns to the flavoring constituents themselves. These four studies (Bitzer, et al., 2018; Khlystov and Samurova (2016); Soussy, et al. (2016); and Wagner, et al., (2018)) use non-standardized methodologies, varying e-liquid products and aerosolizing apparatuses, and provide divergent results. The laboratory analysis by Wagner, et al., evaluated e-cigarette aerosols from 13 commercial refill e-liquids and six of the top-selling commercial e-cigarettes for the presence of combustion-related harmful and potentially harmful constituents (HPHCs) listed by FDA in its ENDS PMTA draft guidance (including three aromatic amines, five volatile organic compounds, and the polyaromatic hydrocarbon benzo[a]pyrene) and found that *none* of the HPHCs were present above the limits of detection. The divergent focuses and results of these four limited studies underscore that they do not provide a reliable basis to reach any generalized conclusions regarding potential harmful health effects of e-liquid flavors in humans.

Additionally, as the divergent methodologies used in just these four studies demonstrate, there is a wide range of methodological variables that are not standardized across analytical laboratory studies, including: brands of e-cigarettes and e-liquids, concentrations of ingredients (i.e., solvents, nicotine, flavorings), conditions to simulate vaping (i.e., apparatus type, power setting, number of puffs, puff duration, puff volume, puff rate), nature of controls, and processes utilized to conduct the actual analytical tests. This wide variability makes it virtually impossible to draw conclusions that might apply to a typical human vaping experience. Indeed, the NASEM report recognized the challenges associated with e-cigarette analytical studies, observing as follows:

> Currently, there is no standardized method for generating and collecting aerosol from e-cigarettes for analytical purposes and laboratory studies. Factors influencing e-cigarette aerosol generation include the e-cigarette device and setup, puffing topography, machine aerosol generation parameters, and aerosol generation techniques. As described in the beginning of this chapter, the design and composition of e-cigarette devices (including e-liquid composition, device battery power, activation voltage, and coil resistance) vary considerably, and these variations influence the e-cigarette aerosol produced. (NASEM Report at 75.)

VTA believes that FDA's publication of its long-awaited guidance document on HPHC testing may help limit the potential confounding role of such methodological variables in future laboratory flavor studies and enable more definitive conclusions regarding potential human health effects of flavor ingredients to be drawn.

2. Cell Culture Studies Are Inconclusive.

The difficulties associated with drawing conclusions regarding potential toxicants in laboratory analyses of flavored e-liquids are also present in cell culture studies. Indeed, the majority of cell culture studies do not even attempt to isolate vaporized flavorings. Of approximately 25 cell culture studies that VTA has identified, approximately one-third evaluated flavored e-liquids, but not their aerosols, and therefore are not relevant in evaluating potential human health effects arising from the inhalation of heated and aerosolized flavoring ingredients. Of the studies that did evaluate aerosols, only 12 included some form of an unflavored base control that would allow isolation of the effects of flavoring constituents in the e-cigarette vapor.

The results of the cell culture studies that have evaluated aerosols and utilized an unflavored base control have thus far been variable. However, there are positive findings from a number of studies. One cell culture study by Leslie, et al., (2017) found that any cytotoxicity seen with e-cigarette vapor extract was significantly lower than cigarette smoke. Three other cell culture studies (Sassano, et al, 2018; Gerloff, et al., 2017; and Misra, et al., 2014) found that there was only a weak or no correlation whatsoever between flavor compounds and cytotoxicity. A study of mydocardial cells by Farsalinos, et al., (2013a) found that only 4 of 20 samples showed cytotoxic properties that were associated with flavorings. Other cell culture studies (Behar, et al., 2018a, 2018b; Bengalli, et al., 2017; Cervellati, et al., 2014; Leigh, et al., 2016; Lerner, et al., 2015; Rowell, et al., 2017; and Ween, et al., 2017) have produced mixed results.

As with the laboratory analyses, there is great variability in the cell culture studies, including methods of exposing cells to the constituents of interest (i.e., vapor extracts versus vapor) and the types of cells or in vitro assays used to measure any biological effect. Again, this high degree of variability does not permit firm conclusions to be drawn that would apply to the typical human vaping experience.

3. No Appropriately Controlled Animal Studies Demonstrate Any Adverse Toxicological Effects Related to Flavored ENDS Vapor.

No appropriately controlled animal studies demonstrate any adverse toxicological effects related to flavorings in ENDS vapor. Only three studies focusing on exposures of animals to flavor constituents have been reported. The only properly controlled study did not find adverse toxicological effects related to flavored vapor. In Panitz, et al., (2015) the authors reported that when larval worms were exposed from hatching to low concentrations of e-liquids of varying flavors (grape, menthol, classic tobacco), the

flavorings did not significantly affect development rate and brood size. The authors also found no evidence that vaporization affected toxicity in the worms.

The other two animal studies published to date do not provide a basis for drawing conclusions related to the flavoring constituents themselves and are, therefore, not relevant to FDA's analysis. One, Zelikoff, et al., (2018) demonstrated that exposure of pregnant and neonatal mice to tobacco-flavored aerosol led to disruption in the developing central nervous system. However, the authors did not include an unflavored base control, so the effects of the tobacco flavoring constituents could not be isolated, rendering the study irrelevant to a toxicological analysis of flavorings. Similarly, Lerner, et al. (2015) found that exposure to e-cigarette aerosol generally was associated with inflammatory responses in mice, but the results varied by flavor and nicotine level and, again, the authors failed to include an unflavored control, so the effect of flavorings could not be isolated.

As with the laboratory analyses and cell culture studies performed to date, the limited animal studies likewise provide no reliable basis to reach any conclusions regarding potential harmful health effects of e-liquid flavors in humans.

4. There Are No Human Studies That Demonstrate Any Adverse Toxicological Effects of ENDS Flavorings.

There is no reliable literature on any potential harmful effects of ENDS flavorings in humans. No human studies have been conducted and any reported literature is, at best, anecdotal and/or speculative. For example, far from being an appropriately controlled human study, a social media study conducted by Li, et al., (2016) analyzed 3,605 unique e-cigarette-related posts on Reddit from January 1, 2011, to June 30, 2015. The authors identified nine body systems where symptoms were reported, including respiratory, neurological, mouth and throat, digestive, sensory, chest, immune, and circulatory. The symptoms reported varied and some were considered positive (i.e., cleared sinuses) while others were considered negative (i.e., cough). The best that the authors could hypothesize was that the vegetable glycerin / propylene glycol ratios, flavors, and nicotine levels could all be related to the various reported symptoms, whether positive or negative.

Similarly, a focus group conducted by Cooper, et al., (2016) of 50 adult e-cigarette users found that 5 had undesirable experiences with certain flavors. Three individuals had nausea after using strawberries and cream or strawberries and honey flavors, another felt a burning sensation after using a cinnamon flavor, and another experienced throat irritation after using cinnamon flavor. Finally, there is also a single case report of an acute allergic reaction to a cinnamon flavored e-liquid (Weiss, et al., 2016). Absent any rigorous or controlled scientific method, these findings amount to little more than anecdotes related to the use of particular flavored e-liquids without the ability to isolate causation to flavor ingredients themselves.

Taken as a whole, as NASEM has found, there is substantial evidence that, except for nicotine, exposure to potentially toxic substances in e-cigarettes is substantially lower than

from cigarettes and thus poses less risk. Further scientific analysis is needed both in the laboratory setting and in human studies to be able to demonstrate any potential toxicological effects of flavorings in aerosols generated by ENDS products on even an *absolute* basis. Despite this, the fact that flavored e-cigarettes have now been widely used for close to a decade, and are now used by millions of adult consumers without more reports of acute adverse health effects, is in itself evidence that is entitled to some weight—especially when compared with the substantial mortality and morbidity associated with combustible cigarettes. Once again, the existing data on the toxicological profiles of flavors must be further developed before FDA could possibly consider taking any action to regulate flavors. VTA welcomes efforts to further advance scientific knowledge in this area and to identify particular flavor compounds of substantial concern.

B. Limiting Access to Non-Tobacco Flavored ENDS Could Have Unintended Negative Public Health Consequences, Including Higher Cigarette Relapse Rates by Current ENDS Users and an Illicit Market for Flavored ENDS Products.

Limiting access to non-tobacco-flavored ENDS products can be expected to lead to unintended negative public health consequences, including increased cigarette relapse rates by current ENDS users and the creation of an illicit market for flavored ENDS products. FDA must, at minimum, collect and consider further data on these unintended consequences prior to considering any tobacco product standard that would limit access to flavored ENDS products.

1. Limiting Access to Flavored ENDS Will Cause Former and Recovering Smokers to Relapse.

As noted above, since the introduction of ENDS to the U.S. market in approximately 2009, combustible smoking rates have declined dramatically from 20.6% of the U.S. population to 15.5% of the population in 2016. The NASEM report on e-cigarettes concludes not only that ENDS are far less harmful than cigarettes, but also that substantial evidence exists that complete switching from combustible cigarettes to ENDS reduces short-term adverse health outcomes. (NASEM Report at 617.)

As described in Section III.B., above, many smokers rely on non-tobacco-flavored ENDS products to aid them in their journey down the risk continuum toward harm reduction and smoking cessation. It is thus logical to conclude that, if such products were no longer available to them because of a non-tobacco-flavor ban or similar restriction, the result would likely be higher smoking relapse rates and other unintended negative public health consequences. Indeed, the literature on the potential effects of a non-tobacco-flavor ban strongly supports this hypothesis.

A discrete choice experiment by Buckell, et al. (2018) attempted to predict the impact of various potential ENDS flavor bans on preferences and demand for combustible cigarettes in both adult smokers and recent quitters. The authors employed a "best-best"

discrete choice experiment to elicit smokers' and recent quitters' preferences with respect to flavors and other tobacco product characteristics. A sample of 2,031 adult smokers and recent quitters completed the online survey and discrete choice experiment. The discrete choice experiment resulted in predictions by the authors that a ban on all non-tobacco flavors in e-cigarettes, while allowing menthol in cigarettes, would result in an 8.3% increase in demand for cigarettes and an 11.1% decrease in demand for e-cigarettes. A ban on all non-tobacco flavors in e-cigarettes and menthol in cigarettes would similarly increase cigarette demand by 2.7% and decrease choice of e-cigarettes by 7.9%. The authors concluded that "[a] ban on flavored e-cigarettes alone would likely increase the choice of cigarettes in smokers, arguably the most harmful way of obtaining nicotine."

A cross-sectional survey (Harrell, et al., 2017a) that included 4,326 young adults ages 18-29 found that of current users of flavored e-cigarettes (i.e., any use in the last 30 days), *74% reported that they would not use e-cigarettes if they were not flavored*. Significantly more young adult females than males (p=0.03) indicated that they would not use e-cigarettes if they were not flavored. These findings support the potential for a ban on non-tobacco-flavored e-cigarettes to cause a substantial number of individuals to relapse to combustible cigarettes.

2. Limiting Access Would Likely Create An Unregulated Black Market for Flavored ENDS.

In addition to a potential increase in consumption of combustible cigarettes, a ban on non-tobacco flavors likely would, as anticipated in the Tobacco Control Act's House report, also lead to the establishment of an illicit black market for banned flavors of e-liquids. Indeed, it would be folly for anyone to suggest that FDA could drastically limit the flavors that are currently being used by 10 million adult consumers, many of whom are desperately trying to quit smoking cigarettes, without acknowledging that a black market would crop up to service a consumer base this large, specifically since the adult vaping population is remarkably committed to their vapor technologies.

Because products sold on such a black market would not be subject to the rigorous inspections of manufacturing facilities that are and will be required of establishments registered with FDA, such an illicit market for banned ENDS products would increase the likelihood of contamination or adulteration of e-liquids. Further, without strict quality controls or cGMPs, contraband flavored e-liquid products might very well contain quantities of nicotine that are far greater than reported on the labels, thus leading to greater nicotine dependence or dangerous levels of exposure to users.

As noted above, section 907(b)(2) of the FDCA requires FDA to consider "all other information submitted in connection with a proposed [tobacco product] standard, including information concerning the countervailing effects of the tobacco product standard on the health of adolescent tobacco users, adult tobacco users, or nontobacco users, such as the creation of a significant demand for contraband . . . ." As the foregoing survey and discrete choice experiment reflect, a ban on non-tobacco flavors in ENDS

products would likely result in a material increase in use of combustible cigarettes by current adult ENDS users, thus erasing the substantial public health gains that have accompanied the precipitous decline in the national smoking rate since the advent of the first generation of e-cigarettes products in the United States. An illicit market for contraband flavored e-liquids would also pose unnecessary risks to public health through potential contamination or adulteration of unauthorized e-liquids that are not manufactured in FDA-inspected facilities. VTA respectfully submits that FDA cannot meet its statutory requirement to properly consider countervailing effects on current and former adult smokers or as regards contraband flavored ENDS products without the development of further data on these points. FDA must, then, refrain from taking any significant action on non-tobacco ENDS flavors.

C. Limiting Access to Non-Tobacco-Flavored ENDS Products Would Create an Even Larger Market for DIY Flavored ENDS Products Than Already Exists, With Increased Attendant Public Health Risks.

Reducing or eliminating access to flavored ENDS products would also have the substantial countervailing effect of increasing the size of the existing market for do-it-yourself ("DIY") flavored e-liquids, as well as increasing the attendant risks to both users and non-users, including children. There currently exists a substantial market for DIY flavored e-liquids in the United States. A Google search for "DIY e-liquid" returns more than 7,010,000 results, including instructional YouTube videos, advertisements for vegetable glycerin and propylene glycol, and links to online sellers of nicotine solutions, bases, and flavors. If FDA were to ban all non-tobacco flavors, is it likely that the market for unregulated DIY inputs would expand and that many vapers would simply turn to producing flavored e-liquids in their own homes.

There has been very little investigation into the size of the current DIY market in the United States or the size of its potential expansion in the event of a ban on non-tobacco flavors. A study by Wong, et al., (2017) of Malaysian consumers of ENDS products provides some insight into this area. That study was a cross-sectional survey of some 851 ENDS users that inquired about use of e-liquids after enactment of a national ban on sales of nicotine-containing e-liquid. Some 87.9% of survey respondents reported continuing to purchase nicotine-containing e-liquid from retailers and 63.1% reported having done so through an online retailer. Importantly, almost one-third (30.8%) of respondents reported fabricating their own homemade e-liquids on a DIY basis, including, no doubt, many of the 54.4% of respondents who purchased zero nicotine e-liquid on the black market. If such a percentage were extrapolated to the U.S. market for flavored ENDS products, approximately 3 million consumers could be expected to be engaged in DIY e-liquid production in their homes.

The potential for expansion of the existing DIY market for flavored e-liquids in the face of a product standard restricting or banning their sale would result in a situation where, rather than tightly regulate a portion of the tobacco industry, as Congress intended through passage of the Tobacco Control Act, FDA would instead be promoting totally

unregulated manufacturing of homemade e-liquids and the increased attendant risks of contamination and nicotine poisoning by users or non-users, including young children. The risks of an even larger and fully unregulated market for DIY flavored e-liquids weighs strongly against adopting a product standard that restricts the availability of non-tobacco flavored ENDS products. At minimum, FDA must further study the potential for such an increased DIY market to meet its obligation to consider potential countervailing effects under Section 907(b)(2) of the FDCA prior to adopting any product standard that would restrict access to any ENDS flavors.

D. Conclusion.

On balance, flavored ENDS products are far less harmful than combustible cigarettes. Indeed, there is not even sufficient science to reach any firm conclusions about potential absolute toxicity of flavored ENDS products in humans. Restricting access to non-tobacco flavored ENDS would likely result in substantial and countervailing adverse public health consequences, including higher cigarette relapse rates among current ENDS users, the creation of an illicit and unregulated market for flavored ENDS products, and growth of the substantial market for DIY flavored ENDS products that already exists, along with increased risks of adverse events to both users and non-users, including children. There is no scientific basis for FDA to limit access to flavored ENDS, as the adverse public health effects of doing so would far outweigh any speculative public health benefit.

VI. INSTEAD OF LIMITING ACCESS TO FLAVORED ENDS PRODUCTS, FDA SHOULD MORE AGGRESSIVELY ENFORCE YOUTH ACCESS RESTRICTIONS AND CONSIDER FURTHER MARKETING AND ADVERTISING RESTRICTIONS.

To address the issue of youth access to ENDS products, rather than limit access to non-tobacco-flavored products, FDA should more aggressively enforce existing restrictions on youth access and also consider further marketing and advertising restrictions to limit youth exposure to ENDS marketing. Based on the nature of the questions posed by FDA in the Advance Notice of Proposed Rulemaking, VTA is concerned that FDA is considering adopting a tobacco product standard that would ban or limit the sale of non-tobacco flavors on the false premise that such flavors are more attractive to youth than they are to adults, including former smokers. Just like FDA, VTA and its members are very concerned about continuing to take steps to ensure that youth are not able to obtain and use ENDS products.

VTA strongly believes that, rather than indirectly attempt to restrict youth access by limiting the availability of non-tobacco flavors, FDA should more strictly enforce the restrictions against sales to minors that are already within its enforcement powers. There are a number of steps that FDA can take to further curtail youth access to ENDS products under FDA's existing authorities. FDA can more rigorously enforce age verification requirements by more clearly requiring all online retailers to conduct third-party authentication of a purchaser's age to ensure that the sale complies with the requirements in the purchaser's state and locale and taking aggressive enforcement action against those online retailers that fail to do so. FDA can also more rigorously restrict improper sales of

ENDS products through third-party marketplaces like eBay and issue no tobacco sale orders against repeat violators.

Should it choose to do so, FDA can also reduce youth exposure to ENDS product advertising through additional marketing restrictions. As a responsible representative of the ENDS industry, in January 2018, the VTA adopted voluntary Marketing Standards for Membership that impose reasonable restrictions on ENDS advertising to limit visibility of such advertising to minors. As noted above, a copy of the VTA Marketing Standards is attached hereto as Appendix 1. Among the voluntary restrictions found therein are:

- a requirement that retailers implement strict underage policies requiring employees to card anyone appearing under the age of 27;

- a requirement that vape shops display signage indicating "Unaccompanied Minors Are Not Allowed on Premises" and "Products are Not for Sale to Minors" or "Underage Sale Prohibited";

- a requirement that all vapor products be displayed behind a counter or in some other enclosed display that is not accessible without the assistance of a sales representative in convenience stores or other retail establishments where minors might be present;

- a requirement that all online sales of ENDS products be restricted to adults through either direct verification of government-issued ID upon delivery or through use of third-party age verification technologies;

- a requirement that packaging and marketing materials include the warning "Not for Sale to Minors" or "Underage Sale Prohibited";

- a requirement that packaging and marketing materials include a "Keep Out of Reach of Children" warning;

- a requirement that marketing content not appeal or be directed to minors, including through (a) product names; (b) cartoons; (c) other imagery; or (d) promotional items;

- a requirement that no channel of marketing or advertising be employed if more than 15% of its audience is minors, including television, print, radio, and event marketing or sponsorship;

- a requirement that products not use names, imagery, or designs that intentionally mimic, play upon, or otherwise infringe existing trademarks, trade names, or trade dress, particularly if associated with products marketed to minors;

- a requirement that all product sampling be restricted to adults;

- a requirement that marketing be intentionally directed toward current users of tobacco products and not to non-users;

- a requirement that contracted spokespeople and endorses be and appear to be at least 25 years of age; and

- a requirement that billboard advertisements not be physically located within 500 feet of any elementary or secondary school, youth-oriented facility, or childcare facility.

VTA respectfully submits that, if FDA were to pursue additional restrictions on marketing and advertising to address head-on concerns about youth access to ENDS, the VTA Marketing Standards would provide an appropriate example of the types of marketing and advertising restrictions that can effectively prevent youth exposure to ENDS marketing messages while still ensuring that adult tobacco users can educate themselves about the many advantages that ENDS products hold over combustible cigarettes. VTA believes that adoption of clear marketing and advertising standards not only would help the industry avoid questionable practices, but would also significantly aid in reducing youth access to and initiation of ENDS product use.

FDA should not take the drastic and counterproductive step of limiting access to non-tobacco-flavored ENDS products on the speculative assumption that such would somehow reduce youth initiation. Rather, FDA should squarely tackle the problem of youth access by more aggressively utilizing the enforcement powers that FDA already has and considering further marketing and advertising restrictions to avoid youth exposure to ENDS product marketing.

VII. CONCLUSION.

The continued availability of non-tobacco flavors in ENDS is critical to encourage cessation in existing smokers, to prevent relapse into combustible cigarettes, and to increase harm reduction as a matter of public health policy. There is no reliable evidence linking access to such flavors to increased use of combustible cigarettes and the science does not definitively link the availability of non-tobacco flavors to either youth initiation of ENDS or short- or long-term physiological harm in humans. Based on the science developed to date, the substantial and immediate public health benefits that non-tobacco flavored ENDS provide to smokers far outweigh the potential physiological and public health risks. There is no valid scientific basis that would justify FDA adopting a product standard that would restrict access to non-tobacco-flavored ENDS products.

It is clear that an innovative U.S. public policy of encouraging ENDS initiation by adult smokers is and will continue to be central to our collective battle to end cigarette smoking in the U.S., saving hundreds of millions of lives and reducing billions of dollars in

health care costs. So, notwithstanding the fact that, as set forth herein, FDA has no legal or scientific basis on which to limit flavors in ENDS products, important progress can be made in addressing the issues raised in this ANPRM. As noted earlier, much as we have done with the VTA Marketing Standards for Members, we also remain committed to continuing the discussion we started on developing the appropriate standards by which ENDS products, including e-liquids and their flavoring components, should be manufactured. The VTA and its members include a wide variety of subject matter experts with deep biochemistry, engineering, and public policy experience in all of the fields relevant to this inquiry. We look forward to having that dialogue with FDA so that we can collectively take steps to deliver on the remarkable promise that is vapor technology.

APPENDIX 1 –
VTA MARKETING STANDARDS FOR MEMBERSHIP

MARKETING STANDARDS FOR MEMBERSHIP

The Vapor Technology Association (VTA) is a leading national trade association in the electronic cigarette and vapor product industry. VTA represents the manufacturers, wholesalers, distributors, vape shop owners, small business owners and entrepreneurs who have developed innovative and quality vapor products, providing adult consumers with a safer alternative to traditional combustible products. VTA and its members are leaders in the vapor community, promoting small businesses and job growth, responsible public policies and regulations, and a high standard of safety within the industry.

To continue to promote high standards, VTA's Board of Directors has developed and adopted these *Marketing Standards for Membership*.

Released January 2018

VTA SALES AND MARKETING PRINCIPLES

VTA Marketing Standards for Membership are based on the following core principles:

1. VTA is committed to educating and informing its members on the best ways to comply with applicable laws and regulations governing electronic cigarettes, vaporizers and related electronic nicotine delivery systems ("Vapor Products"), which laws include, but are not limited to, the Federal Food Drug & Cosmetic Act (21 USC Ch. 9 et seq.) as modified by the Family Smoking Prevention and Tobacco Control Act and 21 CFR Parts 1100, 1140 and 1143 (Deeming Tobacco Products To Be Subject to the Federal Food, Drug and Cosmetic Act, May 10, 2016) (the "Tobacco Control Act") and the Child Nicotine Poisoning Prevention Act of 2015, 15 U.S.C. §§ 1471, et seq.

2. Vapor Products are for adults only and should not be intentionally marketed to, sold to or used by those who have not attained the age of 18 years (or the appropriate age restriction within the subject territory) ("Minors").

3. VTA Members' marketing activities must refrain from knowingly marketing Vapor Products to Minors, which is strictly prohibited.

As described in more detail below, VTA strongly supports efforts to prevent Minors' access to Vapor Products and VTA embraces marketing restrictions that will reduce Minors' exposure to marketing of and promotions for Vapor Products.

At the same time, VTA is committed to ensuring that adult smokers have equal access to truthful and factual information about Vapor Products, as well as a wide array of Vapor Products. Hence, VTA will continue to advocate for new regulations that properly recognize the game changing role that safe and innovative Vapor Products will continue to play in reducing, if not eliminating altogether, adult smokers' dependence on combustible cigarettes.

VTA encourages and expects that its members, if they haven't already, will take the appropriate steps to ensure that their marketing standards reflect the core principles and prescriptions contained in these Marketing Standards for Membership within six months.

PREVENTING MINOR ACCESS TO VAPOR PRODUCTS

Vapor Products should only be sold to and used by adults, 18 and older (or the appropriate age of majority for any given market). To ensure continued limited access of Vapor Products, VTA adopts the following policies and practices:

1. VTA fully supports compliance with the age restrictions embodied in the Tobacco Control Act and other legislation.

2. VTA fully supports compliance with the child resistant packaging requirements of the Child Nicotine Poisoning Prevention Act.

3. VTA fully supports state laws, and local ordinances, that impose penalties on retailers or others who sell or provide vapor products to Minors, and Minors who are found in possession of vapor products.

4. All vape shops and other retailers of Vapor Products should implement strict underage policies requiring that their employees card anyone who appears fewer than 27 years of age.

5. Vape shops shall ask Minors who are unaccompanied by an adult to leave their shop immediately.

6. Vape shops should display signage indicating that (a) "Unaccompanied Minors Are Not Allowed on Premises" and (b) "Products are Not for Sale to Minors" or (c) "Underage Sale Prohibited."

7. All Vapor Products should be displayed behind the counter or in some other enclosed display which is not accessible without the assistance of a sales representative in convenience stores or other retail establishments where Minors may be present.

8. All online sales of Vapor Products should be restricted to adults through either direct verification of government issued photo ID upon delivery of product or through the use of age verification technologies provided by independent third party agencies using public records databases.

9. VTA Members' packaging and marketing materials for Vapor Products must contain a warning which indicates that such products are "Not For Sale to Minors" or "Underage Sale Prohibited" or comparable language whether or not required by law.

10. VTA Members' packaging and marketing materials for Vapor Products must contain a statement which warns "Keep Out of Reach of Children" or comparable language whether or not required by law.

11. All manufacturers, distributors and retailers should forbid the sale of their Vapor Products through any vending machine or unattended kiosk.

VTA MARKETING STANDARDS

1. No Appeal to Minors. Marketing of Vapor Products should not include content which is directed towards Minors. In establishing their marketing, VTA Members should consider that content which may appeal or be directed to Minors could include, without limitation, the following: (a) product names, (b) cartoons, (c) other imagery; and (d) promotional items.

2. Intended Audience for Marketing. Marketing for Vapor Products should not be directed at Minors and no channel of marketing should be employed if more than 15% of its audience is Minors. This restriction includes, but is not necessarily limited to, TV, print and radio advertising, as well as event marketing or sponsorships. For regional (local, city or state) advertising, content must be directed to persons who meet or exceed the specific region's age of majority.

3. No Improper Use of Trademarks or Trade Dress. VTA Members should have a zero tolerance policy for Vapor Products that use in commerce names, imagery or designs that intentionally mimic, play upon, invoke or otherwise infringe upon existing trademarks, trade names or trade dress, particularly if they are associated with products that are or were primarily marketed to Minors.

4. No Smoking Cessation Claims. Vapor Products should not be portrayed as any sort of smoking cessation device or as a product which may be used to help quit smoking.

5. No Claims Regarding Health or Safety.** Vapor Products should not be marketed as providing a therapeutic value, as being safe or healthy for consumers, or as products which do not produce secondhand health effects.

6. No Modified Risk Descriptors or Claims.** Vapor Products should not be marketed or sold using modified risk descriptors or claims (e.g., "light," "low," and/ or "mild"). By way of example only, Vapor Products should not be marketed as (a) having no ash or smoke, (b) having no tar, (c) being less harmful, (d) posing lower risk of disease or (e) as containing reduced or zero levels of harmful ingredients.

7. Ingredients. VTA Members should accurately represent the ingredients contained in their Vapor Products and, in particular, the ingredients contained in any e-liquid. Deceiving any consumer regarding the contents of the Vapor Products is strictly prohibited.

8. Product Sampling. VTA Members shall ensure that all product sampling is restricted to adults and follows all applicable laws.

9. No Health Professionals. VTA Members should not use health professionals to market or otherwise endorse their Vapor Products, directly or indirectly.

*** Litigation challenging the law upon which this standard is based is currently pending. VTA reserves the right to revisit and/or amend this standard in the event that any pending legal challenge is successful.*

10. No Marketing to Non-Tobacco Users. Vapor Product marketing should be intentionally directed towards those who are current users of tobacco products and should not be designed to encourage non-tobacco users to start using Vapor Products.

11. Spokespeople. VTA Members shall ensure contracted spokespeople and individuals endorsing Vapor Products on the company's behalf must be and appear to be at least 25 years of age.

12. Billboards. Billboard advertisements used for the purpose of promoting or marketing Vapor Products shall not be physically located within 500 feet of any elementary or secondary school, youth oriented facility, or childcare facility.

APPENDIX 2 – VTA RESPONSES TO SPECIFIC ANPRM QUESTIONS

VTA provides responses to several of the specific questions posed in the ANPRM (and grouped by category below) as follows:

1. The Role of Flavors (Other than Tobacco) in Tobacco Products

Question 1: Provide studies or information regarding the role of flavors (other than tobacco) generally in tobacco products. If the response relies on research in other areas (e.g., consumer products), discuss the appropriateness of extrapolating from such research to tobacco products.

Response: The role of non-tobacco flavors in ENDS products cannot be viewed through the same policy prism as characterizing flavors in other tobacco products, including cigarettes. Unlike any combustible tobacco product, the naturally occurring flavor of e-liquids prior to the introduction of flavorings is not tobacco because ENDS e-liquids do not contain tobacco.

Unlike the role of characterizing flavors in cigarettes in 2009, today, non-tobacco flavors play a crucial role in the ENDS product category. The ability of millions of adult consumers to reduce their reliance on and, indeed, quit smoking combustible cigarettes altogether, depends in large part on continued, reliable access to non-tobacco-flavored ENDS products. As of 2014, approximately 10.2 million U.S. adults had used non-tobacco-flavored ENDS products in the past 30 days (Bonhomme, et al., 2016). A study by Hsu, et al., (2018) found that there are more than 15,000 distinct flavors of e-liquids that are available to consumers. Some studies suggest that older vapers are less likely to use a variety of different flavors than younger adult vapers (Ashford, et al., 2017; Cataldo, et al., 2015). However, it is scientifically unacceptable to suggest that flavors are solely intended to attract or appeal to youth because the evidence suggests that adults of all ages like many categories of flavors – including fruit, sweet, and cool flavors – and tend to dislike harsh and bitter flavors (Zare, et al., 2018; Harrell, et al., 2017b). This finding has been borne out in multiple surveys (Bonhomme, et al., 2016; Berg, 2016; Bowler, et al., 2017; and Krishan-Sarin, et al., 2014), experimental studies (Goldenson, et al., 2016; Kim, et al., 2016; Garrison, et al., 2018), and focus groups (Soule, et al., 2016; Kim, et al., 2017).

Both anecdotal evidence and a growing body of literature suggests that, as smokers transition from combustible cigarettes to use of ENDS products, they first tend to use tobacco and menthol-flavored e-liquids, but eventually transition to non-tobacco flavors as their dependency on combustible cigarettes decreases (Farsalinos, et al., 2013b; Truman, et al., 2018; Adriaens, et al., 2017; Simmons, et al., 2016). This may be because, as smokers wean themselves off of cigarettes, they tend to gravitate toward non-tobacco flavors to avoid the taste sensations associated with tobacco flavors that they believe may cause them to relapse into smoking. (Farsalinos, et al., 2013b; Simmons, et al., 2016.) The continued availability of non-tobacco flavors is thus critical to encourage cessation in existing

smokers, to prevent relapse into combustible cigarettes, and to increase harm reduction as a matter of public health policy.

VTA incorporates by reference the discussions set forth in Sections II.D., II.E., and III.A., above.

2. Flavors (Other than Tobacco) and Initiation and Patterns of Tobacco Product Use, Particularly Among Youth and Young Adults

Question 3: Provide studies or information regarding the role of flavors (other than tobacco) in initiation and/or patterns of use of noncombusted tobacco products, particularly among youth and young adults.

Response: The science on the role of non-tobacco flavors in ENDS as regards initiation among youth and young adults does not provide a basis to restrict access to non-tobacco flavored ENDS products. As an initial matter, the prevalence of both youth smoking *and* vaping in the United States are on the decline, thus lending less urgency to the question of youth initiation of ENDS products.

The existing literature on flavors and youth initiation cannot properly evaluate the role that flavors *actually* play in initiating use of ENDS products (as opposed to reported "intent to use") and, at best, only suggests that flavors may be one factor among several for why youth and youth adults initiate use of ENDS. As regards youth and young adults, other reasons to initiate use besides the availability of attractive flavors include: (i) curiosity; (ii) the perception that ENDS are less harmful to the user and to others than cigarettes; (iii) the perception that, unlike cigarettes, ENDS do not smell bad; (iv) low cost; (v) use as a smoking cessation tool; (vi) ability to use anywhere; (vii) use by friends and family; and (viii) use by public figures (Ambrose, et al., 2015; Villanti, et al., 2107; Kinouani, et al., 2017).

Surveys (Shiffman, et al., 2015; Pepper, et al., 2016; Pepper, et al., 2016) have also found overall interest in trying e-cigarettes to be low among non-smoking youth and that the presence of non-tobacco flavors does not significantly increase youth interest in trying ENDS products. The only reliable longitudinal study (Bold, et al., 2016) on the use of flavors and initiation among youth demonstrates that while "good flavors" is one reason youth try e-cigarettes, it is not a significant predictor of either continued or more frequent use of e-cigarettes over time. There is not a scientific basis for FDA to consider restricting access to flavored ENDS based on alleged attractiveness to youth.

VTA incorporates by reference the discussion set forth in Section IV., above.

Question 4: Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted tobacco products on initiation of tobacco product use or progression to use of other tobacco products (for example, from noncombusted to combusted tobacco products), particularly among youth and young adults.

Response: The theory of a supposed "gateway" effect is entirely unsubstantiated and provides no basis to limit access to non-tobacco flavored ENDS products. The smoking rate in the United States is at its lowest rate ever and fell over 40% among middle and high school students between 2011 and 2015, the years during which the vapor products industry grew exponentially (Singh, T., et al., 2017). The CDC's statistics also demonstrate that e-cigarette use among youth peaked in 2015 and now remains at a statistically significant reduced level (from 16% down to 11.7%). (Jamal, A., et al., 2017; Wang, et al., 2018.)

There is no reliable scientific literature to support the hypothesis that the availability of non-tobacco flavors supports progression from e-cigarettes to smoking. The only study (Dai and Hao, 2016) that purports to support such a theory by concluding that use of flavored e-cigarettes is associated with significantly higher likelihood of intention to initiate cigarette use among never-smoking youth has multiple significant methodological flaws and should not be given any weight by FDA. Any restriction on ENDS flavors based on the theory that they promote a gateway effect to combustible cigarettes would be entirely without any scientific basis.

VTA incorporates by reference the discussion set forth in Section IV., above.

3. Flavors (Other than Tobacco) and Cessation, Dual Use, and Relapse Among Current and Former Tobacco Product Users

Question 5: Provide studies or information regarding the role of flavors (other than tobacco) in helping adult cigarette smokers reduce cigarette use and/or switch to potentially less harmful tobacco products.

Response: Non-tobacco flavored ENDS play a critical role in smoking cessation and harm reduction efforts and restricting access to them would leave millions of current and future adult smokers without a proven tool for moving down the continuum of risk to less harmful products. The existing reliable scientific literature trends strongly in support of the conclusion that the availability of a wide range of flavors—and particularly non-tobacco flavors—plays a critical role in encouraging switching and cessation among existing smokers and preventing relapse to combustible cigarettes.

Dual use of cigarettes and e-cigarettes among existing smokers is common and is often a necessary step in "switching" from exclusive combustible cigarette use to complete smoking cessation and exclusive e-cigarette use. Survey data show that ENDS use is most common among current smokers, many of whom use a combination of combustible cigarettes and e-cigarettes as they substitute e-cigarettes for smoking. Two reliable

longitudinal analyses of data from the Population Assessment of Tobacco and Health (PATH) Study (Chen, 2018; Buu, et al., 2018) have studied the role of non-tobacco flavors in e-liquids and determined that users of such flavors were more likely to have reduced their cigarette consumption or to have quit smoking altogether. These studies should be given significant weight by FDA.

Other descriptive surveys (Farsalinos, et al., 2013b; Tackett, et al., 2015; Dawkins, et al., 2013; Russell, et al., 2017, Truman, et al., 2018) and experimental studies (Litt, et al., 2016) also show a strong correlation between access to a variety of non-tobacco ENDS product flavors and smoking harm reduction and successful cigarette quit attempts. Several authors (Farsalinos, et al., 2013b; Simmons, et al., 2016; Truman, et al., 2018; and Adriaens, et al., 2017) have proposed that existing smokers may be more likely to first start using tobacco- and/or menthol-flavored ENDS to ease the transition to e-cigarettes and then migrate toward other flavors to prevent the tobacco or menthol flavor from serving as a cue to resume smoking as their need for combustible cigarettes lessens. A large survey conducted by Russell, et al. (2018), found that the number of current and former smokers who had used a non-tobacco flavor as their first ENDS flavor increased substantially between 2011 and 2016 and that tobacco and menthol had dropped below several non-tobacco flavors in terms of ranked preferences, leading the authors to conclude that "[r]estricting access to non-tobacco e-cigarette flavors may discourage smokers from attempting to switch to e-cigarettes."

The only two studies (Dai and Hao, 2016; Weaver, 2018) that suggest that use of flavored e-cigarettes is associated with lower likelihood of intention to quit tobacco use or does not significantly influence quit rates have multiple significant methodological and statistical flaws and should not be given any weight by FDA.

VTA incorporates by reference the discussion set forth in Section III.B., above.

Question 6: Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted tobacco products on the likelihood of: (1) cessation of combusted tobacco products use, (2) cessation of all tobacco product use, and (3) uptake of dual use of combusted and noncombusted tobacco products among current and former tobacco product users. Include information from, and define, all populations: youth, young adults, and adults (and any subgroup thereof, if applicable).

Response: Non-tobacco flavored ENDS are critical to smoking cessation efforts. Limiting their availability would remove a powerful aid to cessation efforts by current and future adult smokers. Non-tobacco flavored ENDS make quit attempts by smokers more likely to be successful and are also unique in that, unlike any other tobacco product, they allow users to titrate down to lower levels of nicotine, thus suggesting that users can reduce their exposure to nicotine over time (Farsalinos, et al., 2013b and 2014).

Dual use of cigarettes and e-cigarettes among existing smokers is common and is often a necessary step in "switching" from exclusive combustible cigarette use to complete smoking cessation and either exclusive e-cigarette use or cessation of use of all tobacco products altogether. Indeed, as Public Health England (Britton and Bogdanovica, 2014) has noted, any concerns about sustained dual use of flavored ENDS by former smokers are largely illogical, as the same principle applies to NRT products. Indeed, FDA itself recognized the inherent contradiction between arguing against dual use and for public health when, in 2013, FDA amended its policy pertaining to dual or poly-use of nicotine replacement products and tobacco products and modified the labeling requirements for NRT products to remove instructions that their use be discontinued if the user relapsed to cigarettes. FDA has thus already recognized that it should not discourage individuals trying to quit smoking using alternative nicotine products by instructing them that dual use is wrong.

VTA incorporates by reference the discussion set forth in Sections III.B., III.C., and III.D., above, and its response to Question 5, above.

Question 7: Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted products on the likelihood of: (1) delayed or impeded cessation among users who would have otherwise quit combusted tobacco product use, or (2) delayed or impeded cessation among users who would have otherwise quit all tobacco product use. Include information from, and define, all populations: youth, young adults, and adults (and any subgroup thereof, if applicable).

Response: There is no basis in the scientific literature to restrict access to non-tobacco flavored ENDS on the theory that they delay or impede cessation of either cigarettes or all tobacco products among smokers who would have otherwise quit. Many smokers are dual users for a time as they undertake the process of switching from exclusive combustible cigarette use to complete smoking cessation and exclusive e-cigarette use. Some exclusive e-cigarette users then quit use of all tobacco products altogether.

While VTA recognizes that there is a concern that an individual could successfully rely on e-cigarettes to quit smoking, but then persist in long-term use of e-cigarettes, rather than ceasing use of all tobacco products altogether, there currently exists no reliable literature that specifically addresses the topic of flavors in e-cigarettes and impeded cessation of all tobacco products. There is, however, limited literature from Farsalinos, et al., (2013b and 2014) to suggest that e-cigarette users tend to reduce the nicotine content of their e-cigarettes over time, thus lending support to the hypothesis that if exclusive vaping continues over a long term, the user's exposure to nicotine will decrease. VTA found no literature that specifically addresses the topic of ENDS flavors and impeded cessation of all tobacco products.

VTA incorporates by reference the discussion set forth in Section III.B., III.C., and III.D., above, and its responses to Questions 5 and 6, above.

Question 8: Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted tobacco products on the likelihood that former combusted tobacco product users relapse. Include information from, and define, all populations: youth, young adults, and adults (and any subgroup thereof, if applicable).

Response: There is no scientific basis to limit the availability of non-tobacco flavored ENDS products on the theory that they promote relapse to smoking by former combusted tobacco product users. As noted in response to Question 4, above, there is no reliable literature to support the notion of a "gateway" effect as to flavored ENDS products in general. Further, there are no scientific studies that have specifically investigated the role of flavors with respect to relapse to smoking. Limited evidence from surveys (Farsalinos, et al., 2013b; Truman, et al., 2018; Russell, et al., 2018) and focus groups (Simmons, et al., 2016) suggests that an array of flavor options may be helpful in preventing relapse to cigarette smoking.

Importantly, since the introduction of ENDS to the U.S. market in approximately 2009, combustible smoking rates have declined dramatically from 20.6% of the U.S. population to 15.5% of the population in 2016. The NASEM report on e-cigarettes concludes not only that ENDS are far less harmful than cigarettes, but also that substantial evidence exists that complete switching from combustible cigarettes to ENDS reduces adverse short-term health outcomes. (NASEM Report at 617.) Multiple studies (Buckell, et al., 2018; Harrell, et al., 2017a) suggest that, in the face of a ban on non-tobacco flavors, many current ENDS users that are also current and former smokers would increase their consumption of combustible cigarettes, potentially undoing the substantial progress that has been made in lowering smoking rates over the last decade and leading to increased morbidity and mortality among the population of current and former smokers.

VTA incorporates by reference the discussion set forth in Sections III.B. and V.B., above, and its response to Question 5, above.

4. Additional Public Health Considerations

Question 9: Provide studies or information regarding the potential toxicity or adverse health effects to the user or others from any flavors (e.g., flavor additives, compounds, or ingredients) in tobacco products. These adverse health outcomes may include, but are not limited to, cancer or adverse respiratory, cardiac, or reproductive/development effects. Of particular interest are studies or information on inhalation exposure to any flavor. Provide studies or information on what, if any, toxic chemicals might be formed from the heating or burning of tobacco products with flavors and the potential toxicity or health risks that might result from these formed chemicals.

Response: The existing literature on potential toxicity and adverse health effects from short-term use of flavored ENDS products does not provide a basis to restrict their use.

Flavored ENDS products are substantially less harmful than their relevant comparison group, combustible cigarettes, and the research conducted to date does not suggest significant short-term adverse human health effects from their use.

In any evaluation of potential toxicity associated with ENDS flavors, paramount importance should be given to NASEM's findings that exposure to potentially toxic substances in e-cigarettes is substantially lower than from cigarettes (NASEM Report at 598) and that substituting e-cigarettes for combustible cigarettes reduces users' exposure to numerous toxicants and carcinogens (NASEM Report at 604). Any discussion about absolute toxicity from e-liquid flavor compounds must occur against the backdrop of the relevant comparison group—combustible cigarettes. Moreover, the substantial public health benefit associated with existing smokers switching from cigarettes to non-tobacco-flavored ENDS must also be weighed against any absolute toxicity concerns.

Although many toxicology studies have been performed on flavored e-liquids and aerosols, ENDS flavorings have not been shown to lead to substantial adverse health effects in humans. Most research into flavor toxicity to date has been through laboratory analyses and cell culture studies and the large numbers of methodological variables and differing outcomes do not lend themselves to firm conclusions. There are no human studies that demonstrate any adverse toxicological effects of ENDS flavorings. Despite the fact that non-tobacco-flavored e-liquids have been used extensively for close to ten years in the United States, only one case report exists of a severe allergic reaction to a cinnamon flavored e-liquid. Further research is needed to draw any firm conclusions regarding any potential harmful physiological effects in humans resulting specifically from exposure to flavor compounds in ENDS products. FDA cannot consider restricting access to flavors based on the current scientific record.

VTA incorporates by reference the discussion set forth in Section V.A., above.

Question 10: Provide studies or information on the impact, whether intended or unintended, of public health efforts by local jurisdictions, States, and members of the international community to impose restrictions on the manufacture, marketing, sale or distribution of all or a subset of tobacco products with flavors (other than tobacco), including but not limited to cigars, ENDS, menthol cigarettes, and smokeless tobacco products.

Response: Limiting the availability of non-tobacco-flavored ENDS products can be expected to result in countervailing effects that could reverse the gains made in reducing the number of U.S. smokers in recent years and harm public health by significantly increasing the relapse rates of current and former smokers who rely on non-tobacco-flavored ENDS and generating a substantial illicit market for flavored ENDS products. FDA cannot meet its statutory requirement under Section 907(b)(2) of the FDCA to properly consider such effects without the benefit of further research on these points.

However, it should be of great concern to FDA's thoughtful and science-based approach to implementing policy on ENDS in general, and flavored ENDS in particular, that local and state jurisdictions are acting precipitously and *without regard to science* to limit or ban flavored ENDS products. As FDA is aware, many of these local and state efforts are being driven by groups purporting to be concerned about public health, but which continue to *mislead* the public on the fact that e-cigarettes are at least 95% safer than cigarettes, on the fact that it is the tar and combustion in cigarettes that kills and not nicotine, and on the fact that adult smokers desperately trying to quit like and need flavors on their cessation journey.

FDA should make it clear to regulators at *all levels of government* that it is presently engaged in a thoughtful, appropriate, and science-based regulatory process that pre-empts all state and local actions on the subject of flavors regulation. The reason is simple: FDA's twin missions of individual and public health will be undermined if it correctly decides that there is no basis on which to regulate flavors in ENDS products at this time. Moreover, a patchwork of state laws and local ordinances will represent nothing but arbitrary decisions on limiting or banning flavors since, as FDA knows, such local and state restrictions will not involve any process that remotely resembles the scientific research and balanced policy analysis that FDA is required to undertake and is undertaking.

In fact, FDA's mission already is being undermined by the likes of the California Department of Public Health, with its painfully misleading and disingenuous flavors website, and by the similar "public health" entities that pushed the San Francisco flavor ban referendum. The more FDA remains silent about such misinformation, the more it permits fringe elements to undermine the serious work that FDA is undertaking.

There is an important reason that the American Cancer Society boldly declared that it was going to expend resources to correct the current consumer misperceptions about the relative safety of ENDS products when compared to combustible products. All the misinformation and hyperbole about protecting youth at the state and local levels, as well as the federal level, will only lead more adult smokers to be lulled into continued deadly combustion.

VTA incorporates by reference the discussion set forth in Section V.B., above.

Question 12: Provide studies or information regarding consumer perceptions, if any, of the addictiveness of tobacco products with flavors (other than tobacco). Include information from, and define, all populations: youth, young adults, and adults (and any subgroup thereof, if applicable).

Response: VTA was unable to identify any relevant peer-reviewed studies on the effect of flavors on perceived addictiveness of ENDS.

5. Tobacco Product Standards

Question 13(a): Are there any specific flavors for which FDA should establish a tobacco product standard? If so, which flavors (e.g., flavor additives, compounds, or ingredients) and why?

Response: As respecting ENDS flavors, no. On balance, the scientific data and the public policy considerations militate against the regulation of any specific flavor at this time. There has been no research that could justify FDA, or any other entity, picking and choosing which flavors should and should not be manufactured and accessible to adult consumers.

Question 13(b): With respect to your response to the previous question, what level (e.g., maximum, minimum, prohibition) should FDA establish to protect the public health, and why?

Response: VTA incorporates its response to Question 13(a).

Question 14: If FDA were to establish a tobacco product standard prohibiting or restricting flavors, to which types of tobacco products should the standard apply (e.g., combusted, noncombusted, both), and why?

Response: As set forth in detail in Sections III., IV., and V., above, FDA cannot establish a tobacco product standard prohibiting or restricting flavors in ENDS. More specifically, Section II. underscores the myriad reasons why ENDS products must be examined and treated as the unique products that they are and cannot be lumped into any regulatory scheme involving other "tobacco products" covered by this ANPRM.

Question 15c: What is the role, if any, that menthol plays in use of tobacco products other than cigarettes, including, but not limited to, cigars and ENDS?

Response: Like all ENDS flavors, including tobacco flavor itself, menthol is an artificial flavor added to the nicotine and propylene glycol / vegetable glycerin base in e-liquids. Like all ENDS flavors, menthol, or its variations of mint, should remain available to adult ENDS users. Menthol is commonly used and is often preferred by current cigarettes smokers who are dual users, likely because of its similarity to the taste of menthol cigarettes. There is limited evidence (Truman, et al. 2015) in the literature that, as with tobacco flavor, ENDS users tend to migrate away from menthol and toward other flavors as they transition from current smoker to former smoker status.

VTA incorporates by reference the discussion set forth in Section III.B., above.

6. Sale or Distribution Restrictions

Question 16: FDA may consider restrictions on the sale and distribution of flavored tobacco products. Possible restrictions could include restrictions on the advertising and promotion of tobacco products with flavors; on access to tobacco products with flavors; and/or on the label, labeling, and/or packaging of tobacco products with flavors. These restrictions could include requirements to bear warnings or disclosure statements. What such restrictions, if any, should FDA consider and why?

Response: FDA should not impose any restrictions on access to any ENDS flavors, including non-tobacco flavors, as such would likely lead to substantial negative public health effects for existing smokers that are dual users of flavored ENDS products and also for former smokers who rely entirely on flavored ENDS products. VTA is concerned that FDA is considering adopting a tobacco product standard that would ban or limit the sale of non-tobacco flavors on the false premise that such flavors are more attractive to youth than they are to adults, including former smokers. VTA believes that, rather than attempt to indirectly address issues of youth access to ENDS by limiting the availability of non-tobacco flavored products, FDA should more strictly enforce the restrictions against sales to minors that are already within its enforcement powers. Steps that FDA can take to further curtail youth access to ENDS products include more clearly requiring all online retailers to conduct third-party authentication of a purchaser's age to ensure that the sale complies with the requirements in the purchaser's state and locale and stepped-up enforcement of improper sales of ENDS products through third-party marketplaces like eBay.

VTA also urges FDA to consider adopting further marketing and advertising restrictions that would limit youth exposure to messaging about all ENDS products. The VTA's self-imposed Marketing Standards for Membership attached as Appendix 1 impose reasonable restrictions on ENDS advertising to limit visibility of such advertising to minors, including requirements that marketing content not appeal to minors through product names, cartoons, other imagery, or promotional items, and through a requirement that no channel of marketing or advertising, including television, print, radio, or event sponsorship, be employed if more than 15% of the audience consists of minors. Stricter prevention of youth access, rather than restricting access to flavors by adults, including current and former smokers, is the proper policy response to the issue of use of ENDS products by youth.

VTA incorporates by reference the discussion set forth in Section VI., above.

7. Other Actions and Considerations

Question 17: To the extent that flavors may pose both (1) potential benefits to adult smokers who might consider switching to a noncombusted flavored tobacco product with lower individual risk and (2) potential risks to nonusers who might initiate use of tobacco

products through flavored tobacco products or to current users who might progress to flavored tobacco products with higher individual risks, how should FDA assess and balance these benefits and risks?

Response: The balancing of interests with respect to flavored ENDS products is relatively easy for FDA: FDA must prioritize helping the adult smoker desperately trying to switch to noncombusted products like ENDS. The short term individual benefits of ENDS have been recognized by NASEM, the relative safety when compared to deadly combustible cigarettes has been heralded by public health experts in the U.S. and around the world, and the potential long-term benefits are so critical to the public health of our nation that these considerations dramatically outweigh the speculative concern about initiation, no matter how much it may be sensationalized.

Moreover, with respect to initiation it bears remembering, we have numerous tools at our disposal to continue to protect youth. For example, we can increase enforcement of our laws banning the sale of products to youth, we can pass laws to punish the possession of products by youth, we can implement marketing standards to further insulate youth, and we can engage in *truthful* public information campaigns to properly educate parents and youth.

However, with respect to cessation, we clearly do not have the tools. Very simply, adult smokers in the U.S. need options, as existing "cessation" products on the market have been proven ineffective. The option is even worse when you consider that those products have had every regulatory and marketing benefit: promotion through hundreds of millions of marketing dollars, making the products available over the counter, eliminating the warnings about dual use with cigarettes, and even encouraging consumers to use those products for longer than originally recommended. And yet, we still have 38 million adult smokers and nearly half a million smoking related deaths in the U.S. every year.

Never before has a revolutionary consumer technology offered an alternative pathway to cessation. And, it wasn't until the advent of ENDS products that we started to see the rapid decline in cigarette smoking that we have enjoyed. So, in assessing the role of flavors in ENDS products, FDA must balance what we know to be true about the relative safety of ENDS and not adopt any policy or implement any standard that would negate the gains to which ENDS have contributed. Moreover, it is clear that ENDS products are so uniquely situated amongst all other "tobacco products" that FDA must recognize the ground-breaking tool that they offer FDA to achieve one of its biggest public health missions: eliminating cigarette smoking. With that goal at the forefront of all considerations, the balancing of interests in favor of ENDS products and flavors is easy.

Additionally, the demonstrable benefits to public health resulting from adult smokers who rely on non-tobacco-flavored ENDS products to reduce their reliance on cigarettes or to quit smoking altogether substantially outweighs any potential risks to nonusers through initiation because (i) there is no reliable evidence of non-tobacco-flavored ENDS products acting as a gateway to more harmful cigarettes; (ii) non-tobacco-

flavored ENDS themselves are, by comparison, far less harmful than cigarettes; and (iii) in absolute terms, there is no conclusive evidence of either short- or long-term serious physiological harm to humans from their use.

As explained above, non-tobacco flavors provide important benefits to adult smokers who switch to harm-reducing ENDS products and make it more likely that former smokers will not relapse into smoking. There is no reliable evidence that non-tobacco flavors promote a "gateway" effect that causes current users to progress to smoking or other flavored tobacco products with higher individual risk. Further, there is evidence from Farsalinos, et al. (2013b and 2014) to suggest that e-cigarette users tend to reduce the nicotine content of their e-cigarettes over time, thus lending support to the theory that if exclusive vaping continues over a long term, the user's exposure to nicotine will decrease.

In light of the lack of scientific evidence of a gateway effect from initiation of ENDS use, the relevant considerations at the heart of the balancing test mandated by Section 907(a)(3)(B) and (b)(2) of the FDCA are the potential harm that would result to existing smokers who are current or potential users of non-tobacco-flavored ENDS products versus the potential harm that would result to current non-users of non-tobacco-flavored ENDS products solely as a result of taking up use of such products.

As to this point, it cannot be emphasized enough that ENDS products as a category—including non-tobacco-flavored ENDS products—occupy a point on the continuum of risk that is at the extreme opposite end from combustible cigarettes. The National Academy of Sciences has already concluded that there is conclusive evidence that completely substituting e-cigarettes for combustible cigarettes reduces users' exposure to numerous toxicants and carcinogens, that there is substantial evidence that switching results in reduced short-term adverse health outcomes, and that ENDS are "far less harmful than combustible tobacco cigarettes." (NASEM Report at 1.)

The existing literature on flavors and youth initiation cannot properly evaluate the role that flavors actually play in initiating use of ENDS products and, at best, only suggests that flavors may be one factor among several for why youth and youth adults initiate use of ENDS. The only reliable longitudinal study (Bold, et al. 2016) on the use of flavors and initiation among youth demonstrates that while "good flavors" is one reason youth try e-cigarettes, it is not a significant predictor of either continued or more frequent use of e-cigarettes over time, and so does not support the hypothesis (under Section 907(a)(3)(B)(i)(III) of the FDCA) that the presence of non-tobacco flavors in ENDS leads to an increased likelihood that those who do not use ENDS products will start using such products on a regular basis. Also, there is no substantial evidence to date of adverse health effects on non-users from use of non-tobacco-flavored ENDS products.

Based on the science developed to date, the potential overall risk profile from regular use of non-tobacco-flavored ENDS is so substantially less than combustible cigarettes that, when the propensity of current and former smokers to rely on non-tobacco flavors when they stop smoking altogether is factored into the equation, there can be no

reasonable dispute but that the broad availability non-tobacco flavors provides public health benefits that far outweigh the potential physiological health risks. When the potential for a substantial illicit market and/or a DIY market for flavored e-liquids of up to 3 million individuals, along with the heightened risks to users and non-users of nicotine poisoning and other adverse events, is factored into the equation, it becomes clear that no additional restrictions should be placed on the availability of non-tobacco-flavored ENDS products.

VTA incorporates by reference the discussions set forth in Sections II., III., IV., and V., above.

Question 18: Provide studies or information on the role of tobacco flavor in tobacco products in initiation, patterns of use of tobacco products (particularly with respect to progression from noncombusted to combusted tobacco products or from combusted to non-combusted), reduction in use of combustible tobacco products and cessation of tobacco products. Include information from, and define, all populations: youth, young adults, and adults (and any subgroup thereof, if applicable).

Response: There is no basis to treat tobacco-flavored ENDS products any differently than non-tobacco flavored ENDS products. There is no reliable evidence to suggest that any ENDS flavors, including tobacco flavor, make use of cigarettes more likely through a supposed "gateway" effect. There is some evidence to suggest that tobacco flavored e-liquids are most likely to be used by current and former smokers (Berg, 2016; Bunch, et al., 2018). There is also some evidence that existing smokers tend to prefer to use tobacco-flavored ENDS products when they first initiate ENDS use and that those smokers then migrate toward non-tobacco flavors as they reduce and eventually cease their use of combustible cigarettes. Some researchers hypothesize that these ENDS users do so in order to avoid the flavor cues that could cause them to relapse back into combustible cigarettes. (Farsalinos, et al., 2013b; Simmons, et al., 2016; Truman, et al. 2018; and Adriaens, et al., 2017.)

VTA incorporates by reference the discussions set forth in Sections III.A., III.B., and IV. above.

Question 20: Provide analyses regarding any other tobacco product standard, regulatory action, or other action that FDA could implement that you believe would more effectively reduce the harms caused by flavors in tobacco products to better protect the public health than the tobacco product standards or other regulatory actions discussed in the preceding questions.

Response: As it relates to our response on behalf of ENDS products, VTA notes that this question incorrectly assumes that there are "harms caused by flavors" or that there is a need to protect "public health" in regards to flavors in ENDS. To the contrary, it is our

contention that based on the rapidly developing science, flavors in ENDS products may in fact offer a significant public health benefit by assisting adult smokers in switching away from and ultimately stopping smoking cigarettes. Alternatively, VTA incorporates by reference its response to Question 16, above.

Question 22: Are there any flavors that especially appeal to youth, young adults, or other specific age groups? If so, how are such flavors distinguished from other flavors?

Response: There is no scientific basis to enact any product standard that would treat tobacco flavored ENDS any differently than non-tobacco-flavored ENDS, including on the faulty premise that non-tobacco-flavored ENDS are more attractive to youth and young adults. The literature does not suggest that there are strong differences in flavor preferences among ENDS users by age group. It appears that all adult ENDS users generally like fruit, sweet, and cool flavors and tend to dislike harsh and bitter flavors, (Zare, et al., 2018; Harrell, et al., 2017b), as has been borne out in surveys (Bonhomme, et al., 2016; Berg, 2016; Bowler, et al., 2017; and Krishan-Sarin, et al., 2014), experimental studies (i.e., Goldenson, et al., 2016; Kim, et al., 2016; Garrison, et al., 2018) and focus groups (Soule, et al., 2016; Kim, et al., 2017). Some studies have, however, suggested that older vapers are less likely to use a variety of different flavors than young adults. (Ashford, et al., 2017; Cataldo, et al., 2015.) Because there are no clear preferences for non-tobacco-flavored ENDS by age groups, there is no basis to enact a product standard that would treat tobacco flavored and non-tobacco-flavored ENDS products differently.

VTA incorporates by reference the discussion set forth in Section III.A., above.

Question 24: If FDA were to establish a tobacco product standard prohibiting or restricting flavors in tobacco products, what evidence is there, if any, that consumers would start to flavor their own tobacco products?

Response: There is already a significant market for do-it-yourself ("DIY") flavored e-liquids in the United States and this market could only be expected to grow if FDA were to adopt a tobacco product standard prohibiting or restricting certain flavors in ENDS products. Both materials to self-manufacture flavored e-liquid products and instructions for doing so are readily available to any U.S. consumer with internet access and a credit card. The risks associated with an even larger and fully unregulated market for DIY flavored e-liquids weigh heavily against adopting such a product standard.

There has been little research into the size of the current DIY market in the U.S. or by how much it might expand if a tobacco product standard was adopted that limited the availability of flavored ENDS products. One survey (Wong, et al., 2017) of Malaysian ENDS users conducted after a ban on the sale of e-liquid in that country found that 30.8% of respondents began producing their own e-liquids in their home. If such a percentage were extrapolated to the U.S. market for ENDS products, approximately 3 million consumers

could be expected to be engaged in DIY e-liquid production in their homes. Apart from existing wholly unsupervised by FDA, such a large DIY market would create greater risks of adverse events from e-liquid contamination and nicotine poisoning, including among young children. At minimum, FDA must further study the potential for such an increased DIY market to meet its obligation to consider potential countervailing effects under Section 907(b)(2) of the FDCA prior to adopting any product standard that would restrict access to any ENDS flavors.

Moreover, prohibiting non-tobacco flavors may also generate a large illicit market for flavored e-liquids that could pose unnecessary risks to public health as a result of increased risk of contamination, adulteration, or nicotine dependence because of deficient quality control practices. FDA should thus refrain from taking any significant action on non-tobacco flavors until the scientific evidence on countervailing effects can be more fully developed.

VTA incorporates by reference the discussion set forth in Sections V.B.2., and V.C., above.

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