IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

AMERICAN ACADEMY OF PEDIATRICS, et al., Plaintiffs, v. FOOD AND DRUG ADMINSTRATION, et al., Defendants.	Civil Action No. 8:18-cv-883-PWG

AMICUS CURIAE BRIEF OF THE RIGHT TO BE SMOKE-FREE COALITION IN SUPPORT OF DEFENDANTS' PMTA COMPLIANCE DEADLINE

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The Right To Be Smoke-Free Coalition ("RSF") respectfully submits the following *amicus* brief in support of the Food and Drug Administration's ("FDA") decision, in the exercise of its enforcement discretion, to establish a revised compliance date of August 8, 2022 for vapor product manufacturers to submit Pre-Market Tobacco Applications ("PMTA") under the Family Smoking Prevention and Tobacco Control Act ("TCA"), 21 U.S.C. §§ 387 *et seq.*, and the Deeming Rule, 81 Fed. Reg. 28,974 (May 10, 2016). RSF's members include large and small manufacturers of e-liquids and devices who are subject to the burdensome PMTA process, and thus are well-positioned to provide insight into the need for an adequate compliance period.[1]

INTRODUCTION

Vaping products "could be among the most significant health innovations of the 21st Century – perhaps saving hundreds of millions of lives," according to over 50 public health, tobacco, and nicotine specialists in a 2014 letter to the World Health Organization emphasizing the importance of reducing smoking-related harms through vaping. Exh. A, FDA147235-41 (Exh. A contains all administrative record citations). Since then, the potential value to the public health of vapor products, and particularly to cigarette smokers, has been well-established. Indeed, Defendant FDA, the National Academies of Sciences ("NAS"), the British Government, and several Plaintiffs in this case, among many others, have concluded vaping is substantially less risky than smoking and can help adults completely transition away from cigarettes – a fact demonstrated by the continuously falling smoking rate in the U.S., which is at an all-time low.[2] The following quotes are just a sampling of supporting statements made by these groups.

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[1] All parties have consented to the filing of this *amicus* brief. No counsel of any party to this proceeding authored any part of this brief. No party or party's counsel, or person other than *amicus* and its members, contributed money for the preparation or submission of this brief.

[2] Forbes, "Poll: U.S. Smoking Rate Falls To Historic Low" (July 26, 2018), https://tinyurl.com/y8x9us8o.

- **FDA** – "FDA agrees that use of [vapor products] is likely less hazardous for an individual user than continued smoking of traditional cigarettes." 81 Fed. Reg. at 29,035; *see also* 81 Fed. Reg. at 29,030, 29,032.

- **FDA Commissioner and Director of FDA's Center for Tobacco Products** – Vapor products, when combined with measures to reduce nicotine levels in cigarettes, "represent[] a promising foundation for a comprehensive approach to tobacco harm reduction."[3]

- **National Academies of Sciences** – "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."[4]

- **National Academies of Sciences** – "While overall evidence from observational trials are mixed, there is moderate evidence from observational studies that more frequent use of e-cigarettes are associated with an increased likelihood of cessation." *Id.*

- **Public Health England** – "It has been previously estimated [by the Royal College of Physicians] that [vapor products] are around 95% safer than smoking. This appears to remain a reasonable estimate." FDA022852.

- **Public Health England** – "Smokers who have tried other methods of quitting without success could be encouraged to try e-cigarettes to stop smoking . . ." FDA022891.

- **Plaintiff American Cancer Society** – "Based on currently available evidence, using current generation e-cigarettes is less harmful than smoking cigarettes" and "switching to the exclusive use of e-cigarettes is preferable to continuing to smoke combustible products."[5]

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[3] Scott Gottlieb, M.D. & Mitch Zeller, *Perspective: A Nicotine-Focused Framework for Public Health*, New Eng. J. Med. (Sept. 21, 2017), https://tinyurl.com/yd2pqafo.

[4] *Public Health Consequences of E-Cigarettes* (2018), at 18, https://tinyurl.com/ycxlymgf.

[5] *Position Statement on Electronic Cigarettes* (Feb. 15, 2018), https://tinyurl.com/ybadn9cl.

- **Plaintiff American Cancer Society** – Addicted smokers "should be encouraged to switch to the least harmful form of tobacco product possible; switching to the exclusive use of e-cigarettes is preferable to continuing to smoke combustible products." *Id.*

- **Plaintiff Truth Initiative** – "Some smokers may be unable or unwilling to quit using nicotine and would benefit by completely switching to a much lower harm nicotine delivery mechanism (including potentially a well-regulated e-cigarette)."[6]

These statements are based on the fact that vapor products do not involve any combustion or burning. Combustible tobacco products, like cigarettes, are significantly more dangerous because smokers inhale tar and other pyrolyzed tobacco constituents, many of which are known human carcinogens and toxicants. FDA155128-30. But research suggests non-combustible vapor products occupy a more favorable position on the "continuum of risk" and are expected to substantially reduce tobacco-related disease and death. FDA155128-43. Further, there is mounting evidence that vaping products may help addicted smokers move away from cigarettes. For example, Public Health England, part of the British government, found almost all of the one million-plus adult vapers in England are current or ex-smokers, many of whom are vaping to help transition from combustible products. FDA183506. Likewise, a just released 2018 consumer survey of almost 70,000 vapers in the U.S. found that 74.6% of former smokers were using vapor products at the time of quitting cigarettes, with most participants "self-report[ing] that they were successful in quitting smoking with the help of e-cigarettes."[7] Further, in a 2015 consumer survey, 87% of the respondents (17,186 participants) indicated they had completely replaced smoking with vaping. Exh. B, Woessner Aff. at ⁋ 15.

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[6] *Action needed on e-cigarettes* (July 19, 2018), https://tinyurl.com/y9hf9vdl.

[7] Konstantinos F., M.D., MPH, *et al.*, *Patterns of flavored e-cigarette use among adult vapers in the United States: an internet survey* (2018), at 6, 20, https://tinyurl.com/yaq7u94l.

Moreover, integral to this switching process is the availability of a wide range of e-liquid flavors. As FDA recognized during the rulemaking, the "availability of alternatives to traditional tobacco flavors in [vapor products] may potentially help some adult users who are attempting to transition away from combusted products." 81 Fed. Reg. at 28,977. Indeed, in the 2018 survey, 87.3% of respondents said flavors were "extremely" or "very" important to their quit attempts. *See supra* note 7, at 22. Similarly, in the 2015 survey, 72% of vapers credited interesting flavors with helping them to completely switch from their smoking habits. Woessner Aff. at ⁋ 15. Both surveys found that vapers used multiple flavors on a daily basis and had to continuously rotate to new flavors to make a successful transition. *See supra* note 7, at 15; Woessner Aff. at ⁋⁋ 6-15.[8]

But these substantial public health benefits would have been seriously jeopardized, at a minimum, if the vaping industry had been required to submit PMTAs within the Deeming Rule's original two-year filing deadline. In FDA's *Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule: Guidance for Industry (Revised)*, the PMTA cutoff date for products on the market as of August 8, 2016 was extended to August 8, 2022, after having been initially set for August 8, 2018.[9] One of FDA's stated reasons for exercising its enforcement discretion was to "give industry more time to comply." *Id.* at 4. Indeed, as demonstrated below, the evidence overwhelmingly demonstrates that no manufacturer would have been able to submit a compliant PMTA within the initial two-year timeframe or, going forward, will be able to do so absent a sufficient compliance period. Not only will manufacturers likely be required to conduct, as part of any PMTA, long-term epidemiological studies that will, as a practical matter, take far longer than two years to complete, but also carry-out numerous

[8] In filing this brief, RSF also supports FDA's recent efforts to curb youth access to vapor products and agrees there is no place for manufacturers or retailers to target underage consumers.

[9] *See* https://tinyurl.com/y8epny9f.

other tests and provide extensive additional information that could not be collected and submitted by August 8, 2018. As such, the vast majority (as found by FDA during the rulemaking) if not the entirety of the vapor industry (along with attendant flavor varieties) would have disappeared. FDA184820 at Table 4.

As Congress made clear in the TCA, FDA must recognize a continuum of risk and regulate accordingly. The TCA "provide[s] new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products." TCA § 3(4). Moreover, FDA is to "promote cessation to reduce disease risk and the social costs associated with tobacco-related diseases" while "continu[ing] to permit the sale of tobacco products to adults in conjunction with measures to ensure that they are not sold or accessible to underage purchasers." TCA §§ 3(7), (9). This is consistent with FDA's exercise of enforcement discretion to provide manufacturers with adequate time to file PMTAs and avoid the total loss of a product that holds so much potential for millions of addicted smokers. As RSF demonstrates below, nothing less than the August 8, 2022 filing deadline is needed by manufacturers to file compliant PMTAs and otherwise survive as an industry. Accordingly, RSF asks this Court to deny Plaintiffs' motion for summary judgment and uphold FDA's current compliance period (whether by dismissing the case based on justiciability grounds or finding for FDA on the merits).

ARGUMENT

I. PMTAs And The Risk Of A Total Ban On Vapor Products

While the TCA offers several pathways for pre-market approval to combustible tobacco products that undeniably cause serious health problems, the only approval route available to

innovative and lower risk vapor products is through the burdensome PMTA.[10] This is the most extensive pre-market review process and requires tobacco product manufacturers to submit, *inter alia*, substantial amounts of information for each new tobacco product showing that marketing the product is "appropriate for the protection of public health." This has become known as the "population effects" standard and requires FDA, when deciding whether a product may be commercialized, to take into account the product's impact on the population as a whole, including the likelihood that people will stop using tobacco products (*i.e.*, cessation), as well as start using them (*i.e.*, initiation). 21 U.S.C. § 387j(c)(4). To satisfy this standard, the TCA provides that a PMTA "when appropriate . . . may include . . . clinical" (*i.e.*, human) studies or, in the alternative, other "valid scientific evidence" that FDA considers "sufficient to evaluate the product." 21 U.S.C. § 387j(c)(5).

In May 2016, when the Deeming Rule was published, FDA also issued a 50-page draft guidance specifically for vapor products – which remains unfinalized – discussing in significant detail the substantial amounts of information that will likely be required for each PMTA.[11] While we outline this draft guidance below, there are three overarching aspects set forth in the

[10] Products commercialized by February 15, 2007 are "grandfathered" under the TCA and do not require pre-market authorization. 21 U.S.C. § 387j(a)(1)(A). Aside from an unidentified, rudimentary "e-cigar" claimed by FDA, no vapor products will be grandfathered. 81 Fed. Reg. at 28,991. As a result, new vapor products are ineligible for the less burdensome alternative Substantial Equivalence ("SE") or SE Exemption pre-market pathways, both of which require a new product to be "substantially equivalent" to a grandfathered product. 21 U.S.C. § 387j(a)(2).

[11] FDA, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (Draft Guidance)* (May 2016) ("FDA draft guidance"), https://tinyurl.com/y8gevr2h. Two weeks ago, just before the initial PMTA deadline would have expired, FDA announced it would soon be issuing additional guidance and begin a new rulemaking regarding the PMTA process. *See* FDA, *Advancing Tobacco Regulation to Protect Children and Families: Updates and New Initiatives*, https://tinyurl.com/y8wked2z. As such, it is not clear how manufacturers would have been able to submit complete applications by the original cutoff if FDA itself is still in the process of finalizing the PMTA framework.

draft that would have made it impossible for even the largest vapor companies to submit compliant PMTAs before the original August 8, 2018 deadline.

First, in FDA's view, a manufacturer should file a separate PMTA for each "finished tobacco product," which includes individual e-liquids or devices packaged and sold to consumers. FDA028360; 81 Fed. Reg. at 28,995. For example "FDA considers each [e-liquid] product with differing flavor variants and nicotine strengths to be a different product." FDA028370. Under this approach, a manufacturer would independently gather information and conduct studies that are applicable to each branded e-liquid and device. It would not be possible, if FDA enforces this policy, to simply rely on generalized data regarding vapor products as a whole. Given that manufacturers can have hundreds, if not thousands, of separate products, it is easy to see how dramatically extensive the PMTA process will be. *See, e.g.*, FDA130192-94 (manufacturer with over 700 products). Indeed, several million tobacco-related products manufactured in the U.S. have already been registered with FDA.[12]

Second, the draft guidance recommends that manufacturers test each product in a range of circumstances to satisfy the PMTA standard. It would not be enough to merely provide FDA with an exemplar e-liquid or device. For instance, tests would be run on the "chemical and physical identity and quantitative levels of emission of aerosols under the range of operating conditions (*e.g.*, various temperature, voltage, wattage settings) and use patterns (*e.g.*, use conditions by light users, typical users, and heavy users) within which consumers are likely to use the new tobacco product." FDA028375. Refillable devices "should be tested with a reasonable range of available e-liquids, particularly those available in different levels of

[12] *See* FDA's Tobacco Product Listings database, https://tinyurl.com/yd7bqq7h.

nicotine." FDA028378. Finally, components and parts "should be tested with the reasonable range of [devices] with which they could be used." *Id.*; *see also* 81 Fed. Reg. at 28,994.

Third, the draft guidance provides that the relative health risks of each new e-liquid or device should be compared to the anticipated risks of other tobacco products on the market, including combustible products like cigarettes and other similar vapor products. For example, regarding a new e-liquid, FDA "recommend[s] a comparison to other e-liquids with similar nicotine content, similar flavors, or other similar ingredients." FDA028366. The purpose is to determine whether marketing of the new product is appropriate for the protection of public health, as consumers using current products may switch to the new product, which may present a higher or lower health risk. *See also* FDA028375; FDA028380; 81 Fed. Reg. at 29,008.

Given these far-reaching requirements, it is no surprise that FDA predicted a two-year compliance period (ending on the original August 8, 2018 deadline) would cause between 95 and 97 percent of all vapor manufacturers to exit the market. FDA184820 at Table 4. Indeed, as shown below, FDA's prediction *overestimated* the number of manufacturers that would be able to file a PMTA before the initial two-year cutoff. The reality is that the original compliance period would have resulted in a virtual ban on vapor products because the long-term epidemiological studies likely required by FDA to satisfy the population effects standard could not have been completed within two years.

II. PMTAs Could Not Be Completed Within The Initial Two-Year Compliance Period

A. Background On Longitudinal Epidemiological Studies

FDA's initial two-year compliance period fell well short of providing vapor product manufacturers sufficient time to generate the massive amounts of data required to satisfy the PMTA's population effects standard. Most concerning is the fact that PMTAs, according to

FDA, will likely require long-term human studies for each product examining health impacts that can only be identified over extended periods of time. Simply taking a brief snapshot of customers using a particular product will not be sufficient. As such, manufacturers will need all of the time granted by FDA through the current compliance period, if not more, to submit PMTAs and otherwise avoid a mass exodus of vapor companies from the marketplace.

Specifically, FDA's guidance says manufacturers will likely need to conduct longitudinal epidemiological studies that consider whether there is a relationship between using a certain vapor product and a particular health outcome. *See* Exh. C, Benson Aff. at ⁋⁋ 5-6; Federal Judicial Center & National Research Council of the National Academies, *Reference Manual on Scientific Evidence* (3rd ed. 2011), at 551 ("FJC Ref. Man."). In short, epidemiology assumes that an observed health effect is not distributed randomly in the general population and asks whether an identifiable subgroup, like those who use a vapor product, may be at an increased risk of a particular health impact. *See* FJC Ref. Man. at 551. Through such studies, researchers can discern an "association" between exposure to a substance or product and a given condition. While an "association" is not "causation," it tells us whether the outcome is occurring more frequently in a population than would be expected through mere chance. *Id.* at 552-53 n.7.

There are various types of epidemiological studies, with some study designs better able than others to detect and evaluate "associations." The most powerful studies are "randomized-controlled clinical trials." These are the "gold standard" and involve study participants who are deliberately exposed to a given substance or product and then compared to participants who were not exposed. Not surprisingly, clinical trials require a substantial cost and time investment. FJC Ref. Man. at 555; Benson Aff. at ⁋⁋ 11-12. Significantly, the TCA focuses on clinical studies when discussing investigations needed to show a product "is appropriate for the protection of

public health." 21 U.S.C. § 387j(c)(4) (such finding "shall, when appropriate, be determined on the basis of well-controlled investigations, which may include 1 or more clinical investigations"). Likewise, in describing human studies that may be required for a PMTA, FDA's draft guidance prioritizes clinical trials. *See, e.g.*, FDA028396 ("In cases where a product's potential impact on the public health has not yet been sufficiently reviewed, new nonclinical and clinical studies may be required."); *id.* ("Alternatives to U.S.-conducted randomized controlled clinical trials may be appropriate when potential bias associated with alternative controls can be addressed.").

In addition, there are epidemiological "observational" studies that can reveal associations, with the two main study designs being cohort studies and case-control studies. In cohort studies, healthy individuals in a population are followed over time to determine whether those who have been exposed to a substance or product eventually experience a health outcome at higher rates than those who are unexposed. These studies are also relatively costly and time intensive. FJC Ref. Man. at 556-57; Benson Aff. at ¶ 13 and Table 1. In contrast, case-control studies compare individuals with an existing health condition ("cases") to those without the condition ("controls") and ask whether exposure to a substance or product explains the difference. While case-control studies are relatively less expensive and are more efficient, they have several design and analytical shortcomings. FJC Ref. Man. at 559-60; Benson Aff. at ¶ 13 and Table 1. FDA's draft guidance states that, under certain conditions, manufacturers can use observational studies in lieu of clinical trials. *See, e.g.*, FDA028389; FDA028396.

Finally, there are other types of epidemiological studies – including cross-sectional, ecological, and descriptive design studies – but these approaches are substantially limited in their ability to evaluate associations. FJC Ref. Man. at 560-62; Benson Aff. at ¶ 13 and Table 1.

B. FDA's Extensive Guidance Regarding Epidemiological Studies

When discussing human-based research used to support a PMTA, FDA's draft guidance outlines (FDA028387-88) numerous scenarios to be considered by manufacturers that will take years to investigate before the studies provide any useful data, including:

- Tobacco users who may switch from other tobacco products to the new tobacco product;
- Tobacco users and nonusers who, after adopting the new tobacco product, may switch to or switch back to other tobacco products that may present higher levels of health risk;
- Tobacco users who may opt to use the new tobacco product rather than cease tobacco use altogether;
- Tobacco users who may opt to use the new tobacco product rather than an FDA-approved tobacco cessation mediation (*e.g.*, nicotine patch);
- Tobacco users who may use the new tobacco product in conjunction with other tobacco products;
- Nonusers, such as youth, never users, and former users, who may initiate or relapse tobacco use with the new tobacco product;
- The health effects in users of the new tobacco product; and
- Nonusers who experience adverse health effects from the new tobacco product.

Moreover, the number of issues that may need to be evaluated when conducting studies of these health effects is sweeping in scope. For each new product subject to a PMTA, FDA recommends (FDA028387-91) that the manufacturer evaluate:

- Likelihood of initiation and cessation by both users and non-users;
- Consumer perceptions (*e.g.*, how consumers perceive product risk);
- Product use patterns (*e.g.*, how frequently consumers use a product);
- Labeling comprehension (*e.g.*, how consumers understand the label);
- Human factors (*e.g.*, normal use and foreseeable misuse);
- Abuse factors (*e.g.*, nicotine addiction and exposures);
- Biomarkers of harm and exposure (*e.g.*, tracking nicotine in the body); and
- Health outcomes (*e.g.*, health effects from exposure to flavorings).

Collectively, the long-term studies also would likely need to involve a sufficiently large sample size and cover a broad range of consumers for each new product (*e.g.*, users, nonusers, youth, young adults, pregnant women, vulnerable populations) so the results are "generalizable" to the U.S. population as a whole. FDA028388; FDA028391; Benson Aff. at ¶¶ 5, 17. Under the

draft guidance, it would not be enough to merely follow a handful of customers or conduct focus groups. Before a manufacturer could even initiate some of these studies (*e.g.*, observational), it would need sufficient market penetration for its product – a process that could take years – so there is an ample customer base to investigate.[13]

C. Epidemiological Studies Require Many Years To Complete

Recent statistics for on-going, long-term epidemiological studies looking specifically at vapor products show just how unrealistic the initial two-year compliance period would have been for manufacturers. For purposes of this brief, RSF asked Cardno ChemRisk, a global consulting firm specializing in product health and safety, to review estimated timeframes for various types of epidemiological studies of tobacco products that were federally-funded in 2017. The results are telling. In particular, the average estimated time for completing the clinical trials was 6.67 years and for the observational cohort studies it was 5.11 years. Even cross-sectional (2.75 years), ecological (1.92 years), and descriptive design studies (2.25 years) – again, research approaches that are more efficient, but do not have strength of study design to evaluate associations – had average reported times that approach or reach beyond two years. In fact, some individual study estimates far exceed any of these averages. Benson Aff. at ¶¶ 9-10, 12-13 and Table 1.

Perhaps even more instructive is FDA's own epidemiological study of tobacco and vapor products called the Population Assessment of Tobacco and Health Study ("PATH"). This study, which was launched in 2011, is still on-going seven years later and will take several more years to complete. Benson Aff. at ¶¶ 14-16.[14] PATH is a joint effort undertaken by FDA and the National

[13] While some epidemiological study designs allow researchers to look "retrospectively," such as cohort studies, those typically involve situations where extensive health records have been maintained on individuals over many years, such as in industrial occupational settings. Benson Aff. at ¶ 13. This is obviously not the case with a disparate vaping consumer base.

[14] *See* PATH Study Overview, https://tinyurl.com/yaczvdm9.

Institutes of Health that will "inform FDA's actions related to tobacco products, thereby helping to achieve the goals" of the TCA.[15] It is a "nationally representative, longitudinal cohort study" that is following approximately 50,000 individuals from across the country, including users and non-users.[16] Study participants are assessed annually for at least three years. *Id.* Importantly, PATH focuses on the same issues that must be addressed by manufacturers under the population effects standard and might eventually be cited for support in PMTAs. Benson Aff. at ¶ 14. As FDA notes, PATH "informs us about why and how people are using – or not using – different types of tobacco products (not just cigarettes) and how use may effect health."[17]

In fact, PATH's stated goals and objectives substantially track the PMTA population effects requirements. Specifically, it is looking at: (i) reasons why some people use tobacco and others do not; (ii) how and why people start using different types of tobacco products, use two or more products, and switch from one tobacco product to another; (iii) how people quit using tobacco; and (iv) why some people who quit using tobacco start using it again. Benson Aff. at ¶ 14.[18] PATH is thus focused on identifying the same cessation and initiation patterns, behavioral and health impacts, and consumer attitudes that FDA believes the TCA and Deeming Rule require companies to assess for their PMTAs. *Id.* And PATH is explicitly designed to look at vaping products. *See, e.g.*, 81 Fed. Reg. at 29,029 (assessing "potential smoking cessation among e-cigarette users"); *id.* at 29,038 (providing "information about the overall population health impacts of [vaping products]").[19]

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[15] *See* FDA and NIH Study: PATH, https://tinyurl.com/y78jff5e.

[16] *See* FDA: PATH, https://tinyurl.com/yb77al5m.

[17] *See* PATH FAQs for Participation, https://tinyurl.com/y7l6ucgn.

[18] *See* PATH Research Objectives, https://tinyurl.com/y877mt37.

[19] *See supra* note 15 (noting PATH is evaluating initiation and use patterns of vapor products).

Yet completing this government-sponsored epidemiological work has taken well beyond two years. PATH is divided into four waves of participant surveys and collection of biospecimens (*e.g.*, blood). To date, data has only been collected from participants for three waves, with the fourth wave still underway.[20] Moreover, while third wave survey and biomarker data were recently released, the analyses of these data have not been completed. Benson Aff. at ¶ 16. Assessing the third wave survey results is important for understanding changes in the use of tobacco products over time, and evaluating the biospecimen data is crucial to investigating exposure and potential harm related to the use of tobacco products. *Id*. In short, given that FDA, with all of its resources and expertise, cannot complete its cohort study within two years, it was more than rationale for FDA to conclude that it was unrealistic to demand that individual manufacturers, most of whom are small companies, must complete similar studies within two years or else withdraw from the market.

Further, it was for these very reasons that manufacturers submitted comments during the rulemaking that a two-year compliance period would be inadequate and not allow for such long-term research to be completed before August 8, 2018. *See* FDA145304 (requesting a minimum 48-month compliance period due to "FDA's current knowledge deficit and the likelihood that new tests and equipment will need to be developed and validated for use by industry in the interim"); FDA161104 (suggesting more than 24 months after FDA completes a "final" PMTA guidance document (which FDA has yet to complete) to initiate and conduct "long-term" studies); FDA140979 (stating that clinical studies on consumer perception, use patterns and health impacts "will take significantly more than two years to develop and complete").

[20] *See supra* note 15.

As one manufacturer explained, "[c]redible long-term studies could not possibly be conducted in that [two year] arbitrary timeframe." FDA130180. The commenter continued:

> Developing such population-level data generally requires conducting long-term epidemiological studies. While this standard may be feasible for combustion tobacco products that have been marketed for decades and the subject of extensive studies, it would be impossible to meet for new categories of products, especially e-cigarettes. While some studies have been conducted on e-cigarettes, the product has existed for barely ten years and widely marketed for less than half that time. In short, they have not existed for a long enough period of time for such studies to have been conducted. . . . [I]t is unclear that such studies could even be *commenced* in that timeframe, because current methodologies and procedures are likely inadequate to address the TCA's new mandates for population-level public health data. Even if such a study were started today, it could take many more years for the data to be collected and analyzed in accordance with sound methodological principles. . . . Put simply, the FDA proposes . . . [a] classic Catch-22: unless a product is available to the public, long-term population-level studies of its effects cannot be conducted.

FDA130179-80 (emphasis in original).

D. FDA Will Likely Require Epidemiological Studies For PMTAs

Granting manufacturers adequate time to conduct longitudinal studies is critical as FDA has stated repeatedly that they will likely be required in PMTAs. *See, e.g.*, 81 Fed. Reg. at 28,997 ("However, in cases where there have been few or no scientific studies of a product's potential impact on the public health, new nonclinical and clinical studies may be required for [PMTAs]"); FDA028382 ("Due to the emerging nature of [vaping] products . . . FDA acknowledges that there may be limited nonclinical or clinical research conducted on specific [vaping] products. Thus, it is likely that applicants will conduct certain investigations themselves and submit their own research findings as part of their PMTA."); FDA028384 (FDA noting that "nonclinical studies alone are generally not sufficient to support a determination that marketing of the product is appropriate for the protection of public health (PMTAs would generally need clinical data).");

FDA028396 ("In cases where a product's potential impact on the public health has not yet been sufficiently reviewed, new nonclinical and clinical studies may be required.").[21]

Indeed, this is consistent with the only PMTA approved by FDA to date, which contained extensive clinical and observational data. Since the TCA was adopted in 2009, nearly 400 PMTAs have been submitted to FDA, the vast majority of which the agency has either outright refused to accept, or refused to file for scientific review, presumably because they were not compliant in some form. To date, the *only* PMTA that has ever survived scientific review and been approved is for a Swedish Match "snus" smokeless (*i.e.*, chewing) tobacco product (which resulted in separate marketing orders for eight varieties of that product).[22] Snus has been marketed for over 30 years and, as a result, its PMTA was accompanied by "data spanning several decades," including four clinical pharmacology studies, two clinical trials regarding cessation effects, longitudinal and cross-sectional studies on consumer use patterns, and substantial epidemiological studies regarding health effects.[23]

While FDA has indicated that manufacturers may rely, in part, on published studies and research conducted on similar products, FDA has also concluded that, at the time the Deeming Rule was promulgated, long-term data regarding vaping products did not exist. *See, e.g.*, 81 Fed.

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[21] In the *Nicopure v. FDA* litigation (Case No. 17-5196) (D.C. Cir.), RSF is arguing FDA had a statutory obligation to tailor the PMTA process to less risky vapor products and allow the vapor industry to submit compliant PMTAs that do not include product-specific epidemiological studies; instead, industry could rely on an existing scientific literature review showing that vapor products present substantially less risk than cigarettes on the whole and are thus appropriate for the public health. *See* RSF Opening Mem. at 55 (Doc. #1734702). Indeed, Congress gave FDA such authority within the PMTA provision itself, only requiring clinical studies "when appropriate" and permitting use of other "valid scientific evidence." 21 U.S.C. § 387j(c)(5).

[22] *See* FDA, Tobacco Product Marketing Orders, https://tinyurl.com/y75jlqbq.

[23] *See* Premarket Tobacco Application (PMTA) Technical Project Lead (TPL) Review (2015), at 7, 20, 25-26, 29, https://tinyurl.com/yd4sumku.

Reg. at 28,984 ("there have not yet been long-term studies conducted"); *id.* at 29,028 ("long-term studies are not yet available"); *id.* at 29,031 ("no adequate data on long-term health effects"); *id.* at 29,041 ("[l]ong-term studies are not available"); FDA028366 ("Given the relatively new entrance of [vaping products] on the U.S. market, FDA understands that limited data may exist from scientific studies and analyses); FDA028382 ("Due to the emerging nature of [vaping] products . . . FDA acknowledges that there may be limited . . . clinical research").

More importantly, FDA was not aware of any completed longitudinal studies necessary for manufacturers to explicitly address the population effects standard in a PMTA. *See, e.g.*, 81 Fed. Reg. at 28,984 ("[T]here have not yet been long-term studies conducted" indicating whether vaping products "may eventually be shown to have a net benefit on or harm to public health at the population level"); *id.* at 29,028 ("[W]e do not have sufficient data to determine what effects e-cigarettes have on public health at the population level"); *id.* ("[L]ong-term studies are not yet available to determine" the impact of [vaping] products on underage use); *id.* at 29,030 ("Given the relatively new entrance of [vaping products] on the market, consumers have not had the duration of use for researchers to fully assess the morbidity and mortality effects for [vaping products] on either the individual or the population"); *id.* at 29,041 ("Long-term studies are not available to conclude that [vaping products] are a proven cessation product").

Finally, even if a few studies resembling longitudinal investigations had been completed in the last two years (*i.e.*, before the initial August 8, 2018 filing deadline), it is unlikely that those would have replaced the need for each manufacturer to conduct some product-specific epidemiological research. At least under the standards previously suggested by the FDA in its draft (and still unfinalized) guidance, manufacturers will be able to rely only on studies of substantially similar products and will bear the burden of demonstrating that the comparison is

appropriate, meaning that the comparator product (whether an e-liquid or device) must involve the same materials, ingredients, design, composition, heating source, and other features. Moreover, the purportedly similar product must have been used in the same manner, under similar conditions, and for the same duration and frequency as the product subject to the PMTA. FDA028366; FDA028375; FDA028387; FDA028396. There is no evidence in the record or otherwise showing that this would have been possible for most, if not all, manufacturers and products currently on the market.

E. FDA Will Likely Require Extensive Non-Epidemiological Information

In addition to the long-term clinical and observational studies, FDA recommends that a whole host of other non-epidemiological data and information be generated by manufacturers as part of a compliant PMTA. As detailed in the FDA draft guidance (FDA028374-87; FDA0283891-95), these include:

Constituent Testing – E-liquids and aerosols/vapor produced by a particular device should be tested for over 30 substances under a range of operating conditions (*e.g.*, various temperature, voltage, and wattage settings) and use patterns (*e.g.*, light users, typical users, and heavy users).

Toxicological and Pharmacological Testing – Each ingredient, mixture of ingredients, and aerosols should be tested for potential health impacts, under both intense and non-intense use conditions, including *in vitro* (*i.e.*, laboratory) studies, *in vivo* (*i.e.*, animal) tests, and computational modeling. This includes a review of any flavor additives.

Aerosolization Properties Testing – The manufacturer should determine how each ingredient is aerosolized, the particle size of each ingredient, and how those particles can be deposited in the lungs through inhalation. This analysis also should reflect expected daily exposures or conditions of intended use for each product and substance.

Storage and Stability Testing – The established shelf life of a product, including how it is affected by storage conditions (like moisture and temperature), should be established, as well as how such conditions impact the product's performance over its lifetime (*e.g.*, change in pH levels and aerosol constituent levels).

Environmental Assessment – Manufacturers should prepare comprehensive Environmental Assessments under the National Environmental Policy Act ("NEPA") to ascertain the environmental consequences (*e.g.*, disposal) of commercializing a certain vapor product.

Literature Review – A thorough literature review, including of any available toxicology databases, should be conducted on all of the ingredients in the e-liquids and aerosols.

Finally, the above requirements are in addition to still other types of information, according to FDA, that should be furnished in a PMTA, including detailed descriptions of the product design and manufacturing processes (FDA028379-81), extensive background and analysis of each non-clinical and epidemiological study submitted (*e.g.*, protocols and methodologies, source data, laboratory practices, statistical analysis plans, strengths and limitations of study design, etc.) (FDA028383-84; FDA028397), and a comprehensive description of device properties and characteristics (*e.g.*, batteries, atomizers, coils, wicks, and operational software) (FDA028392-95).

When coupled with long-term epidemiological investigations, it simply strains credulity to argue that manufacturers could have filed completed PMTAs within the original two-year compliance period. It was eminently reasonable for the FDA to respond to that reality by extending the compliance deadline, thus giving the industry a more realistic – if still very demanding – timeline for meeting the PMTA mandates that FDA appears poised to impose under the regulations and draft guidance.

CONCLUSION

Based on the foregoing, RSF requests that this Court deny Plaintiffs' motion for summary judgment and uphold FDA's PMTA compliance deadline of August 8, 2022.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on August 14, 2018, I electronically filed the foregoing brief with the Clerk of the Court of the District of Maryland by using the CM/ECF system. All parties and *amici* are registered CM/ECF users and will be served through the CM/ECF system.

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