IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

MEMORANDUM IN OPPOSITION TO DEFENDANTS' MOTION TO DISMISS AND CROSS-MOTION FOR SUMMARY JUDGMENT AND IN FURTHER SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

FDA's opposition confirms that the Guidance's categorical suspension of premarket review requirements for almost 25,000 e-cigarette and cigar products exceeds the agency's statutory authority. FDA acknowledges that Congress expressly crafted "a statutory grace period" under the Tobacco Control Act, but one limited in scope. Defs.' Opp./Cross-MSJ Br. 1 (Dkt. 36-1) ("Opp."). It recognizes that Congress included "no statutory grace period" for later-deemed products. *Id.* Yet, the agency claims that it has "inherent discretion"—unrestrained by judicial review—to "extend a similar grace period" to thousands of tobacco products, exempting them from statutory requirements for years to come. *Id.* at 4. Were FDA correct, that boundless view of "enforcement discretion" could justify the suspension of premarket review for decades, and, more generally, would arrogate to agencies *carte blanche* to annul or modify unambiguous statutory requirements. But FDA is incorrect. FDA's position conflicts not only with the text, structure, and purposes of the Act, but with case law establishing agencies' duty faithfully to administer, rather than deliberately to countermand, congressional enactments.

Nor does FDA provide any persuasive defense of its clear-cut violation of its procedural obligations under the APA or its multiple, overlapping failures of reasoned decisionmaking. Congress structured the Act to combat tobacco use and nicotine addiction, especially among the Nation's youth. But by suspending key statutory obligations for as many as 25,000 new tobacco products, the Guidance—without the benefit of notice and comment—has thrown gasoline on the fire of an accelerating public health epidemic with respect to youth use of e-cigarettes and cigars. Nothing in the administrative record provides a reasoned explanation for this seismic shift in regulation; nothing demonstrates that FDA reasonably accounted for the deep and lasting harm to public health caused by the Guidance; and nothing justifies FDA's circumvention of notice and comment. This Court should vacate the Guidance and award appropriate equitable relief.

ARGUMENT

I. PLAINTIFFS' CHALLENGES TO THE GUIDANCE ARE JUSTICIABLE

Eager to avoid judicial review of the merits, FDA fires a volley of threshold objections: standing, nonreviewability, and the lack of final agency action. Each lands wide of the mark.[1]

A. Plaintiffs Have Standing To Challenge The Guidance

Plaintiffs have Article III standing because they have "'(1) suffered an injury in fact, (2) that is fairly traceable to [the Guidance] … and (3) that is likely to be redressed by a favorable judicial decision.'" *Kenny v. Wilson*, 885 F.3d 280, 287 (4th Cir. 2018). Congress passed the Act based on its finding that "[t]he use of tobacco products by the Nation's children is a pediatric disease of considerable proportions" and that, absent effective regulation, the Nation risked "new generations of tobacco-dependent children and adults." Family Smoking Prevention and Tobacco Control Act ("TCA"), Pub. L. No. 111-31, § 2(1), 123 Stat. 1776, 1777 (2009). To that end, Plaintiffs work daily on the front lines of a multi-faceted effort to eradicate tobacco addiction and to avert the creation of new generations of addicted children and adults. As implemented by the Deeming Rule, the Act would have enabled sustained progress toward that goal by subjecting hazardous and addictive products such as cigars and e-cigarettes to premarket review—requiring manufacturers to supply data and other information to FDA showing that the products they seek to market advance the public health, directing FDA to issue public orders determining whether the statutory public health standard has been met, and prohibiting the marketing of those products for which premarket orders have not been issued.

The Guidance has suspended that statutory process for almost 25,000 products, and in

[1] Because FDA's nonreviewability position overlaps significantly with the merits of Plaintiffs' *ultra vires* claim, Plaintiffs address that argument in Part II.B, below.

doing so, has "impede[d] [Plaintiffs'] efforts" to "carry out [their] mission[s]," *Lane v. Holder*, 703 F.3d 668, 674 (4th Cir. 2012)—directly, concretely, and in an ongoing way. It is enough that a single Plaintiff have standing. *Wilson*, 885 F.3d at 287. Here, all Plaintiffs do.

1. Plaintiffs Have Suffered Concrete Injuries That Are Caused By The Guidance And Would Be Redressed By Its Vacatur

a) Organizational Standing

Six Plaintiffs—the American Academy of Pediatrics ("AAP"), the American Cancer Society Cancer Action Network ("ACS CAN"), the American Heart Association ("AHA"), the American Lung Association ("ALA"), the Campaign for Tobacco-Free Kids ("CTFK"), and Truth Initiative (collectively, "Organizational Plaintiffs")— have standing because FDA's Guidance "perceptibly impair[s]" their ability to accomplish their missions in at least two ways. *Havens Realty Corp. v. Coleman*, 455 U.S. 363, 379 (1982); *see Lane*, 703 F.3d at 674.

First, FDA's suspension of premarket review requirements for approximately 25,000 new tobacco products deprives Organizational Plaintiffs of access to vital scientific and health information necessarily generated as a part of that process—information Plaintiffs need to carry out their missions. Were FDA performing its statutorily required premarket review responsibilities, FDA would be disclosing to the public significant information about new tobacco products that Organizational Plaintiffs would use to further their missions. *See, e.g.*, CTFK Decl. ¶¶ 10-17 (Ex. A). Denial of "'access to information'" that leads to the "'inhibition of [an organization's] daily operations'" can constitute injury in fact cognizable under Article III. *PETA v. USDA*, 797 F.3d 1087, 1094 (D.C. Cir. 2015) (quoting *Action All. of Senior Citizens of Greater Phila. v. Heckler*, 789 F.2d 931, 937-938 (D.C. Cir. 1986)).

Contrary to FDA's position, it is not necessary for Plaintiffs to establish that the Tobacco Control Act "'create[s] a legal right to access [that] information.'" Opp. 19. An organizational

plaintiff alleging that it is injured by an agency's failure to release mission-critical information need only show that the information "is essential to the injured organization's activities" and that "the lack of the information will render those activities infeasible." *Competitive Enter. Inst. v. NHTSA*, 901 F.2d 107, 122 (D.C. Cir. 1990); *see also Animal Legal Def. Fund, Inc. v. Espy*, 23 F.3d 496, 501 (D.C. Cir. 1994). That principle was recently reaffirmed in the D.C. Circuit's decision in *PETA*, which found Article III standing on the basis of allegations an agency had failed to take enforcement actions that would lead it to produce "investigatory information" that, in turn, would allow the organization to pursue its mission of "educat[ing] the public," 797 F.3d at 1095—all without asking whether disclosure of such information was required by law.[2]

Nonetheless, if standing doctrine required Plaintiffs to demonstrate a legal entitlement to information, that requirement is satisfied here. One of Congress's express "purpose[s]" in passing the Act was "to require … manufacturers to disclose research which has not been previously made available … relating to the health and dependency effects or safety of tobacco products" to "ensure that consumers are better informed." TCA § 3(6). The Act effectuates that goal in many ways, including through premarket review. It requires manufacturers to disclose to FDA, as part of premarket review, information about the health effects of new products. *See,*

[2] The Supreme Court's statement in *FEC v. Akins*, 524 U.S. 11, 21 (1998), that a plaintiff may *also* obtain Article III standing by showing an "inability to obtain information … that, on [their] view of the law, the statute requires" be made public—much like the Fourth Circuit's reiteration of that principle, *see Dreher v. Experian Info. Sols., Inc.*, 856 F.3d 337, 345 (4th Cir. 2017)—is not to the contrary. *Akins* set out an *alternative* path by which plaintiffs may establish injury in fact, predicated solely on the deprivation of information that a statute or regulation requires be made public with no additional showing of harm. *See Spokeo, Inc. v. Robins*, 136 S. Ct. 1540, 1549 (2016) (describing *Akins* as case in which "plaintiff … need not allege any *additional* harm beyond" deprivation of information); *Friends of Animals v. Jewell*, 828 F.3d 989, 992 (D.C. Cir. 2016) (same); *Kean for Cong. Comm. v. FEC*, 398 F. Supp. 2d 26, 36 (D.D.C. 2005) (same). Here, Organizational Plaintiffs have demonstrated concrete injuries flowing from the absence of information, and need not rely on this alternative standing showing.

e.g., 21 U.S.C. § 387j(a)(4), (b)(1). And the Act requires the agency to summarize and make public those data in a variety of formats—requiring, for example, FDA to issue "detailed information" about the "adverse health effects" of products for which SE reports are approved, *id.* § 387j(a)(4)(B), and directing it to issue "orders" adjudicating PMTA applications, *id.* § 387j(c)(1).[3] Consistent with those mandates, FDA in fact releases to the public orders and detailed summaries of FDA's analysis of approved premarket applications for new tobacco products. *See* CTFK Decl., Att. 1 (67-page summary of FDA's decision to approve Swedish Match "snus" product, including a detailed analysis of its health effects).

Thus, in suspending premarket review for nearly 25,000 tobacco products, the Guidance has denied and will continue to deny Organizational Plaintiffs access to important scientific and health information. *See, e.g.*, ACS CAN Decl. ¶¶ 10-13 (Ex. B); AHA Decl. ¶¶ 7-8 (Ex. C); ALA Decl. ¶ 16 (Ex. D); CTFK Decl. ¶¶ 10-17. These organizations (i) have in the past relied on information released through premarket review to help advance their missions and (ii) would do so today were FDA performing its statutory responsibilities. *See, e.g.*, AHA Decl. ¶ 6 (AHA "could and would use [premarket review] information"); ALA Decl. ¶ 16 (similar); CTFK Decl. ¶¶ 10-14 (detailing use of order in proposing product standard); Truth Decl. ¶ 9 (Ex. E) (detailing use of order in educating public). They are correspondingly "impair[ed]" in their ability to do so by the Guidance. *Havens Realty*, 455 U.S. at 379; *PETA*, 797 F.3d at 1094-1095. Furthermore,

[3] FDA's passing suggestion (Opp. 20 n.11) that such orders could be kept secret from the public flies in the face of foundational administrative-law principles against which Congress enacted the Act, *see* 5 U.S.C. § 552(a)(2) ("orders" must be made available for "public inspection"); it conflicts with Congress's reservation of only limited non-disclosure protections in connection with premarket review, *see* 21 U.S.C. § 387f(c); and it violates FDA's own regulations requiring that "all [FDA] records shall be made available for public disclosure" absent specific exemption, 21 C.F.R. § 20.20(b); *see Action All.*, 789 F.2d at 937-938 (finding informational injury in case where plaintiffs alleged violation of regulations).

this injury is not hypothetical: The Guidance's constraint on the flow of information *currently* impairs Plaintiffs' ability to carry out their missions—whether in educating or counseling the public or seeking redress from FDA—and will continue to do so for years. *See, e.g.*, AAP Decl. ¶¶ 45-51 (Ex. F) (describing AAP programs adversely affected by absence of premarket review); AHA Decl. ¶¶ 8-14 (similar); ALA Decl. ¶¶ 5-15 (similar); CTFK Decl. ¶¶ 15-16 (similar); Truth Decl. ¶¶ 5-14 (similar).

This case is thus on all fours with the D.C. Circuit's decision in *PETA*, 797 F.3d 1087. There, PETA sued to compel USDA to exercise its authority under the Animal Welfare Act ("AWA") with respect to birds. PETA argued that it had standing because the agency's failure to act meant that "USDA was not creating bird-related inspection reports that PETA could use to raise public awareness." *Id.* at 1091. The D.C. Circuit agreed, explaining that "USDA's allegedly unlawful failure to apply the AWA's general animal welfare regulations to birds," by denying PETA access to "bird-related AWA information," had "'perceptibly impaired [PETA's] ability' both to bring AWA violations to the attention of the agency charged with preventing avian cruelty and continue to educate the public." *Id.* at 1095. Because PETA had expended resources in response, the court concluded that its "injuries fit comfortably within … organizational-standing jurisprudence." *Id.* at 1097. All of that is true here: FDA's failure to implement the Act faithfully deprives Organizational Plaintiffs of access to information they would use to educate and counsel the public regarding tobacco use and to seek regulatory redress. And because they have "expended resources to counter these injuries," they have "established Article III organizational standing." *Id.* at 1095.

Second, separate and apart from informational injury, the Guidance interferes with Organizational Plaintiffs' missions of advancing the public health by allowing nearly 25,000

unreviewed products to remain on the market—requiring Plaintiffs to expend more resources to monitor the marketplace and to counsel and educate the public about e-cigarettes, cigars, or both. FDA itself has found that new products "have proliferated in the absence of FDA regulation"; that "consumers have highly imperfect information for choosing among products"; and that "acutely toxic products may be offered for sale." AR30,038. This burden falls most heavily on Organizational Plaintiffs, whose missions center on educating the public about the dangers of such products. *See* ACS CAN Decl. ¶ 15; AHA Decl. ¶¶ 15-17. And it has required Plaintiffs to expend more resources carrying out those missions than they otherwise would have expended—requiring some to divert such resources away from other important programs.

Plaintiff AAP, for instance, has expended "approximately 2000 hours on e-cigarette work" since FDA issued the Guidance, AAP Decl. ¶ 15—hours spent updating and offering educational programs focused on e-cigarettes, *id.* ¶¶ 16-25; developing and issuing educational curricula and clinical materials, *id.* ¶¶ 30-34; and researching and publishing a policy statement on e-cigarettes, *id.* ¶¶ 35-44. The "massive increase in time that [AAP has] had to spend on e-cigarette work in light of the proliferation of products without premarket review" has required the organization to reduce staffing on other projects, postpone new initiatives, spend funds that it would not have otherwise had to, and forgo grant funding—all as a direct result of the Guidance. *Id.* ¶¶ 45-51. Other Organizational Plaintiffs attest to similar resource expenditures. *See, e.g.*, ALA Decl. ¶¶ 11-14; ACS CAN Decl. ¶ 15; AHA Decl. ¶¶ 15, 17.

These resource-related injuries easily satisfy Article III. An organization "suffer[s] an injury in fact when a defendant's actions impede its efforts to carry out its mission"—and such an impediment can take the form of a "drain on [the organization's] resources." *Lane*, 703 F.3d at 674-675; *see also Havens Realty*, 455 U.S. at 378-379; *Centro de la Comunidad Hispana de*

Locust Valley v. Town of Oyster Bay, 868 F.3d 104, 111 (2d Cir. 2017) (resource diversion "has been repeatedly held to be independently sufficient to confer organizational standing"). The Guidance here has "frustrated [P]laintiff[s'] mission" to educate the public about the risks of new tobacco products, *Equal Rights Center v. Equity Residential*, 483 F. Supp. 2d 482, 486-487 (D. Md. 2007), and created "new obstacles" that "unquestionably make it more difficult for [them] to accomplish their primary mission" of combatting tobacco use, *League of Women Voters of United States v. Newby*, 838 F.3d 1, 9 (D.C. Cir. 2016).

b) Associational Standing

AAP independently has associational standing (as does its Maryland chapter) because (1) its pediatrician "'members would otherwise have standing to sue"; (2) "the interests it seeks to protect are germane to [AAP's] purpose"; and (3) nothing "requires the participation of individual members.'" *Lane*, 703 F.3d at 674 n.4. The second and third standards are easily met here: FDA's suspension of premarket review is "germane" to AAP's purpose of ensuring the health of American children, *see* AAP Decl. ¶ 5, and AAP's members are not needed to participate in this lawsuit.

AAP's members also have "standing to sue in their own right," *Hunt v. Washington State Apple Advertising Commission*, 432 U.S. 333, 343 (1977), and AAP thus has standing to sue on their behalf. It is well-established that interference with the practice of one's profession is injury in fact. *See Planned Parenthood of Idaho, Inc. v. Wasden*, 376 F.3d 908, 917 (9th Cir. 2004) (physician's "interests, both financial and professional, in practicing medicine" are protected by Article III); *Pennsylvania Psychiatric Soc. v. Green Spring Health Servs., Inc.*, 280 F.3d 278, 289 (3d Cir. 2002) (standing where defendants' alleged conduct "undermined [psychiatrists'] ability to provide quality health care"). FDA's decision not to implement premarket review for nearly 25,000 new tobacco products interferes with AAP members' practice of medicine.

First, by depriving pediatricians of health information that would otherwise be available and impeding AAP's ability to provide evidence-based recommendations for treating e-cigarette and cigar use, the Guidance undercuts pediatricians' ability effectively to counsel and treat patients. AAP member Dr. Levy attests that her practice has been made substantially more difficult by the proliferation of new tobacco products—notably e-cigarettes—and by FDA's failure faithfully to administer the Act. As Dr. Levy attests, "[n]early every child [she] treat[s] or assess[es] uses some form of e-cigarette product," Levy Decl. ¶ 8 (Ex. G), requiring her to conduct substantial additional research into new products on the market, "just to be able to perform her duties as a medical professional," *id.* ¶ 15. The information vacuum created by the Guidance means that Dr. Levy and others are reduced to searching publicly for data that is often unavailable. *See id.* ¶ 14; *see also* Camenga Decl. ¶ 12 (Ex. H) (same for AAP member Dr. Camenga). The lack of publicly available data about these tobacco products—data that would be available in the decision summaries released by FDA on approval of a new tobacco product, *see* CTFK Decl., Att. 1—has also interfered with AAP members' ability to conduct research on substance abuse and prevention. Camenga Decl. ¶¶ 19-21; *see* Levy Decl. ¶¶ 18-19.

Second, the Guidance harms AAP members by increasing the volume and complexity of patient needs they must confront. The number of patients who present respiratory ailments and symptoms of nicotine addiction, as well as comorbid addiction to multiple substances, has increased alongside the rise of e-cigarettes. Levy Decl. ¶ 7; Winickoff Decl. ¶¶ 6-7 (Ex. I). AAP member Dr. Winickoff explains that the rise of unapproved tobacco products—especially e-cigarettes—now requires him to spend "as much as a third of a visit" counseling patients on tobacco use—time that "either takes the place of time [he] can counsel [his] patients on other important health issues, such as exercise or STD protection, or lengthens [his] sessions so that

[he] can see fewer patients—with a corresponding effect on both [his] patients' health and [his] practice's income." *Id.* ¶ 10; *see also id.* ¶ 5 (proliferation of e-cigarettes has harmed patients and his "practice's income and expenses"); Levy Decl. ¶ 19 (similar with respect to research).

c) Individual Standing

Finally, Plaintiffs Dr. Brasch, Dr. Fishman, Dr. Goldstein, Dr. Hirsch, and Dr. Myles (collectively, "Pediatrician Plaintiffs") have standing. As explained above, interference with one's profession is a cognizable injury, and FDA's decision not to carry out premarket review has inhibited or undermined the Pediatrician Plaintiffs' practice in two ways.

First, the Guidance interferes with their ability to counsel and treat their patients by limiting information available to them about the myriad new tobacco products on the market. An increasing number of their patients use e-cigarettes and other new tobacco products. *See* Brasch Decl. ¶ 3 (Ex. J); Fishman Decl. ¶¶ 5-8 (Ex. K); Hirsch Decl. ¶¶ 5-7 (Ex. L); Myles Decl. ¶ 3 (Ex. M). But Pediatrician Plaintiffs lack the evidence-based empirical data and practical clinical aids they need to counsel patients effectively. *See* Brasch Decl. ¶¶ 4-5; Fishman Decl. ¶ 11; Hirsch Decl. ¶ 8; Myles Decl. ¶¶ 5-6. For example, many of Dr. Brasch's teenage patients tell her that they use "low-percentage nicotine" vaping liquid. Brasch Decl. ¶ 6. But because such manufacturers will not have to submit premarket review applications until 2022, there are no evidence-based resources that Dr. Brasch can consult about the actual content of such products, "limiting [her] ability to carry out [her] responsibility to [her patients] as their physician." *Id.*

Second, the Guidance increases the complexity of patient needs confronting Pediatrician Plaintiffs. Use of newly deemed tobacco products has soared in the last two to three years. *See* Brasch Decl. ¶ 3; Fishman Decl. ¶¶ 5-8; Hirsch Decl. ¶¶ 5-7. Today, Dr. Fishman attests, as many as one third of her adolescent patients reporting using or trying e-cigarettes. Fishman Decl. ¶ 8. That dramatic rise directly affects Pediatrician Plaintiffs' medical practices. As Dr.

Fishman explains, when she learns a patient is using e-cigarettes, she "need[s] to spend some of [her] limited time counseling them," which in turn "reduces the amount of time [she] can spend on other issues," including "health and safety issues such as diet or sexual activity." *Id.* ¶ 9. The number of unregulated and unapproved products on the market—directly attributable to FDA's suspension of premarket review—thus "significantly impedes [Dr. Fishman's] ability to assist [her] patients and improve their health outcomes." *Id.* ¶ 16; *see* Brasch Decl. ¶ 6; Hirsch Decl. ¶ 9; *see also* Brasch Decl. ¶ 7 (similar for plaintiff Dr. Goldstein). By making it more difficult for Pediatrician Plaintiffs to treat their patients, the Guidance gives rise to Article III standing.

2. FDA's Contrary Arguments Are Unpersuasive

FDA's objections to Plaintiffs' standing lack merit. *First*, FDA leans heavily on *Cigar Ass'n of America v. FDA*, 323 F.R.D. 54 (D.D.C. 2017), arguing that the court there rejected the same standing arguments Plaintiffs make here. *See* Opp. 14-15. Not so. *Cigar Association* was an across-the-board challenge to the Deeming Rule brought by cigar manufacturers that had nothing to do with the Guidance. *See* 323 F.R.D. at 58. By the time the district court addressed a motion to intervene by Organizational Plaintiffs in this case, the manufacturers had winnowed their legal challenges, focusing on a constitutional challenge to cigar warning-label requirements. *Id.* at 57. The question there was thus not whether Organizational Plaintiffs were injured by FDA's failure to perform premarket review, but whether they would be injured by invalidation of warning-label requirements. The district court made this very point, affirmatively citing *PETA* and distinguishing it on the ground that *PETA* involved an agency's allegedly unlawful failure to "collect information" that deprived an organization of "information it needed" to communicate with the public. *Id.* at 61. That was not the case in *Cigar Association*—because FDA's failure to conduct premarket review was not at issue—but, of course, it is here.

Even apart from that key difference, the factual proffers here materially differ in scope

and kind from those in *Cigar Association*. The court there found the declarations wanting because, in its view, they were too speculative as to what might happen "if the [Deeming] Rule is vacated." 323 F.R.D. at 62. Moreover, the declarations had been submitted before the manufacturers had narrowed their claims to focus on warning-label requirements, and the court found the declarations did not specifically tie the asserted harm to those narrow requirements. *Id.* at 63. Those concerns are absent here: The Guidance is now in effect; it has already suspended premarket review for nearly 25,000 tobacco products for years; and, as explained above, the Guidance is presently injuring Plaintiffs. In addition, the court in *Cigar Association* found that AAP had only "vague[ly]" described how pediatricians would be affected by the lack of cigar warning-labels, *id.* at 65, while the declarations here describe specifically and concretely how FDA's suspension of premarket review interferes with pediatricians' medical practices.

Second, FDA argues that Plaintiffs' injuries are "too speculative" because it is unknown whether the Guidance will cause manufacturers to "delay [the] submission of premarket review applications" and "continue to market" products covered by the Guidance. Opp. 16. That is a brazen claim. FDA has never questioned that the Guidance would cause manufacturers to delay applications; indeed, that was its purpose.[4] FDA "expect[ed] that manufacturers … [would] continue to market their products without FDA authorization" if it delayed the premarket review process, AR11,918, and that is the logic behind its assertion that manufacturers need "additional

[4] Publicly available evidence also suggests that the intended delay is precisely what has happened. *See* FDA, *Tobacco Product Marketing Orders* (no PMTA order issued since 2015); FDA, *Cumulative Number of Premarket Tobacco Product Applications (PMTA) Received Since Program Inception* (no "final actions" of any PMTA applications since June 2017). And the hyperbolic claims in the industry *amicus* brief that manufacturers may not be able to meet even the Guidance's deadlines should put to rest conjecture that the industry will hasten to act rather than take advantage of FDA's multi-year delay. *See* Dkt. 37-1 at 9 ("manufacturers will need all of the time granted [by the Guidance] … if not more").

time to develop higher quality, more complete applications." GAR412. FDA's newfound agnosticism as to whether industry will take advantage of the multi-year exemption from regulatory review announced by the Guidance thus cannot be taken seriously.

Third, FDA contends that, if manufacturers do delay the submission of applications, that will not put Plaintiffs "in a worse position than the one in which they have always been." Opp. 17. This confuses the relevant baseline for standing. Plaintiffs "need not show that the [agency action] rendered them worse off than the status quo ante. They may alternatively show that, had the [agency] taken the course of action that they claim the law required, they would have been better off." *Nat'l Envtl. Dev. Assoc.'s Clean Air Project v. EPA*, 752 F.3d 999, 1006 (D.C. Cir. 2014); *see also Animal Legal Def. Fund, Inc. v. Glickman*, 154 F.3d 426, 441 (D.C. Cir. 1998). Here, the question is not whether the Guidance impedes Plaintiffs' ability to carry out their mission relative to the pre-2017 status quo, but whether the Guidance impedes Plaintiffs' ability to do so relative to a world in which the Guidance had never been issued. As explained above, Plaintiffs have readily made that required showing of injury.

Finally, FDA argues Plaintiffs "cannot show" redressability because they do not seek to compel manufacturers to file applications or to force FDA to bring enforcement actions. Opp. 21. But FDA's implication that, were the Guidance vacated, *no* manufacturer of the nearly 25,000 products on the market would file an application is facially absurd. It also contradicts FDA's own statement (in the Deeming Rule litigation) that, even under the original compliance period, between "266 and 332 vaping devices, and between 900 and 1,800 e-liquids, will remain on the market at the end of the compliance period," Final Brief for Appellees 27, *Nicopure Labs, LLC v. FDA*, No. 17-5196 (D.C. Cir. June 5, 2018) (citing AR23,991), a finding that presupposes manufacturers will file applications. In all events, in the fanciful scenario FDA posits—in which

no manufacturer ever filed an application—Plaintiffs' informational injuries might not be redressed, but the many injuries caused by an unregulated marketplace would be.[5]

B. The Guidance Constitutes "Final Agency Action"

"The APA embraces a 'strong presumption in favor of judicial review of administrative action.'" *Doe v. Tenenbaum*, 900 F. Supp. 2d 572, 601 (D. Md. 2012), *rev'd on other grounds*, 749 F.3d 246 (4th Cir. 2014). While the APA limits review to "final agency action," 5 U.S.C. § 704, finality requires only that the action (1) "mark the 'consummation' of the agency's decisionmaking process" and (2) be "one by which 'rights or obligations have been determined,' or from which 'legal consequences will flow.'" *Bennett v. Spear*, 520 U.S. 154, 177-178 (1997). Both conditions of this "'pragmatic and flexible'" finality test, *Rhea Lana, Inc. v. Dep't of Labor*, 824 F.3d 1023, 1027 (D.C. Cir. 2016), are satisfied here.

First, as FDA does not seriously dispute, there is nothing "tentative" about the Guidance. *Bennett*, 520 U.S. at 178. Tentativeness would not allow, as the Guidance purports to do, manufacturers to "continue to market" newly deemed tobacco products for years to come without premarket review. GAR412. FDA points to boilerplate language that the Guidance represents the agency's "current thinking." Opp. 31. But that is true of every agency action. The "possibility" of future revision does not change the fact that the Guidance embodies FDA's "definitive decision" to exempt approximately 25,000 products from premarket review until 2021 or 2022, at the earliest. *U.S. Army Corps of Engineers v. Hawkes Co.*, 136 S. Ct. 1807, 1813-1814 (2016); *see Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1022 (D.C. Cir. 2000).

[5] At the very least, Plaintiffs have standing to challenge FDA's failure to comply with the APA's notice-and-comment procedures, given that the agency's failure has "impair[ed]" their "concrete interests" in combatting nicotine addiction. *Pye v. United States*, 269 F.3d 459, 467 (4th Cir. 2001); *see also WildEarth Guardians v. Jewell*, 738 F.3d 298, 306 (D.C. Cir. 2013).

FDA's across-the-board exemption, far from being "a 'moving target,'" thus represents "a 'final and binding determination.'" *Safari Club Int'l v. Jewell*, 842 F.3d 1280, 1289 (D.C. Cir. 2016); *see Real Truth About Abortion, Inc. v. FEC*, 681 F.3d 544, 555 n.4 (4th Cir. 2012).

Second, "[t]he definitive nature of [the compliance deadlines] also gives rise to 'direct and appreciable legal consequences.'" *Hawkes*, 136 S. Ct. at 1814.[6] As explained below, the purpose and effect of the Guidance are to create a legal exemption for manufacturers of nearly 25,000 tobacco products from substantive requirements under the Act. *See infra* pp. 17-22. Absent the Guidance, manufacturers could not lawfully market their products without a marketing order from FDA; under the Guidance, they can do just that. Indeed, absent the Guidance, tobacco manufacturers would have had to submit their premarket applications by this month and FDA would have begun reviewing those applications. The Guidance thus "has direct and appreciable legal consequences." *Bennett*, 520 U.S. at 178.

FDA's contention that the Guidance is nonetheless not final because it says it has no legally binding effect (Opp. 31) is meritless. Such "boilerplate" disclaimers, contained in "all [FDA] guidance documents," do not bar judicial review. *Appalachian Power*, 208 F.3d at 1023. The Supreme Court has "long taken" a flexible and "'pragmatic' approach … to finality." *Hawkes*, 136 S. Ct. at 1815; *see Abbott Labs. v. Gardner*, 387 U.S. 136, 149-151 (1967). What matters is "the effect" of the challenged action—not the agency's label or designation. *Hawkes*, 136 S. Ct. at 1814. In *Hawkes*, as here, the agency represented that the challenged action had

[6] As elsewhere explained, the Guidance is a binding substantive rule, *see* Br. 16-20; *infra* pp. 38-40, which necessarily satisfies *Bennett*'s second prong, *see Ctr. for Auto Safety v. NHTSA*, 452 F.3d 798, 806 (D.C. Cir. 2006). But this Court's review of final agency action is not limited to substantive rules. *Compare* 5 U.S.C. § 551(13) (defining "agency action") *with id.* § 553(b) (exempting certain rules from notice and comment, but not other APA requirements). Even were the Court to determine that notice and comment were not required, that would not preclude the Court from reaching Plaintiffs' other claims.

"no legally binding effect on [its] enforcement decisions." *Id*. at 1817 (Kennedy, J., concurring). But the Court rejected that *ipse dixit* as insufficient to bar judicial review. The dispositive fact here, as in *Hawkes*, is that FDA's bright-line compliance deadlines create a *de facto* "safe harbor"—"a 'legal consequence[]' satisfying the second *Bennett* prong." *Id*. at 1814.

None of the cases FDA cites (Opp. 31-32) is on point. The Guidance does not merely "reiterate[] a previously stated agency policy," *Ctr. for Auto Safety, Inc. v. NHTSA*, 342 F. Supp. 2d 1, 24 (D.D.C. 2004), or set forth an interpretation the agency has not yet "'relied upon,'" *Am. Tort Reform Ass'n v. OSHA*, 738 F.3d 387, 395 (D.C. Cir. 2013). To the contrary, the "clear-cut" compliance deadlines revise existing policy and, for all practical purposes, were treated as "effective immediately upon" FDA's issuance of the Guidance. *Abbott Labs.*, 387 U.S. at 152.

Relying on *Flue-Cured Tobacco Cooperative Stabilization Corp. v. EPA*, 313 F.3d 852, 859 (4th Cir. 2002), FDA argues that finality cannot be premised upon harm to Plaintiffs from "manufacturers postpon[ing]" filing "applications." Opp. 32. That confuses finality with "the separate question" of standing. *Bennett*, 520 U.S. at 177; *supra* pp. 2-14. "The second [*Bennett*] prong does not require that the agency action confer rights or obligations *on the plaintiff*." *Doe*, 900 F. Supp. 2d at 602 (emphasis added); *accord Clean Air Council v. Pruitt*, 862 F.3d 1, 6 (D.C. Cir. 2017) (stay of standard was final agency action subject to challenge by environmental organizations not regulated by stayed action); *Nat'l Ass'n of Home Builders v. U.S. Army Corps of Engineers*, 417 F.3d 1272, 1281 (D.C. Cir. 2005). Accepting FDA's argument would lead to the nonsensical result that agency action can be final for certain challengers but not others. In *Flue-Cured Tobacco*, the Fourth Circuit held that an agency report on the health hazards of secondhand tobacco smoke was nonfinal because it "carrie[d] no 'direct and appreciable legal consequences'" *for anyone*. 313 F.3d at 859. That is not the issue here. The Guidance creates

an exemption from and dates certain for compliance that neither the industry nor FDA is free to ignore. That is binding administrative action. *See Clean Air Council v. Pruitt*, 862 F.3d 1, 6-7 (D.C. Cir. 2017) (stay "suspend[ing] … compliance deadlines" is final agency action).

II. THE GUIDANCE IS *ULTRA VIRES*

A. The Guidance Violates The Tobacco Control Act

On the merits, the Guidance is patently unlawful. The Guidance nullifies the Act's premarket review provisions on an unqualified basis for at least a half-decade—despite the fact that Congress imposed mandatory premarket filing obligations on manufacturers and directed FDA to conduct premarket review, pairing those clear-cut obligations with express exceptions when it saw fit. *See* Br. 9-13. By revising that calibrated statutory scheme to satisfy FDA's own aims, and by allowing potentially dangerous and addictive tobacco products to remain on the market for years without public health review required by Congress, the Guidance constitutes paradigmatic "ultra vires" agency action. *City of Arlington v. FCC*, 569 U.S. 290, 297 (2013).

In response, FDA makes no serious effort to square the Guidance with the premarket review regime Congress actually established in the Act. Instead, it doubles down on its view that the Guidance is an exercise of unreviewable "enforcement discretion." That is manifestly wrong, as Plaintiffs have already explained, Br. 13-16, and explain further below, *see* Part II.B. But the statutory arguments FDA does make are equally unavailing.

FDA claims that it has "inherent discretion" under the Act, Opp. 4—discretion that, FDA believes, gives it *carte blanche* to decide when and under what circumstances to administer the Act's premarket review requirements. Nothing in the statute supports that position, and much condemns it. The "larger scheme" established by Congress in the Act—including text, structure, and purpose—*Graham Cty. Soil & Water Conservation Dist. v. U.S. ex rel. Wilson*, 559 U.S. 280, 289 (2010), evinces Congress's intent that premarket review is a mandatory and essential

feature of the Act. As Plaintiffs have explained, under the Act, manufacturers *must* submit applications containing important information about new products before placing those products on the market, 21 U.S.C. § 387j(a)(2), (c)(1)(A)(i), and FDA *must* issue either "an order that the new product may be introduced" or "an order that [it] may not be introduced" after submission, *id.* § 387j(c)(1)(A). When Congress wanted to create exceptions to those requirements, it did so expressly. *Id.*; 21 U.S.C. §§ 387j(a)(2)(B), 387e(j)(2); *id.* § 387j(g); *see Tennessee Valley Auth. v. Hill*, 437 U.S. 153, 188 (1978) (Congress's creation of express exemptions demonstrates intent that there be no other exemptions).[7] Read together and in light of the purposes of the Act, those interlocking statutory provisions impose synchronized duties on manufacturers *and* FDA—manufacturers must submit applications that FDA must review and act on—that are clearly meant to be accomplished before a new product is marketed to the public. That is why the statutory regime is called "[p]remarket review." 21 U.S.C. § 387j(a)(2).

Congress's statutory findings reinforce this point. Congress found that it is "essential" that manufacturers "demonstrate that [tobacco] products will meet a series of rigorous criteria" "prior to marketing such products." TCA § 2(36). Similarly, Congress determined that "[t]he only way to effectively protect the public health" is to ensure new products are "reviewed in advance of marketing." *Id.* § 2(43). FDA's assertion that it nonetheless retains "inherent discretion" (Opp. 4) to decline to apply premarket review provisions and to permit manufacturers to market potentially dangerous and addictive products, subject to *post*market review years down

[7] FDA does not base its "inherent discretion" theory on *Chevron* deference, nor does it invoke *Chevron* in response to Plaintiffs' statutory arguments. FDA has thus "forfeited any claims to *Chevron* deference." *Neustar, Inc. v. FCC*, 857 F.3d 886, 894 (D.C. Cir. 2017). If FDA means that "inherent discretion" exists outside of the Act, that ignores that an agency's authority derives only from Congress. *See La. Pub. Serv. Comm'n v. FCC*, 476 U.S. 355, 374 (1986).

the road, stands this statutory scheme on its head.[8]

Attempting to avoid the straightforward implications of statutory text and structure, FDA repeats the refrain that the Guidance supposedly does not affect *FDA's* obligations because, FDA says, the agency will perform premarket review of any applications filed in advance of the "compliance deadlines" and thus the only parties who might plausibly be disregarding the Act are "*manufacturers*, not the FDA." Opp. 27-28. This reasoning falls short for multiple reasons.

First, as explained above and in Plaintiffs' opening brief, the Act demonstrates that Congress intended a mandatory premarket review structure—not a regime in which FDA may pick and choose the circumstances in which manufacturers and FDA must comply with premarket review. Courts do not "interpret federal statutes to negate their own stated purposes." *N.Y. State Dep't of Soc. Servs. v. Dublino*, 413 U.S. 405, 419-420 (1973). But FDA's "inherent discretion" theory would do just that. Under FDA's view of "inherent discretion," FDA could announce, for example, that manufacturers of new tobacco products are no longer required to submit premarket applications for decades, in an effort to relieve FDA of its responsibility to review and act on those applications. It cannot be the law that FDA may evade *its* statutory duties by announcing to the world that regulated parties need not comply with their predicate obligation to file applications. That would unlawfully transform what Congress intended to be a *mandatory*, *pre*market review regime into a largely *volitional*, *post*market review structure

[8] FDA says that it "blinks reality" to describe the Guidance as "'a form of *postmarket* review'" because, it claims, there were 11,000 e-cigarettes on the market when the Deeming Rule took effect and, even under the original compliance policy, those products would have undergone postmarket review. Opp. 35. But the lawfulness (or not) of the Deeming Rule's policy is not at issue. The final agency action challenged here is the Guidance; any prior unlawful acts are no defense. *See Judulang v. Holder*, 565 U.S. 42, 60-61 (2011). FDA suggests that Plaintiffs have waived a legal objection to the Guidance, Opp. 35, but Plaintiffs cannot possibly be faulted for not filing comments objecting to the Guidance because FDA (unlawfully) issued the Guidance without notice and comment, depriving interested parties of just that opportunity.

bearing vanishing resemblance to the statute that Congress enacted.

Second, FDA implausibly asks that the Court turn a blind eye to facts that are obvious: The desired effect of the Guidance's multi-year extension of "compliance deadlines" is that rational manufacturers will not submit applications during that exemption period, and as a result, FDA will not review them. *See, e.g.*, AR11,918 (FDA "expect[s] that manufacturers … will continue to market their products without FDA authorization"). The Guidance thus relieves both manufacturers and FDA of statutory duties. In fact, publicly available information demonstrates that FDA has taken no action on any PMTA applications since issuing the Guidance, *see supra* p. 12 n. 4, and one of FDA's (ill-explained) rationales for the Guidance is that FDA does not have sufficient guidance in place to review such applications, Opp. 44-45. It strains credulity to deny that FDA has effectively shuttered premarket review for whole classes of tobacco products.

Third, even if the Act could be read to sanction the Guidance's circumvention of FDA's statutory duties, the Guidance would still be *ultra vires* because it grants a blanket license to manufacturers to keep new tobacco products on the market absent premarket review, in violation of federal law. *See* Br. 14-15. To its credit, FDA does not hide this purpose. FDA acknowledges that Congress created a *statutory* grace period; it observes that Congress created "no statutory grace period for products later deemed subject to the Act," Opp. 1; and it candidly admits that, through the Guidance, FDA "extend[ed] a similar grace period" to new tobacco products, *id.* at 4. FDA thus admits what is clear: The Guidance is not an exercise of enforcement discretion, but rather a blanket, preemptive authorization of industry non-compliance. It is thus an attempt to "establish with the force of law that []prohibited conduct"—marketing new products absent premarket review—"will not violate" federal law. *Util. Air Regulatory Grp. v. EPA*, 134 S. Ct. 2427, 2445 (2014) ("*UARG*"). Whether FDA can relieve

itself of its obligations, it cannot "alter[] the statutory requirements" for *manufacturers*. *Id.* at 2445. "The power of executing the laws … does not include a power to revise clear statutory terms that turn out not to work in practice," *id.* at 2446—yet that is exactly what FDA admits that it is doing in creating an extra-statutory "grace period."

FDA objects that the Guidance does not "create any exceptions to the substantive requirements of the statute," Opp. 34, but that position—which must come as some surprise to manufacturers who presumably believe they are not in outright violation of federal law—is not defensible. FDA acknowledges its exemptive purpose in establishing a "grace period," Opp. 4, designed to "give manufacturers time to come into compliance" with the Act, *id.* at 2, and that mimics the exemption created by Congress. By definition, this is an exception to substantive requirements. Moreover, the agency transparently justified the compliance policy on the ground that tobacco manufacturers will "continue to market their products" absent premarket review, AR11,918, thus sanctioning conduct that Congress deemed illegal.

FDA's preferred description of the Guidance as implementing a "compliance period" (Opp. 2, 6, 7, 8, 9, 11, 19, 27, 30, 35) reflects this understanding. Under the Guidance, manufacturers are *not* out of "compliance" with the Act in marketing new tobacco products without premarket review until August 2021 or 2022. Surely, for example, manufacturers availing themselves of the new grace period are not reporting to investors or other agencies that they are presently engaged in conduct brazenly violative of federal law. Instead, they assuredly view the Guidance as creating a *de facto* exemption—precisely as FDA intended. The Guidance is thus an "alteration of … statutory requirements" that exceeds an agency's authority—and the kind of action FDA "cannot[] defend … as an exercise of … enforcement discretion." *UARG*, 134 S. Ct. at 2445; *see* Zachary S. Price, *Enforcement Discretion and Executive Duty*, 67 Vand.

L. Rev. 671, 704 (2014) ("[E]xecutive officials lack inherent authority either to prospectively license statutory violations or to categorically suspend enforcement of statutes for policy reasons.").

FDA responds that *UARG* is distinguishable, Opp. 34, but the distinction it advances is threadbare. In *UARG*, EPA needed to "go beyond merely exercising its enforcement discretion" by creating an effective exemption from substantive requirements in order to avoid private citizen-suit enforcement. 134 S. Ct. at 2445. True, the Act here does not have a citizen-suit provision, Opp. 34, but that provision was relevant in *UARG* only because it showed that EPA had gone beyond non-enforcement. Here, as described above, there are multiple indicia that the Guidance, as in *UARG*, goes "beyond merely exercising enforcement discretion," and instead creates a prospective license for manufacturers to engage in conduct that Congress affirmatively prohibited. *See supra* pp. 20-22. It is that distinction—between agency non-enforcement and agency approval of unlawful conduct—that underlies *UARG*. *See* 134 S. Ct. at 2446 ("An agency … may change its own conduct, but it cannot change the law.").[9]

B. The Guidance Is Not Unreviewable "Enforcement Discretion"

With no basis in the Act to defend the Guidance, FDA labors mightily to show that this Court is powerless to remedy FDA's defiance of law under 5 U.S.C. § 701(a)(2), which bars judicial review of agency action "committed to agency discretion by law," and by *Heckler v. Chaney*, 470 U.S. 821 (1985), which interpreted that provision to preclude review of agency

[9] Any doubt about the proper interpretation of the Act would be resolved, under the canon of constitutional avoidance, against FDA's claimed authority to dispense with premarket review. *See* Br. 12-13. FDA responds that the Take Care Clause binds only the President, Opp. 35-36, but its own authority contradicts that assertion. *See Printz v. United States*, 521 U.S. 898, 922 (1997) (Clause applies to appointed "officers"). Nor does it matter whether the Clause provides a "cause of action" (Opp. 36) because the APA supplies one, 5 U.S.C. §§ 702, 706(2)(B).

decisions "not to take enforcement action," *id.* at 832. *See* Opp. 21-30. FDA is wrong.[10]

Section 701(a)(2) establishes a "narrow exception" to the APA's general presumption of reviewability, applicable only "in those rare instances where statutes are drawn in such broad terms that in a given case there is no law to apply." *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 410 (1971) (internal quotation marks omitted). "Congress rarely intends to prevent courts from enforcing its directives to federal agencies," *Mach Mining, LLC v. EEOC*, 135 S. Ct. 1645, 1651 (2015), and "each category of non-reviewability must be construed narrowly," *Amador Cty. v. Salazar*, 640 F.3d 373, 379 (D.C. Cir. 2011). Consistent with these principles, FDA's claim of nonreviewability fails for multiple reasons. *See* Br. 13-16.[11]

1. Congress Cabined Any FDA Discretion Under The Act

a. At the threshold, FDA's invocation of "enforcement discretion" is misplaced because the Act confines any discretion FDA would otherwise be presumed to have, for all the reasons explained above and in Plaintiffs' opening brief, *supra* Part II.A; Br. 9-13, 14. The

[10] FDA points to comments made by certain Plaintiffs on the Deeming Rule, *e.g.*, Opp. 2, to suggest that Plaintiffs blessed FDA's exercise of enforcement discretion here. That makes too much out of too little. What many of the Organizational Plaintiffs said is that FDA's proposed compliance approach would "permit deemed products" to be marketed that "would otherwise be illegal." AR145,604. Were FDA to take that step, those Plaintiffs insisted that the agency impose guardrails to help safeguard the public health, *id.*, restrictions FDA did not adopt. The notion that, in making that limited point, those Plaintiffs forever signed off on the legality of any enforcement discretion claim that FDA might conjure up is far-fetched. In any event, FDA identifies no legal import to the comments, and Plaintiffs are aware of none. There is certainly no estoppel or waiver given that Pediatrician Plaintiffs did not sign those comments and cannot now, years later, be barred from objecting to the Guidance as *ultra vires* based on past comments filed by other Plaintiffs addressing a separate agency action.

[11] Section 701(a)(2) is no bar to review of the notice-and-comment claim. "[W]hether an agency action required notice-and-comment rulemaking is a pure question of law," *Abington Mem'l Hosp. v. Burwell*, 216 F. Supp. 3d 110, 130 (D.D.C. 2016)—a question with obvious "law to apply." Nor does § 701(a)(2) preclude review of the arbitrary-and-capricious claim. The Act, Congress's purposes underlying it, as well as the Deeming Rule and its record, provide ample "law to apply." *E.g.*, *Robbins v. Reagan*, 780 F.2d 37, 45 (D.C. Cir. 1985); *Planned Parenthood of Wis., Inc. v. Azar*, No. 18-cv-1035, 2018 WL 3432718, at *5 (D.D.C. July 16, 2018).

gravamen of Plaintiffs' statutory claim is thus that there is "law to apply" that renders the Guidance *ultra vires*—namely, the text, structure, and purposes of the Act. *See Delta Air Lines, Inc. v. Exp.-Imp. Bank of the U.S.*, 718 F.3d 974, 977 (D.C. Cir. 2013).

Indeed, *Chaney* was clear that an agency cannot invoke enforcement discretion as authority to "disregard legislative direction in the statutory scheme that [it] administers," 470 U.S. at 833, and that a "pattern of nonenforcement of clear statutory language" is outside *Chaney*'s presumption, *id.* at 839 (Brennan, J., concurring). That should be the end of the matter here. The text, structure, and purposes of the Act reveal that Congress carefully considered the "[a]pplication" of premarket review to "post-February, 2007 products," and it carved out *one* exception with a defined scope, for products introduced after February 15, 2007 but before March 22, 2011, for which an SE report was filed. 21 U.S.C. §§ 387e(j)(2), 387j(a)(2)(B). Congress also delegated to FDA authority to exempt a *single* category of products—those "intended for investigational use"—from premarket review. *Id.* § 387j(g).

Given those express statutory exceptions carefully paired with mandatory obligations, were FDA to announce that through regulatory fiat it was expanding the exemption period beyond 21 months after June 22, 2009, or extending it beyond products for which a substantial equivalence report had been filed, or that it was enlarging § 387j(g) beyond products for investigational use, courts would not hesitate to set aside that action as *ultra vires*. *E.g.*, *Alabama Power Co. v. Costle*, 636 F.2d 323, 356 (D.C. Cir. 1979) (where agency acknowledged regulation was attempted "'expansion' of [a statutory] exemption," action "f[ell] well beyond the agency's [statutory] authority"); *see also NRDC v. EPA*, 755 F.3d 1010, 1019 (D.C. Cir. 2014) (similar). FDA cannot circumvent that outcome by invoking its "enforcement discretion" to accomplish the same alteration of unambiguous statutory requirements.

FDA's contrary position has no natural stopping point and would set a dangerous precedent for agency evasion of statutory requirements. Take an example: Imagine a statute declaring that imported fruit may be marketed only after agency review for public safety. Imagine the statute created exceptions for only two types of fruit: a one-year grace period (permitting marketing without agency review) for oranges, and a similar grace period of two years for apples. Under FDA's capacious notion of "enforcement discretion," the agency could effectively set a grace period of *three* years for apples, oranges, and *all* fruit—amending the statutory scheme in all but name. Were FDA's view correct, agencies would have virtual blank checks to pick and choose which statutory requirements had the force of law for significant periods. That would be an extraordinary power—one that would subvert the principle that agencies are bound by Congress, not vice versa. *Cf. Alexander v. Sandoval*, 532 U.S. 275, 291 (2001) ("Agencies may play the sorcerer's apprentice but not the sorcerer himself.").

b. In addition, the Guidance is reviewable because FDA has "'consciously and expressly adopted a general policy' that is so extreme as to amount to an abdication of its statutory responsibilities." *Chaney*, 470 U.S. at 833 n.4. The Guidance is unquestionably a "policy"—one adopted "consciously" (i.e., deliberately) and "expressly" (i.e., openly). FDA nonetheless maintains that no "abdication" has occurred because the Guidance is "limited in duration" (Opp. 27). But shuttering a mandatory statutory regime is no less an abdication simply because there is an endpoint, particularly when FDA's theory would allow it to extend that endpoint without apparent limit. And refusing to administer the premarket review regime for nearly 25,000 products for five years or more (longer than a presidential administration) is not "limited" under any natural use of that term. It is equally irrelevant whether the Guidance, per FDA's account, is "part and parcel of a broader regulatory plan" (Opp. 27): A desire to limit

nicotine in cigarettes (a laudable goal) neither justifies nor demands FDA puncturing a wide hole in a mandatory statutory regime for years on end.

FDA turns somersaults attempting to distinguish cases applying statutory abdication (Opp. 28-29), but those efforts fail. In *Adams v. Richardson*, the *en banc* D.C. Circuit held that a challenge to an agency's failure to enforce Title VI restrictions on funding to institutions practicing segregation was reviewable. 480 F.2d 1159 (D.C. Cir. 1973). The court stressed that the case was "not" a challenge to the agency's "decisions with regard to a few school districts," but, as here, a challenge to a "general policy" of nonenforcement. *Id.* at 1162. Although the statute did not specify when and how the agency must enforce the prohibition (as opposed to seeking voluntary compliance), the D.C. Circuit held that "[a] consistent failure" to enforce the statute was a "dereliction of duty reviewable in the courts." *Id.* at 1163. Just so here. Plaintiffs do not challenge FDA's decisions to bring this or that enforcement action, but FDA's across-the-board policy of failing to implement, administer, or enforce premarket review mandates.

FDA also claims that *NAACP v. Secretary of HUD*, 817 F.2d 149 (1st Cir. 1987) (Breyer, J.), is off-point because a statutory provision there embodied Congress's goal that the agency "administer" "programs and activities in a manner affirmatively to further the policies" of the statute. Opp. 28. That is no distinction at all. In enacting the Act, Congress specified in even stronger terms that "[i]t is essential that [FDA] review [tobacco] products sold or distributed" and that "[i]t is essential that manufacturers, prior to marketing such products, be required" to satisfy premarket review. TCA § 2(36). As in *NAACP*, this Court is surely capable of determining whether FDA's announced "pattern [and] practice" of nonenforcement is consistent with the agency's statutory duties and congressional purpose. 817 F.2d at 158-159.

In short, if FDA's refusal faithfully to administer a critical component of the Nation's

tobacco laws for more than 25,000 products for years is not an "abdication of … statutory responsibilities," *Chaney*, 470 U.S. at 833 n.4, it is difficult to understand what would be.[12]

2. *Chaney* Does Not Apply To A Categorical, Policy-Based Non-Enforcement Determination Such As The Guidance

Independently from those rationales, *Chaney* is inapposite because the Guidance is a categorical, policy-based determination—a functionally *legislative* judgment about how the statute ought to work—not a case-by-case enforcement decision—the traditional domain of *executive* authority. *Chaney* itself, and multiple appellate decisions FDA does not address, reflect this fundamental distinction. *See* Br. 15-16.

Chaney involved a challenge brought by capital inmates who believed that use of certain drugs in their executions was unlawful. *See* 470 U.S. at 823-24. Because the inmates had requested a judicial order requiring FDA to "take … enforcement actions" against drug manufacturers, *id.* at 837-38; *see id.* at 823-24, the Supreme Court held that their suit fell within § 701(a)(2) and was unreviewable. But § 701(a)(2) has no bearing "when an agency *does* act," *id.* at 832, because that action "provides a focus for judicial review" and "can be reviewed to determine whether the agency exceeded its statutory powers," *id.*—that is, whether the agency has "disregard[ed] legislative direction in the statutory scheme that [it] administers," *id.* at 833.

[12] None of the grab-bag of cases cited by FDA (Opp. 23-30) is to the contrary. All were decided before *UARG*, which limited agencies' use of "enforcement discretion" to rewrite statutory obligations. None involved a statutory structure like the one here, with mandatory synchronized obligations on industry and the agency and limited statutory exceptions to those mandates. And each concerned either a challenge to a discrete enforcement action, *see Ass'n of Irritated Residents v. EPA*, 494 F.3d 1027, 1029 (D.C. Cir. 2007) (challenge to settlement agreements); *Int'l Ctr. for Tech. Assessment v. Thompson*, 421 F. Supp. 2d 1, 6-8 (D.D.C. 2006) (challenge to agency's decision "not to take any enforcement actions with in connection with" specific product), or are otherwise inapposite, *see Jerome Stevens Pharm., Inc. v. FDA*, 402 F.3d 1249, 1257 (D.C. Cir. 2005) (plaintiff did "not dispute any of the district court's legal conclusions" with respect to statutory regime); *United States v. Sage Pharm., Inc.*, 210 F.3d 475, 480 (5th Cir. 2000) (plaintiff alleged enforcement action was "arbitrary and capricious").

This case is far afield from *Chaney*. As FDA itself concedes, "Plaintiffs do not ask the Court to … compel the FDA to take enforcement action against any manufacturer that fails to [submit applications]." Opp. 21. And, unlike in *Chaney*, Plaintiffs challenge an affirmative decision by FDA to suspend premarket review, a decision expressly set out in the Guidance—a document that, in *Chaney*'s words, "provides a focus for judicial review" and "can be reviewed to determine whether the agency" acted unlawfully. 470 U.S. at 832. Finally, the Guidance is not based on resource constraints, or a determination of which legal violations FDA intends to target—the indicia of enforcement discretion identified in *Chaney*. *See id.* at 831. The Guidance instead reflects programmatic considerations about how the statute ought to operate that are the hallmarks of legislative judgments for Congress. *See* Br. 15-16.

Multiple federal courts of appeals—none of which FDA acknowledges—have drawn these very distinctions from *Chaney*. Those courts have recognized that § 701(a)(2) bars suits seeking to compel agencies to take specific, discrete enforcement actions, but not challenges to an agency's categorical and express policy of nonenforcement. *See OSG Bulk Ships, Inc. v. United States*, 132 F.3d 808, 812 (D.C. Cir. 1998) ("agency's adoption of a general enforcement policy is subject to review"); *Kenney v. Glickman*, 96 F.3d 1118, 1123 (8th Cir. 1996) ("*Chaney* applies to individual, case-by-case determinations of when to enforce existing regulations rather than permanent policies or standards"); *Crowley Caribbean Transp., Inc. v. Pena*, 37 F.3d 671, 676 (D.C. Cir. 1994). This makes good sense: Unlike a "single-shot non-enforcement decision," an agency's global policy of non-enforcement is "[b]y definition … abstracted from the particular combinations of facts the agency would encounter in individual enforcement proceedings." *Crowley*, 37 F.3d at 676-77. Because the Guidance is plainly such a policy, it is beyond the scope of *Chaney*'s presumption of nonreviewability and it is "reviewable for legal

sufficiency" by this Court. *Id.* at 676.

FDA has no good answer. It claims that the Guidance is not "categorical" because it does not suspend other statutory provisions or apply to new products that enter the market after August 2016. Opp. 29. Those are not serious distinctions. The Guidance exempts—on an unqualified, across-the-board basis—as many as 25,000 new tobacco products (including e-cigarettes and cigars) from a central mandate of the Act. That is precisely the type of universal annulment, as opposed to case-by-case decision, to which *Chaney* has no defensible application.

FDA's fallback position that *Chaney*, too, involved a categorical policy does not make sense. As discussed above, *Chaney* involved inmate demands for discrete FDA enforcement actions against identified individuals and entities. *See Chaney v. Heckler*, 718 F.2d 1174, 1177-1178 (D.C. Cir. 1983) (describing citizen petition submitted by inmates), *rev'd*, 470 U.S. 821 (1985). Moreover, the inmates in *Chaney* did not seek review of an express policy of non-enforcement, because FDA had not issued one. Saying that *Chaney* involved a categorical policy would thus erase the line between global nonenforcement policies and "single-shot non-enforcement decisions" that multiple courts have recognized. *Crowley*, 37 F.3d at 676.

3. *Chaney* Does Not Apply Because Affirmative Authorization Of Illegal Industry Conduct Is Not "Enforcement Discretion"

Finally, *Chaney* is independently not controlling because its presumption does not attach to an agency's "affirmative act of approval," *Chaney*, 470 U.S. at 831, or to its determination that "otherwise-prohibited conduct" by regulated entities "will not violate [a statute]." *UARG*, 134 S. Ct. at 2445; Br. 14-15. That is dispositive here. As explained fully above, in design and effect, the Guidance establishes an across-the-board license for manufacturers to market e-cigarettes and cigars without premarket review, thus establishing an agency-created exemption

that goes well beyond the statutory exemption in the Act.

Preemptively permitting regulated entities to engage in unlawful conduct—as the Guidance does—is not "enforcement discretion," no matter how many times FDA invokes that label. Were it otherwise, agencies could shirk all manner of statutory duties and effectively rewrite comprehensive and carefully structured statutory schemes at will. FDA fails to confront the fundamental point that the Guidance "cannot" be "defend[ed] … as an exercise of … enforcement discretion" because it "purports to alter [Tobacco Control Act] requirements" and to pronounce that "otherwise-prohibited conduct" "will not violate the [Act]." *UARG*, 134 S. Ct. at 2445; *cf. Texas v. United States*, 787 F.3d 733, 757 (5th Cir. 2015) ("[d]eclining to prosecute does not convert an act deemed unlawful by Congress into a lawful one").

III. THE GUIDANCE IS ARBITRARY AND CAPRICIOUS

The Guidance must also be vacated as arbitrary and capricious because (i) FDA provided no reasoned, rational justification for abruptly departing from its prior compliance policy and (ii) FDA wholly failed to account for the predictable, and devasting, public health consequences that would follow establishing a multi-year exemption from premarket review regime for nearly 25,000 new tobacco products. *See* Br. 21-25. FDA's contrary arguments are unpersuasive.

A. FDA Failed To Reasonably Justify The Guidance

The APA demands that an "agency must give adequate reasons for its decisions." *Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2125 (2016). To satisfy this requirement, "conclusory statements will not do; an 'agency's statement must be one of reasoning.'" *Amerijet Int'l, Inc. v. Pistole*, 753 F.3d 1343, 1350 (D.C. Cir. 2014). "[T]o accept an agency's blanket conclusions at face-value" where it has failed to explain "'facts found'" and the "rational connection" between those facts and the agency's decision would "abdicate [the judicial] role." *Sierra Club v. U.S. Dep't of Interior*, No. 18-1082, 2018 WL 3717067, at *24 (4th Cir. Aug. 6,

2018). And while an agency may change course, "it must provide 'a reasoned explanation … for disregarding facts and circumstances that underlay or were engendered by the prior policy.'" *Air All. Houston v. EPA*, No. 17-1155, 2018 WL 4000490, at *12 (D.C. Cir. Aug. 17, 2018).

This case well implicates those principles. In the face of a massive administrative record underlying the Deeming Rule and despite prior findings driving FDA's determinations that a much more limited compliance period would best balance competing objectives, FDA abruptly changed course and effected a substantial change in the regulation of nearly 25,000 new tobacco products. In laboring to explain and justify this change, FDA relies on an agency "press release," and accompanying speech. Opp. 44-45. From those limited materials, FDA's lawyers glean three purported justifications for suspending premarket review: (1) to promote "innovation"; (2) so that FDA may develop "product standards"; and (3) to give industry more time to submit applications (and, relatedly, for FDA to issue new guidance). *Id.* If one of those rationales is arbitrary and capricious, that would demand vacatur. *See Nat'l Fuel Gas Supply Corp. v. FERC*, 468 F.3d 831 (D.C. Cir. 2006). Here, *all* of the justifications fail.

1. FDA's "Innovation" Justification Is Unfounded

FDA's lead justification for the Guidance is a need to promote "innovation." Opp. 10, 11, 45, 48. That rationale is arbitrary and capricious for multiple reasons. *First*, the record is devoid of any reasoned explanation, much less findings, by FDA as to how or why applying premarket review to new tobacco products as Congress intended, particularly under the original compliance policy, would dampen innovation or why innovation outweighs other public health objectives. FDA's "conclusory," vague, and unexplained "statements" regarding innovation are wholly insufficient, *Pistole*, 753 F.3d at 1350, as courts do not "simply accept whatever conclusion an agency proffers merely because the conclusion reflects the agency's judgment," *Tripoli Rocketry Ass'n, Inc. v. ATF*, 437 F.3d 75, 77 (D.C. Cir. 2006).

Second, FDA's failure is particularly glaring given that its innovation claim directly contradicts prior findings. FDA previously explained that the balance struck by the Deeming Rule and the original compliance policy "will not stifle innovation but could, instead, encourage it." AR11,915-16. It further found that premarket review "will incentivize development of tobacco products that pose less risk to human health by limiting market access by riskier competitor products." *Id.*; *see* AR11,952 (similar). FDA made those determinations on the basis of a robust record, informed by comments developed over a multi-year rulemaking. By contrast, the Guidance and the press release—issued without any apparent fact-finding and absent notice and comment—pretend those findings do not exist, defying the cardinal principle that "[a]n agency cannot simply disregard contrary or inconvenient factual determinations that it made in the past." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 537 (2009) (Kennedy, J., concurring); *see Air All. Houston*, 2018 WL 4000490, at *12-13 (similar).

Third, FDA's innovation theory is internally incoherent, and the "unexplained inconsistencies" render the Guidance arbitrary and capricious. *Dist. Hosp. Partners, LP v. Burwell*, 786 F.3d 46, 59 (D.C. Cir. 2015) (collecting authority). The Guidance creates an extended exemption from premarket review for nearly 25,000 products on the market as of August 2016; according to FDA, no exemption exists for any new tobacco product placed on the market after that date. FDA's innovation argument assumes (contrary to its prior conclusions) that premarket review discourages innovation in new, reduced risk products; yet the Guidance applies only to products already on the market and preserves premarket review for products not yet introduced. Accepting FDA's own reasoning, the Guidance thus *creates* massive incentives not to innovate. That unexplained disconnect between the agency's proffered rationale and the Guidance renders FDA's action arbitrary and capricious.

Finally, "innovation" cannot possibly justify the Guidance's application to cigars. FDA speaks of the need to encourage "innovations" in products that "generally do not produce the smoke delivered by combustible tobacco products," Opp. 10, and the Guidance and FDA's comprehensive policy are based on the premise that "combustible forms of tobacco" cause significant "harm." GAR406. Cigars, however, are *combustible*. Thus, by its own terms, FDA's rationale for its multi-year suspension of premarket review could not possibly apply to cigars and other combustible products. Why, then, are cigars given an across-the-board exemption? FDA offers no explanation, and none is apparent, as to how its desire to reduce the use of combustible tobacco justifies *loosening* regulation of combustible tobacco. Nor does the record show any ongoing or potential "innovation" in cigars that could possibly advance the public health objectives of the Act or justify a multi-year exemption for the entire cigar industry.

2. FDA's "Products Standard" Justification Is Unfounded

FDA's position that the Guidance is justified by FDA's desire eventually to develop product standards is similarly arbitrary. *See* Opp. 10, 30, 44, 47. *First*, FDA's authority to develop "product standards" is a separate, *discretionary*, authority (21 U.S.C. § 387g) from FDA's *mandatory* premarket review responsibilities (21 U.S.C. § 387j). That authority is neither dependent upon premarket review, nor does it require that product standards precede premarket view. Neither the Guidance nor the press release explains why it is sensible to delay a mandatory requirement—which Congress viewed as essential to public health protection—for half a decade or more so that the agency may develop discretionary standards addressing things like "'batter[ies]'" and "'liquid nicotine'" for e-cigarettes. Opp. 10 (quoting GAR412). Those standards may be important, but promulgating them does not require rendering premarket review a dead letter. In fact, conducting such review would help inform product standards by allowing FDA to learn about new tobacco products. *See* AR11,909 ("information provided as part of

premarket review … will provide critical information on these [new tobacco] products").

Second, like the innovation justification, FDA's product standards claim is irrationally inconsistent with the design of the Guidance. FDA has set forth no explanation—much less a reasoned one—for its inconsistent determination that the approximately 25,000 new products on the market as of August 2016 should be exempt from premarket review because of a desire to develop product standards, while at the same, products marketed after August 2016 should undergo review, absent those product standards. That "unexplained inconsistenc[y]" is fatal to the Guidance. *District Hosp. Partners*, 786 F.3d at 59.

Third, in promulgating the Deeming Rule, FDA considered and rejected proposals to delay premarket review or other Act authorities until it issued product standards. AR11,911. FDA found that "[it] would not protect the public health to forego implementation [of the TCA] until FDA can issue final product standards and tobacco product manufacturing practice regulations." *Id*. FDA, of course, may change its mind, but it must acknowledge that change and provide a non-conclusory, reasoned explanation for it. It did neither here.

3. FDA's "Additional Time for Industry" Justification Is Unfounded

Finally, in yet another unsupported reversal, FDA claims that the Guidance is "designed to build in time for the FDA 'to issue regulations outlining what information the agency expects to be included in [p]remarket applications,'" Opp. 30, and "give manufacturers time to come into compliance," *id.* at 2. These related rationales are unavailing.

First, FDA issued its first guidance on PMTA applications in September 2011—almost seven years ago. *See* FDA, *Guidance for Industry: Applications for Premarket Review of New Tobacco Products* (Sept. 2011). And when FDA promulgated the Deeming Rule, it issued another guidance document on the same topic, focused on e-cigarettes. *See* AR28,350. In neither the Guidance at issue here nor the press release has FDA provided any reasoned

explanation as to why this prior agency guidance is deficient or incomplete.

Second, FDA's assertion that tobacco manufacturers need "additional time" to come into compliance is wholly unsubstantiated. GAR412. In crafting the original compliance period, FDA time and again rejected industry objections—recycled in the industry *amicus* brief here—that more time was needed. *See* Br. 23-24. To start, FDA found that "manufacturers … ha[d] been on notice for more than 4 years," since 2011, "that these products could and likely would be regulated." AR11,901. Moreover, based on a robust record, FDA explained that the original period "takes into account the time for firms to generate and submit the information for a PMTA," AR11,909; FDA found the original policy (with much shorter deadlines) would give "sufficient time" for "high quality applications," AR11,920; and FDA rejected a 5-year compliance period similar to the Guidance, *id.* In addition, in Deeming Rule litigation, FDA has stated in no uncertain terms that "self-serving predictions," such as those made by industry *amici* here, "that [industry] will be unable to meet the August 2018 compliance date should be rejected." Reply in Support of Defs.' Cross-Mot. for Summ. J. 12, *Nicopure Labs, LLC v. FDA*, No. 16-cv-878 (D.D.C. Sept. 9, 2016), ECF No. 48; *see id.* at 12-13.

In changing course, FDA failed to provide a reasoned explanation as to why what the agency had found before was wrong and did not even attempt to identify any new facts or offer a different reading of prior facts that would justify its abrupt shift in regulation. The D.C. Circuit recently rejected an analogous agency action for very similar reasons, *see Air All. Houston*, 2018 WL 4000490, at *12-13, and this Court should do the same.

B. FDA Failed To Justify The Public Health Consequences Of The Guidance

Independently, the Guidance is arbitrary and capricious because FDA failed to account for the foreseeable and devastating costs to public health that would arise from the Guidance's suspension of premarket review. As demonstrated in Plaintiffs' opening brief and by a legion of

public health organizations as *amici*, the Guidance has enabled and amplified a fast-developing public health crisis with respect to e-cigarettes and cigars, especially among the Nation's youth. *See* Dkt. 34-1. But nothing in the administrative record demonstrates whether or how FDA took account of those serious "disadvantages." *Michigan v. EPA*, 135 S. Ct. 2699, 2707 (2015).

FDA asserts that it "considered the potential public health effects" of the Guidance, Opp. 48, but it points to nothing other than a sentence in a speech to support that assertion—no internal qualitative or quantitative analysis; no memoranda weighing advantages and disadvantages; and no factual findings. Based on that speech, FDA claims that the Guidance's health benefits flow from "delaying the immediate market exit of innovative, potentially less harmful tobacco products." *Id.* (citing GAR405-410). That explanation—the apparent sum-total of FDA's weighing of health effects—is inadequate. To begin with, it could not possibly justify suspending premarket review for cigars until 2021 because, as FDA found in the Deeming Rule—and has consistently asserted in litigation defending that Rule, *see* Defs.' Cross-Mot. for Partial Summ. J. 9-11, *Cigar Ass'n of America v. FDA*, No. 16-cv-1460 (D.D.C. Oct. 24, 2017), ECF No. 74—all cigars present health risks because they involve combustion. Equally significant, FDA assumes that manufacturers lacked sufficient time under the Deeming Rule's compliance policy to file applications, a position that directly contradicts FDA's prior findings and its litigation positions, as explained above. Finally, FDA's fear of "market exit" irrationally ignores the other side of the public health ledger—namely, the "substantial" public health benefits that premarket review would entail that FDA itself previously described. AR11,911.

Nothing in the Guidance or the administrative record demonstrates whether and how FDA "face[d] the trade-off[s]" between industry conjecture about market exit, on the one hand, and the concrete benefits of premarket review, on the other. *Competitive Enter. Inst. v. NHTSA*,

956 F.2d 321, 323-324 (D.C. Cir. 1992). FDA's failure to account for these public health consequences is especially indefensible given Congress's repeated findings about the public interest in preventing new generations of the Nation's youth from becoming addicted to nicotine. *E.g.*, TCA §§ 2(1), 2(15), 2(20), 2(21), 2(24), 3(2). Youth tobacco usage was thus an "important aspect of the problem" FDA was obligated to consider and account for before issuing the Guidance. *United Solid Waste Activities Group v. EPA*, No. 15-1219, 2018 WL 4000476, at *9 (D.C. Cir. Aug. 21, 2018) (per curiam). But in its rush to suspend premarket review, FDA wholly failed to account for those devastating public health consequences.

IV. THE GUIDANCE WAS PROMULGATED WITHOUT REQUIRED NOTICE AND COMMENT

Finally, even if FDA had unfettered authority to recalibrate the Act in the manner accomplished by the Guidance (it does not), that type of substantive, significant agency action must comply with APA's notice-and-comment requirements. Likewise, in issuing the Guidance, FDA sharply departed from the Deeming Rule's compliance policy—which itself was a product of notice-and-comment rulemaking—without providing for meaningful public input. Br. 16-20. FDA's deliberate failure to "expose" the Guidance "'to the test of prior examination and comment,'" *National Helium Corp. v. Federal Energy Admin.*, 569 F.2d 1137, 1146 (Temp. Emer. Ct. App. 1977), resulted in agency action that, substantively, is ill-advised, arbitrary and capricious, and has already had disastrous consequences for public health, as explained in Part III, above. But FDA's failure to abide by APA notice-and-comment requirements—a procedural question this Court reviews with no deference to the agency's views, *Chocolate Mfrs. Ass'n of U.S. v. Block*, 755 F.2d 1098, 1103 (4th Cir. 1985)—itself requires vacatur of the Guidance.

In response, FDA has one argument. FDA claims that the Guidance is a "statement of policy" exempt from notice and comment. Opp. 37. This "claim of exemption from APA rulemaking requirements"—which courts "'narrowly construe[] and only reluctantly

countenance[]'"—cannot withstand scrutiny. *Envtl. Def. Fund, Inc. v. Gorsuch*, 713 F.2d 802, 816 (D.C. Cir. 1983). Judicial scrutiny is particularly "exacting" where, as here, FDA seeks "to 'undo'" the prior compliance policy it promulgated in the Deeming Rule "'without giving all parties an opportunity to comment on the wisdom of repeal.'" *Id*. at 816-817.

To qualify as an exempt policy statement, the Guidance would have to (1) operate only prospectively to inform future agency decisionmaking—while having no "present effect"—and (2) "genuinely leave[] the agency and its decision-makers free to exercise discretion." *Am. Bus Ass'n v. United States*, 627 F.2d 525, 529 (D.C. Cir. 1980). The Guidance does neither: First, like the challenged pronouncement in *American Bus*, the Guidance took effect upon publication "without further action by" FDA, and as a result, "restrictions previously imposed … have been lifted." *Id*. at 531. The Guidance thus "does not … operate only prospectively," but "is 'finally determinative'" of the immediately applicable deadlines for regulatory compliance. *Id*. Second, the Guidance does not "'contemplate that" FDA officials "will exercise an informed discretion in the various cases that arise.'" *Id.* at 530. Leaving case-by-case discretion to agency officials would in fact negate the Guidance's purpose—which is to draw a clear line permitting non-compliant activity before the deadline, but not after. Here, as in *American Bus*, because the statutory obligations of premarket review are themselves "legally enforceable," FDA cannot avoid notice-and-comment rulemaking by "us[ing] a policy statement to release" the industry from complying with those obligations. *Id*. at 533.

FDA's contrary argument depends almost entirely on unjustified formalism. But courts "look … at the actual function and effect of the rule," not the agency's labels or its recitation of disclaimers. *Associated Dry Goods Corp. v. EEOC*, 720 F.2d 804, 809 (4th Cir. 1983); *see* Br. 18. As to practical effect, FDA does not deny that the Guidance accomplishes a multi-year delay

of statutory and regulatory compliance, and the agency admits that "[s]uspending a *rule's* effective date" would require notice and comment because it "alters the underlying legal norm." Opp. 41. Yet the Guidance does the same thing in effect, if not name, by delaying so-called "compliance dates" for statutory premarket review, GAR425, establishing an atextual statutory exemption, as explained above, *see supra* pp. 20-22. Moreover, FDA identifies no meaningful distinction between delaying the effective date of a rule—which it agrees is substantive regulation—and delaying the compliance date for a statutory provision—which it insists is not.

FDA's related assertion that the Guidance is "neither categorical, nor an exemption" (Opp. 39) is also unconvincing, again for reasons already explained. *See supra* p. 29. By its terms, the Guidance "applies to all categories of newly regulated products that were on the market on August 8, 2016," GAR424, without qualification. That is explicitly categorical. And the Guidance "exten[ds]," "revises," and "supersed[es]" the previously extended compliance periods in the Deeming Rule, GAR424-425—during which the agency, in its own words, "expect[s] that manufacturers … will continue to market their products without FDA authorization," AR11,918. That is nothing if not an exemption.

None of the cases FDA cites (Opp. 39-40) involved agency actions of this type. To the contrary, in each, "the agency [was] 'genuinely le[ft] … free to exercise discretion.'" *Clarian Health W., LLC v. Hargan*, 878 F.3d 346, 357-358 (D.C. Cir. 2017) (instructions described "criteria" for "enforcement priorities," but agency "expressly retained discretion to deviate"); *Prof'ls & Patients for Customized Care v. Shalala*, 56 F.3d 592, 598 (5th Cir. 1995) ("none of the nine factors listed … establish 'fixed criteria to control the agency's decisions'"); *Brock v. Cathedral Bluffs Shale Oil Co.*, 796 F.2d 533, 538 (D.C. Cir. 1986) (agency "retained [its] discretion"); *Int'l Union, UAW v. Brock*, 783 F.2d 237, 251 n.18 (D.C. Cir. 1986) (memorandum

simply advised on "enforcement priorities"); *Ctr. for Auto Safety*, 342 F. Supp. 2d at 18 (agency was left with "case-by-case basis" discretion).[13]

In contrast, the Guidance—while purporting to set "compliance date[s] … as a matter of enforcement discretion," GAR425—does not suggest that FDA will continue to enforce premarket review on a case-by-case basis. Quite the opposite: The Guidance functions as an on-off switch that "release[s]" manufacturers from compliance in the interim. *Am. Bus*, 627 F.2d at 533. As Plaintiffs have explained, and FDA does not rebut, such a years-long deferral and wholesale revision of the compliance policy in the Deeming Rule is indistinguishable from revisions to "effective dates" long held to be substantive. *See* Br. 18-19. In both cases, setting and altering those dates operates with "the rigor of a rule, not the pliancy of a policy." *McLouth Steel Prods. Corp. v. Thomas*, 838 F.2d 1317, 1320-1321 (D.C. Cir. 1988).

CONCLUSION

The Court should vacate the Guidance and award appropriate equitable relief.[14]

[13] FDA's cited cases involving rescission of DACA are similarly inapposite. Those cases relied in part on the fact that DACA itself was announced without notice and comment in concluding that its rescission was exempt from notice and comment. *See NAACP v. Trump*, 298 F. Supp. 3d 209, 237 (D.D.C. 2018); *Casa De Maryland v. DHS*, 284 F. Supp. 3d 758, 772 (D. Md. 2018). But the Guidance repeals a compliance policy that FDA concedes (Opp. 42) was the result of notice and comment alongside the Deeming Rule.

[14] Industry *amici* assert vacatur will prompt "*en masse*" market exit. Dkt. 37-1 at 3. Although vacatur is the baseline APA remedy, this Court may "tailor its remedy to the occasion," *NAACP*, 817 F.2d at 160-161, and Plaintiffs expressly seek equitable relief. Plaintiffs thus respectfully suggest that, if the Court determines that the Guidance is unlawful, it may invite remedial briefing, asking FDA within 14 days of the Court's decision to submit a proposed remedy, with corresponding time for Plaintiffs to brief whether that remedy sufficiently redresses the legal violations found by the Court and Plaintiffs' injuries.

Dated: August 28, 2018

Respectfully submitted,

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF MATTHEW L. MYERS

I, Matthew L. Myers, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am the President of the Campaign for Tobacco-Free Kids ("Tobacco-Free Kids.")

3. Tobacco-Free Kids is a tax exempt non-profit corporation under section 501(c)(3) of the Internal Revenue Code, organized under the laws of the District of Columbia. Its principal place of business is 1400 I Street, NW, Suite 1200, Washington, D.C. 20005.

4. Tobacco-Free Kids works to reduce tobacco use and its deadly toll in the United States and around the world. It engages in public education about the dangers of cigarettes, cigars, e-cigarettes, and other tobacco products, including sponsoring activities to prevent kids from using tobacco products, help users quit, and protect everyone from secondhand smoke. It also researches and advocates public policies that reduce kids' exposure to the dangers of tobacco products.

5. Through its youth initiatives, Tobacco-Free Kids sponsors youth activities to educate young people about the dangers of tobacco use, including use of e-cigarettes, and engage them in activities designed to discourage youth from initiating use of tobacco products and encourage young users of tobacco products to quit. For example, Tobacco-Free Kids sponsors Kick Butts Day, a national day of activities that engage youth to speak up against the dangers of tobacco use, generating more than 1,000 events across the United States. The youth participants plan and conduct events that focus attention on the deadly dangers of tobacco use, including e-cigarette and cigar use, and urge their peers to be tobacco-free.

6. Tobacco-Free Kids also participates in the FDA regulatory process on tobacco products by communicating to FDA, both informally and through formal comments, its ideas for the agency to make the most effective use of FDA's regulatory authority over tobacco products to serve public health. For example, Tobacco-Free Kids participated extensively in the development and promulgation of the deeming rule that is the subject of this litigation. From the time FDA announced that it was planning to issue a deeming rule to cover other tobacco products, including e-cigarettes, Tobacco-Free Kids urged FDA to issue the rule and to ensure that it made all tobacco products subject to FDA jurisdiction. Prior to the issuance of the deeming rule, Tobacco-Free Kids corresponded with FDA, participated in FDA working groups and other public sessions, and met with FDA personnel to urge them to issue the deeming rule. Tobacco-Free Kids wrote to President Obama on September 19, 2013 and again on April 1, 2014, urging the issuance of the deeming rule.

7. On August 8, 2014, Tobacco-Free Kids, in coalition with other public health organizations, submitted extensive comments to FDA on the proposed deeming rule and also submitted separate comments in the same docket. In addition, after FDA promulgated the

proposed deeming rule in April 2014, Tobacco-Free Kids met with the staff of the Office of Information and Regulatory Affairs of the Office of Management and Budget ("OIRA") to urge OIRA to act promptly to ensure that the rule would be issued and without weakening revisions.

8. Tobacco-Free Kids also has filed formal comments on various Draft Guidances FDA has issued concerning premarket review of tobacco products, including the Draft Guidance for Industry on Applications for Premarket Review of New Tobacco Products, issued September 2011 (comments joined by plaintiffs American Cancer Society Cancer Action Network, American Heart Association, American Lung Association and Truth Initiative (then known as Legacy)) and the Draft Guidance for Industry issued May 2016 on Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (comments joined by plaintiffs American Heart Association and American Lung Association).

9. As structured by Congress, the Tobacco Control Act's premarket review process requires manufacturers to submit substantial information and data about newly deemed products to FDA. After reviewing a premarket tobacco application, FDA must issue an order approving or denying the application and setting forth the basis for its determination. FDA's decision, including a summary of its findings, must then be made publicly available. These orders necessarily provide a wealth of scientific and other data and information about newly deemed products, information generally not available through other means. Tobacco-Free Kids has reviewed and used this information to urge FDA to adopt tobacco product standards and to advise the public about the health risks (or benefits) associated with the use of particular products. FDA's suspension of premarket review of thousands of newly-deemed products on the market as of August 8, 2016 deprives Tobacco-Free Kids and the other plaintiffs of this unique information and materially and adversely affects Tobacco-Free Kids' ability to educate the

public about specific tobacco products and to use that information to urge FDA to adopt regulatory policies that will enhance the agency's use of its regulatory authority to serve public health.

10. For example, Tobacco-Free Kids and other plaintiffs in this action have used information disclosed by FDA as a result of the premarket review process to urge FDA to adopt a product standard to reduce the toxicity of smokeless tobacco products. In November 2015, FDA authorized the marketing of eight Swedish snus smokeless tobacco products by Swedish Match North America, Inc. As part of that authorization, FDA issued a Decision Summary explaining its assessment of the products. (A true and accurate copy of the Decision Summary is attached to this Declaration as Attachment 1.) This was the first PMTA issued by FDA and Mitch Zeller, Director of FDA's Center for Tobacco Products observed, in an accompanying agency press release, that the order "demonstrates that the premarket tobacco application process is a viable pathway under which products can be marketed as long as the public health can be protected."

11. The Swedish Match premarket review order disclosed a wealth of information that aids Tobacco-Free Kids in understanding and educating about the risks of tobacco products and the relative risk among products. For example, it explained how standards in Swedish Match's manufacturing process help ensure lower levels of certain carcinogens; the relative disease risk of Swedish snus vs. cigarettes and other forms of smokeless tobacco; and the contribution of various harmful and potentially harmful constituents to disease risk.

12. Most importantly, in the course of reviewing the Swedish snus products, FDA found, and disclosed for the first time to the public, the specific reduction in cancer risk if users of other kinds of smokeless products were to switch entirely to products with a lower level of N-

Nitrosonornicotine ("NNN"), a carcinogen in smokeless products that is found at a lower level in the Swedish snus.

13. Tobacco-Free Kids and co-plaintiff Truth Initiative used this and other previously unavailable information revealed by the premarket review decision to urge FDA to develop and issue a product standard that would limit the carcinogen NNN in all smokeless tobacco products to the level in Swedish snus. On February 3, 2016, Tobacco-Free Kids and Truth Initiative prosed the product standard to FDA in a letter explaining that the premarket review order established (1) that reduction in the level of NNN in smokeless tobacco products would substantially reduce the risk of cancer to users of smokeless tobacco products; and (2) it is feasible to produce smokeless tobacco products that would substantially reduce this risk because Swedish Match had done so. On January 23, 2017, FDA published a proposed rule much like the one we urged, proposing to set a tobacco product standard for NNN in smokeless tobacco products, 82 Fed. Reg. 8004 (January 23, 2017).

14. Once again using the disclosures in the Swedish Match PMTA order, Tobacco-Free Kids, joined by co-plaintiffs American Academy of Pediatrics, American Cancer Society Cancer Action Network, American Heart Association, American Lung Association and Truth Initiative, submitted a letter to Acting FDA Commissioner Stephen Ostroff expressing support for the proposed rule. Finally, on July 10, 2017, Tobacco-Free Kids, joined by 28 public health and medical organizations, including all the plaintiffs in this action, filed additional formal comments urging FDA to make final the proposed rule, again citing FDA's findings in the Swedish Match PMTA order.

15. Tobacco-Free Kids also issued press releases using FDA's disclosures in the Swedish Match PMTA order to educate the public about the relative risk of smokeless tobacco

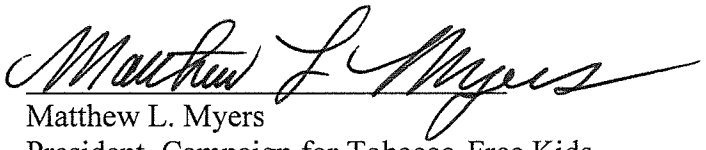
products, based on the knowledge we gained from the premarket review decision. Were it not for completion of the premarket review process in the Swedish Match proceeding, Tobacco-Free Kids could not have educated the public as effectively about the substantial differences in disease risk among specific smokeless tobacco products, nor about the feasibility of reducing the toxicity of smokeless tobacco across-the-board.

16. FDA's suspension of premarket review of new tobacco products makes it more difficult and costly for Tobacco-Free Kids to successfully educate young people about the hazards of specific newly-emerging products and to discourage use of tobacco products by young people. For example, a new e-cigarette device called JUUL has become, in the words of FDA Commissioner Gottlieb, "wildly popular among kids," in part because it is small, highly concealable, looks like a flash drive and can be recharged in a laptop's USB drive. It is therefore difficult for parents and teachers to recognize or detect. Its e-liquid pods come in a variety of flavors that appeal to kids, including mango and fruit medley. Even though JUUL does not physically resemble a conventional cigarette, it delivers a powerful and addictive dose of nicotine.

17. Had FDA not suspended the premarket review process for e-cigarettes until August 2022, the manufacturer of JUUL, by this month, would have had to submit extensive information about the product and its use to FDA; moreover, FDA would have to determine whether JUUL is "appropriate for the protection of public health." An agency decision as to a JUUL PMTA would have either removed JUUL from the market, thereby enhancing the efforts of Tobacco-Free Kids to reduce the use of tobacco products by young people, or, even if a PMTA were granted for JUUL, would have disclosed critical information about JUUL that would have enhanced the efforts of Tobacco-Free Kids to educate young people about the risks

associated with usage of JUUL. Conversely, FDA's suspension of premarket review directly impedes those public education efforts and makes them more costly for Tobacco-Free Kids to pursue.

Signed under the pains and penalties of perjury this 27th day of August, 2018



Matthew L. Myers
President, Campaign for Tobacco-Free Kids

ATTACHMENT 1

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Center for Tobacco Products
Office of Science

Premarket Tobacco Application (PMTA) Technical Project Lead (TPL) Review

Submission Information			
Applicant	Swedish Match North America, Inc.		
Submission Date	March 11, 2015	**FDA Receipt Date**	March 11, 2015
PM0000010: General Loose			
Product Category	Smokeless Tobacco		
Product Sub-Category	Loose Snus		
Package Type	Cardboard Can with Plastic Lid		
Package Quantity	45.0 g		
Tobacco Cut Size:	(b) (4)		
Characterizing Flavor	None		
PM0000011: General Dry Mint Portion Original Mini			
Product Category	Smokeless Tobacco		
Product Sub-Category	Portioned Snus		
Package Type	Plastic Can		
Package Quantity	6.0 g		
Portion Count:	20 pouches		
Portion Mass:	300 mg		
Portion Length:	28 mm		
Portion Width:	14 mm		
Portion Thickness:	5 mm		
Tobacco Cut Size:	(b) (4)		
Characterizing Flavor	Mint		
PM0000012: General Portion Original Large			
Product Category	Smokeless Tobacco		
Product Sub-Category	Portioned Snus		
Package Type	Plastic Can		
Package Quantity	24.0g		
Portion Count:	24 pouches		
Portion Mass:	1000 mg		
Portion Length:	33 mm		
Portion Width:	18 mm		
Portion Thickness:	6 mm		
Tobacco Cut Size:	(b) (4)		
Characterizing Flavor	None		

[1] The applicant provided (b) (4) buckets to characterize the tobacco cut size. Therefore, the tobacco cut size cannot be represented with a single value and corresponding range limit.

PM0000013: General Classic Blend Portion White Large - 12ct	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	10.8 g
Portion Count:	12 pouches
Portion Mass:	900 mg
Portion Length:	34 mm
Portion Width:	14 mm
Portion Thickness:	5 mm
Tobacco Cut Size:	(b) (4)
Characterizing Flavor	None
PM0000014: General Mint Portion White Large	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Portion Count:	24 pouches
Portion Mass:	1000 mg
Portion Length:	34 mm
Portion Width:	18 mm
Portion Thickness:	5.5 mm
Tobacco Cut Size:	(b) (4)
Characterizing Flavor	Mint
PM0000015: General Nordic Mint Portion White Large - 12ct	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	10.8 g
Portion Count:	12 pouches
Portion Mass:	900 mg
Portion Length:	34 mm
Portion Width:	14 mm
Portion Thickness:	5 mm
Tobacco Cut Size:	(b) (4)
Characterizing Flavor	Mint

PM0000016: General Portion White Large	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Portion Count:	24 pouches
Portion Mass:	1000 mg
Portion Length:	34 mm
Portion Width:	18 mm
Portion Thickness:	5.5 mm
Tobacco Cut Size:	(b) (4)
Characterizing Flavor	None
PM0000017: General Wintergreen Portion White Large	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Portion Count:	24 pouches
Portion Mass:	1000 mg
Portion Length:	34 mm
Portion Width:	18 mm
Portion Thickness:	5.5 mm
Tobacco Cut Size:	(b) (4)
Characterizing Flavor	Wintergreen

	STN	Submission Date	Solicited Y/N
Amendment(s)	PM0000018	3/31/2015	Y
	PM0000019	3/31/2015	Y
	PM0000020	3/31/2015	Y
	PM0000021	3/31/2015	Y
	PM0000022	3/31/2015	Y
	PM0000023	3/31/2015	Y
	PM0000024	3/31/2015	Y
	PM0000025	3/31/2015	Y
	PM0000026	6/3/2015	Y
	PM0000027	6/23/2015	Y
	PM0000029	7/8/2015	Y

	Cross Referenced Submission	Industry Meetings	Other Related Submission STN(s)
Related Submissions	MR0000020		SE0000140, SE0010524
	MR0000021		SE0000139, SE0010525
	MR0000022		SE0000143, SE0010526
	MR0000024		SE0010528
	MR0000025		SE0000141, SE0010529
	MR0000027		SE0010531
	MR0000028		SE0000144, SE0010532
	MR0000029		SE0000145, SE0010533
Product Use	☒ For Consumer Use ☐ For Further Manufacturing		
Product Type	☒ Complete ☐ Component, Part, or Accessory		

DISCIPLINES REVIEWED	DATE OF REVIEW
Behavioral Pharmacology	October 21, 2015
Chemistry	October 30, 2015
Clinical Pharmacology	October 21, 2015
Engineering	October 2, 2015
Environmental Science	October 8, 2015
Epidemiology	October 6, 2015
Medical	October 20, 2015
Microbiology	October 15, 2015
OCE Review (DEM & DPAL)	October 6, 2015
Social Science	October 2, 2015
Statistics	September 28, 2015
Toxicology	October 16, 2015

Recommended Action(s)

☒ Issue a Marketing Authorization letter; application contains sufficient evidence to demonstrate the product is appropriate for the protection of public health.

☐ Issue a No Marketing Authorization letter; application does not contain sufficient evidence to demonstrate the product is appropriate for the protection of public health.

Technical Project Lead Name:

CTP/OS Ii-Lun Chen, MD
Director, Division of Individual Health Science

Digitally signed by Iilun Chen -S
Date: 2015.11.02 15:44:09 -05'00'

Signatory Decision:

☒ I concur with TPL recommendation and basis of recommendation

☐ I concur with TPL recommendation and am providing additional comments (see separate memo)

☐ I do not concur with TPL recommendation as stated in my separate memo

Signatory: David Ashley, Ph.D.
CTP/OS RADM, U.S. Public Health Service
Director
Office of Science

Digitally signed by David Ashley -S
Date: 2015.11.03 13:25:56 -05'00'

Premarket Tobacco Application Technical Project Leader Review

I. Executive Summary

On March 11, 2015, Swedish Match North America (SMNA) submitted eight General brand snus premarket tobacco product applications (PMTAs) to FDA seeking authorization under Section 910(b) of the Federal Food, Drug and Cosmetic Act (FD&C Act).

Scientific review of these eight applications demonstrates that these eight products have the following qualities:

- Produced with a voluntary, proprietary standard using acceptable manufacturing processes as confirmed by both application review and on-site inspections. The applicant's heat treatment process distinguishes Swedish snus from other types of smokeless tobacco (ST), including snus-like products sold in the US market. The proprietary quality standard for Swedish snus products was developed to ensure product quality. The principal components of this standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a "best before" date. The constituent standards set maximum levels that must not be exceeded for selected constituents in the finished products.

  The proposed products contain significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market. Since NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers using ST products. Assuming persons who would have used other US ST products use these product instead, an individual using these products with reduced NNN levels could decrease the excess cancer risk[2] by 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of United States (US)-style snus, and 92% compared to use of dry snuff. Even further reductions in excess cancer risk could occur with the corresponding reductions in NNK; however, a quantitative contribution cannot be determined at this time due to the absence of a NNK cancer slope factor.

- Levels of other harmful and potentially harmful constituents (HPHC)(including As, Cd, acetaldehyde, crotonaldehyde, formaldehyde, and BaP) are similar to or lower than levels of ST products currently on the US market. Certain HPHCs (such as acrolein, acetaldehyde, cadmium, and nickel) have been identified as constituents of more toxic concern in the smoke of combusted products as compared to smokeless products.

- When used as exclusively instead of other smokeless tobacco products or cigarettes on the US market, these products offer potential for reductions in oral cancer risk.

[2]The excess lifetime cancer risk is a toxicological tool to estimate the probability of cancer incidence in a population of individuals for a specific lifetime from projected intakes (and exposures) and dose-response data (i.e., slope factors) for a specific chemical.

- When used as exclusively instead of combusted tobacco products, these products offer lower risk of developing respiratory diseases (i.e., chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis) and cancers (such as oral, esophageal, and lung) than smokers.

- If nonusers were to initiate or users decrease cessation, there would be negative health consequences.

- Use of Swedish snus products is not risk-free and its use is associated with adverse health risks such adverse pregnancy outcomes, oral disease, increased risk of fatal cardiovascular events, pancreatic cancer, diabetes, and all-cause mortality.

- It is anticipated that the marketing of the proposed products, as described in the PMTAs, there is a low likelihood of nonuser uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

Information from national tobacco use studies and other studies submitted by the applicant indicate that migration of smokers to exclusive use of these proposed snus tobacco products while possible is expected to be limited. It is more likely that uptake of the proposed products occurs among current smokeless tobacco users. Given the above listed justifications based on information gathered from nonclinical and clinical product evaluations as well as substantial epidemiological studies, the totality of evidence provided in the applications support authorization of these products so that current ST product users will have additional options for less toxic tobacco products, thereby potentially decreasing the negative health impact from tobacco product use making the marketing of these proposed products appropriate for the protection of public health.

II. Review of PMTA

1. Background and Regulatory History

A new tobacco product, including a tobacco product modified in any way ("including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient" (section 910(a)(1)(B)), after February 15, 2007 requires premarket review and an order from FDA authorizing the marketing of the product.

A PMTA must be submitted to FDA under section 910(b) of the FD&C Act and a marketing authorization order must be received from FDA under section 910(c)(1)(A)(i) prior to marketing any new tobacco product, unless FDA has found that the product is substantially equivalent to a tobacco product commercially marketed in the US as of February 15, 2007 (see section 910(a)(2)(A)(i)) or is exempt from a substantial equivalence determination pursuant to regulation (see section 910(a)(2)(A)(ii)).

FDA will deny a PMTA and issue a no marketing authorization order that the product may not be introduced or delivered for introduction into interstate commerce under section 910(c)(1)(A)(ii) where FDA finds that:

- there is a lack of a showing that marketing the product is appropriate for the protection of the public health;
- the methods, facilities, or controls used in manufacturing, processing, or packing do not conform to manufacturing regulations issued under section 906(e) (21 U.S.C. 387f(e));
- the proposed labeling is false or misleading; or
- it is not shown that the product complies with any tobacco product standard in effect under section 907 (21 U.S.C. 387g), and there is not adequate information to justify deviation from the standard.

The statute provides that the finding as to whether the marketing of a product for which a PMTA is submitted would be appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account ─

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Regulatory History

On March 11, 2015, Swedish Match North America (SMNA) submitted eight General brand snus PMTAs to FDA seeking authorization under Section 910(b) of the Food, Drug and Cosmetic Act. The PMTAs [PM00000010-PM00000017] were submitted in connection with the June 10, 2014 Modified Risk Tobacco Product Applications (MRTPA) for the same eight snus products. However, the PMTAs are for the eight General brand snus products without any modified risk claims (proposed product labeling submitted March 31, 2015 [PM0000018-PM0000025]).

Significant regulatory interactions include the following:

- March 11, 2015: FDA received PMTAs for eight snus products.
- March 25, 2015: FDA issued eight acknowledgment letters.
- March 26, 2015: FDA held a teleconference with SMNA requesting SMNA submit one label that includes one of the health warnings for each tobacco product because SMNA did not submit specimen labels specific to the PMTAs.
- March 31, 2015: SMNA submitted amendments, PM0000018-PM0000025, in response to a teleconference held on March 26, 2015.
- March-April 2015: FDA conducted on-site clinical and manufacturing inspections of domestic and foreign clinical sites related to the SMNA MRTPAs. FDA inspected clinical study sites (Indianapolis, IN and Serbia), manufacturing sites (Sweden), and a SMNA laboratory facility (Sweden).

- April 2, 2015: FDA conducted a follow-up teleconference with SMNA regarding the status of samples being shipped to Southeastern Regional Laboratory (SRL) for testing.
- April 23, 2015: FDA issued eight Sample Acknowledgement letters acknowledging SRL's receipt of samples on April 15, 2015 from SMNA.
- April 9-10, 2015: A meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) discussed the ten submitted MRTPAs, including the adequacy of the scientific evidence to support proposed health claims of substantially reduced health risk in comparison with cigarettes.
- May 7, 2015: FDA determined that the eight PMTAs met the filing requirements for a PMTA seeking a marketing order under section 910(c)(1)(A)(i) of the FD&C Act. A Filing letter was issued to SMNA.
- May 20, 2015: FDA issued an Advice/Information (A/I) Request letter to SMNA.
- June 3, 2015: SMNA submitted an amendment, PM0000026, in response to FDA's May 20, 2015 A/I letter.
- June 12, 2015: FDA issued an A/I Request letter to SMNA.
- June 23, 2015: SMNA submitted an amendment, PM0000027, in response to FDA's June 12, 2015 A/I letter.
- June 29, 2015: FDA held a teleconference with SMNA to discuss engineering deficiencies for their PMTA and MRTP applications.
- July 8, 2015: SMNA submitted an amendment, PM0000029, in response to a teleconference held on June 29, 2015.

Current Submission Tobacco Product

Swedish Match General brand snus is an oral ST product that is moistened to facilitate use in the oral cavity. The applicant defines "snus" as an ST product that is produced and used in Sweden and manufactured using a heat treatment process according to a proprietary standard. This process distinguishes Swedish snus from other types of ST, including snus-like products sold in the US market. Swedish snus is made mainly from air-dried tobacco varieties, various salts, flavoring, and moisture-preserving substances. SMNA describes the snus products as "moist (% moisture) to semi-moist % moisture) oral smokeless products which are typically placed between the upper lip and the gum and do not require expectoration during use." In contrast, American ST products are typically placed between the lower lip and gum and require expectoration during use (Hatsukami et al., 1988). In Sweden, the product is classified as food, contains only food-approved ingredients, and is manufactured in a way that is consistent for food production.

Swedish Match currently markets other snus products in the US in two packaging formats: loose snus and portioned snus.

- **Loose Snus:** Traditional variant of Swedish snus that is formed by pinching a desired amount upon use.
- **Portioned Snus:** Consists of pre-packed pouches wrapped in a non-woven fabric for discrete and hygienic usage. The pouches are available in different sizes and weights (e.g., from 0.3 g to 1.0 g/pouch). Swedish Match produces two types of pouch products, original and white.

2. Overview of ST Products on the US Market

According to the August 2014 Euromonitor International report, in 2013 the tobacco industry had US sales totaling $112.2 billion (including cigarettes, cigars, ST tobacco, cigarettes including RYO stick equivalent). ST accounted for $7.4 billion. Therefore, ST accounted for 6.6% of tobacco sales in 2013. ST products are marketed in the US in categories such as US-style moist snuff, chewing tobacco, Swedish-style snus, dry and hard snuff. US style moist snuff comprises greater than 82% of the ST market based on sales in the US. ST users purchase moist snuff as pouched products or loose tobacco products. Chewing tobacco, Swedish-style snus, dry snuff, hard snuff products account for approximately 18% of the US ST market. Chewing tobacco consists of products such as plug, twist, and chew. Dry snuff is often inhaled through the nose, or may be a pouched product placed in the mouth. The eight new snus products in this PMTA are categorized as Swedish-style snus, which follows the manufacturing procedures provided by a voluntary industrial quality standard for Swedish snus. This standard aims to reduce selected, undesired constituents in the finished products, such as tobacco-specific nitrosamines (TSNAs), metals, benzo(a)pyrene(BaP), and nitrite, by implementing a series of procedures that includes: tobacco leaf selection, controlled heat treatment that reduces the natural microbial flora, and manufacturing in a closed system to prevent external microflora contamination.

3. Product Science (Chemistry/Engineering/Microbiology)

General Product Description

The eight Swedish snus products are made from (b) (4), and (b) (4) t tobaccos along with various salts, flavorings, and moisture-preserving substances. The applicant indicates that all the products are designed to contain (b) (4) % (weight) nicotine with moisture levels between (b) (4) % and (b) (4) % and pH values between (b) (4) and (b) (4). The total nicotine in the eight snus products ranges from (b) (4) mg/g for PM0000010 and PM0000012-17, and (b) (4) mg/g for PM0000011. These nicotine values are within the reported ranges for other marketed US moist snuff, therefore the abuse potential for these products is similar to other marketed smokeless tobacco products. Other than tobacco, the basic formulations for all the products consist of various salts, flavorings, processing aid, and humectants. The applicant claims that all ingredients other than tobacco are approved for food use. In terms of quantity, water ((b) (4) %), a humectant according to the applicant, is the most abundant ingredient besides tobacco in each product. Except for PM0000011, all of the products also contain (b) (4) or both (b) (4) and (b) (4) as humectants ((b) (4) %). (b) (4) ((b) (4) %) is used as a taste enhancer and preservative. (b) (4) (b) (4) (b) (4) %) are used as pH adjusters. Small quantities of (b) (4) ((b) (4) %) are used as a processing aid. For non-mint and non-wintergreen flavored products (PM0000010, PM0000012-PM0000013, and PM0000016), flavors account for (b) (4) % of the finished products by weight. However, the three mint-flavored products (PM0000011 and PM0000014-PM0000015) and one wintergreen-flavored product (PM0000017) contain higher levels of flavor (b) (4) % by weight). The flavored products also contain an artificial sweetener, (b) (4) ((b) (4) %). For most of the products included in these PMTAs, the vast majority of the ingredients other than tobacco are listed as flavor, which are typically present at very low concentrations (ppm or ppb levels), except for the mint and wintergreen flavor ingredients

as described. Non-portioned snus (PM0000010) is not allocated into a defined serving size; instead, the consumer decides the amount per use. Portioned snus (PM0000011-PM0000017) is allocated into a defined serving size via pouch paper, individual pieces, or other means. In this case, the products utilize pouch paper.

The chemistry evaluation took into consideration product formulation (including HPHCs), chemistry design (nicotine, moisture, pH), tobacco blend, ingredients other than tobacco, manufacturing steps and controls, performance criteria and stability. More specifically, HPHCs evaluated include: acetaldehyde, arsenic, BaP, cadmium, crotonaldehyde, formaldehyde, nicotine (free and total), NNN (N-nitrosonornicotine), NNK ((4-methylnitrosamino)-1-(3-pyridyl)-1-butanone), and pH. Compared to the literature data, we found that the levels of NNK, NNN, B[a]P, and crotonaldehyde in these new snus products are significantly lower than those in the major types of traditional smokeless tobacco products (STPs) on the US market (e.g., moist snuff). These reductions can be mainly attributed to the differences in the types of tobacco (no use of dark-fire cured and fermented tobacco) and manufacturing process (steam heat-treatment versus fermentation). Also, there are no increased levels of formaldehyde, acetaldehyde, arsenic, and cadmium compared to the traditional STPs. Additionally, these new snus products do not contain a wide range of HPHCs that are typically found in mainstream cigarette smoke.

The applicant states that the product for PM0000010 is packed in paraffin-coated cardboard cans with plastic lids and the products for PM0000011-PM0000017 are packed in either round or square plastic cans with plastic lids. The applicant provides the ingredients (e.g., (b) (4) (b) (4)) contained in the packaging materials and states that all ingredients and materials in the new products are food grade, generally recognized as safe (GRAS), or are approved for food contact. The plastic lid, plastic base, cardboard can base, and wax coating used in the new products are the same as other products currently on the market from SMNA. No chemistry or toxicology concerns with the containers were identified based on the information provided. Overall, the chemistry evaluation determined that there was adequate information to characterize the proposed products and that the property parameters, manufacturing and processing were acceptable. Refer to the individual chemistry, engineering and microbiology reviews for a full description of unique properties by product. This review only provides an overview of the products.

Tobacco Blend

PMTA	Product	Quantity (Target with minimum and maximum limits in parenthesis) (mg/g or mg/pouch)*			
		Tobacco Leaf – (b) (4)	Tobacco Leaf – (b) (4)	Tobacco Stem – (b) (4)	Total
PM0000010	General Loose	(b) (4)			
PM0000011	General Dry Mint Portion Original Mini				
PM0000012	General Portion Original Large				
PM0000013	General Classic Blend Portion White Large (12 ct)				
PM0000014	General Mint Portion White Large				
PM0000015	General Nordic Mint Portion White Large (12 ct)				
PM0000016	General Portion White Large				
PM0000017	General Wintergreen Portion White Large				

* mg/g for PM0000010 and mg/pouch for PM0000011-PM0000017.

Overview of Product[3]

Brand	FDA Submission Tracking Number (STN)	Package Type	Can Weight	Can Dimensions	Pouch Size	Pouches per Can	Portion Mass
General Loose	PM0000010	Cardboard Can with Plastic Lid	45.0 g	70.5 x 23 mm			
General Dry Mint Portion Original Mini	PM0000011	Plastic Can	6.0 g	66 x 19 mm	14 x 28 x 5 mm	20	0.3 g
General Portion Original Large	PM0000012	Plastic Can	24.0 g	70 x 24 mm	18 x 33 x 6 mm	24	1.0 g
General Classic Blend Portion White Large	PM0000013	Plastic Can	10.8 g	56.6 x 86 x18 mm	14 x 34 x 5 mm	12	0.9 g
General Nordic Mint Portion White Large	PM0000014	Plastic Can	13.5 g	56.6 x 86 x18 mm	14 x 34 x 5 mm	24	0.9 g
General Nordic Mint Portion White Large	PM0000015	Plastic Can	10.0 g	56.6 x 86 x18 mm	14 x 34 x 5 mm	12	0.9 g
General Portion White Large	PM0000016	Plastic Can	24.0 g	70 x 24 mm	18 x 34 x 5.5 mm	24	1.0 g
General Wintergreen Portion White Large	PM0000017	Plastic Can	24.0 g	70 x 24 mm	18 x 34 x 5.5 mm	24	1.0 g

General Product Design

The applicant identifies the products' components and subcomponents (e.g., tobacco, pouch, can) as well as some of the applicable specifications and a description of the intended function for each. Design parameters are assessed to understand the comprehensive design of the products as each parameter contributes to the overall constituent yields:

- Tobacco cut size is directly related to the particle surface area and the accessibility of saliva to tobacco surfaces, thereby affecting the amount and rate of constituents released from the product.[4]

[3] This table supersedes the tables presented in the clinical pharmacology, behavioral pharmacology, and medical reviews.

[4] Dash S, Murthy PN, Nath L, Chowdhury P (2010). Kinetic modeling on drug release from controlled drug

- Tobacco moisture (tobacco leaf, blend, and final) may affect microbial growth in the product, extraction efficiency, and total exposure to nicotine, NNN, and NNK.[5,6,7]
- Portion mass may affect user exposure to the tobacco product and, in turn, the HPHCs contained in each portion.[8]
- Portion length may affect the constituents in each portion.[8]
- Portion width is directly related to product surface area, which is proportional to the amount and rate of constituents released from the product.[9]
- Portion thickness is directly related to product surface area, which is directly proportional to the amount and rate of constituents released from the product.[9]
- Pouch paper basis weight, the weight of paper per meter area, influences the interactions between the tobacco and oral cavity, thereby affecting the amount and rate of constituents released from the product.[10]
- Pouch paper porosity/permeability influences the interactions between the tobacco and oral cavity, thereby affecting the amount and rate of constituents released from the product.[10]
- Pouch paper wicking allows the transport of tobacco constituents from the tobacco filler to the pouch surface, thereby affecting the amount and rate of constituents released from the product.[11] In this submission, the applicant's nicotine uptake trials demonstrate the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in these new products. Therefore, wicking values are not needed for these products.

Compared to currently-marketed smokeless products, the applicant provided some of the target specifications and upper and lower range limits necessary to evaluate ST products. Industry average ranges are used to compare the design parameters of PM0000010-PM0000017 to typical values that FDA anticipates based on previous submissions. The products chosen for

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delivery systems. Acta Poloniae Pharmaceutica – Drug Research 67(3):217-223.

[5] U.S. Food and Drug Administration (2013). Evaluation and Definition of Potentially Hazardous Foods - Chapter 3: Factors that Influence Microbial Growth. Available at: http://www.fda.gov/Food/FoodScienceResearch/SafePracticesforFoodProcesses/ucm094145.htm (The "tobacco juice" generated when snus is consumed can be ingested similar to foods, thus this reference is relevant here.)

[6] Gale N, Errington G, McAdam K (2013). Effects of product format on nicotine and TSNA extraction from snus pouches. British American Tobacco 67th Tobacco Science Research Conference, Williamsburg, VA, September 15-18, 2013.

[7] Djordjevic MV, Hoffman D, Glynn T, Connolly GN. U.S. commercial brands of moist snuff, 1994. I. Assessment of nicotine, moisture, and pH. Tob Control. 1995;4:62–6.

[8] Stepanov I, Jensen J, Biener L, Bliss R, Hecht SS, Hatsukami DK (2012). Increased pouch sizes and resulting changes in the amounts of nicotine and tobacco-specific N-nitrosamines in single pouches of camel snus and malrboro snus. Nicotine Tob Research 14(10):1241-1245.

[9] Zhang H, Zhang J, Streisand JB (2002). Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. Drug Deliv Sys 41(9):661-680.

[10] Lewis S, Subramanian G, Pandey S, Udupa N (2006). Design, evaluation and pharmacokinetic study of mucoadhesive buccal tablets of nicotine for smoking cessation. Indian J Pharm Sci 68:829-31.

[11] Morrow NR (1970). Physics and thermodynamics of capillary action in porous media. Ind Eng Chem Res 62(6): 32-56.

comparison are those that are in similar product categories and subcategories as the new products. The table below lists typical smokeless design parameter ranges.

Average Industry Ranges for Smokeless Design Parameters*

Design Parameter	Industry Range	PM0000010-PM0000017 Within Industry Range**
Final Moisture (%)	3.6-57	Yes
Portion Mass (mg)	230-1820	Yes
Portion Length (mm)	10-36	Yes
Portion Width (mm)	6.65-18	Yes
Portion Thickness (mm)	5-5.79	Yes
Pouch Paper Basis Weight (g/m^2)	1-29	Yes
Caliper (µm)	195	Yes

* Data source is FDA database of engineering parameters found in SE Reports submitted to FDA (version 5/9/14); final moisture range determined from portioned and non-portioned smokeless products; portioned parameters determined from portioned smokeless products.
**Due to testing variability, values for the new products that are out of industry range by less than 5% are considered to be within range and acceptable.

The final tobacco moisture level is within the industry range and no other issues are identified. Also, portion mass, length, width, thickness, and caliper are within the industry ranges for all of the new products and no other issues are identified. Furthermore, the tobacco types utilized in the new products are similar to or the same as products currently marketed. Therefore, the new products do not appear to be different from available smokeless products with regard to the tobacco and the design parameters provided. In summary, the results analyzed indicate these products fall in the normal range, and the actual design feature values do not appear to raise concerns related to how these products might adversely impact public health through risk to the user, increased initiation or decreased cessation as compared to the existing ST market.

Sample Testing
The applicant submitted samples of each of its products in support of its PMTAs to FDA's SRL on April 15, 2015. Samples were shipped via UPS from Swedish Match North Europe to the Swedish Match North America Owensboro, Kentucky facility. These samples were then shipped at ambient temperature from the Owensboro facility to SRL.

The CTP Office of Science (OS) requested testing of the PMTA product samples and examples of testing performed:

- Nicotine (filler/SL), pH, TSNA (filler), nicotine (free), NNN, NNK, pouch thickness, pouch width, pouch length, % oven volatiles, portion mass
- Chemistry Tests: Three to four replicates at 1g each; composite from at least two pouches; quantity expressed in units/gram ("as is" [wet] weight)
- Engineering Tests: Three to four replicates; quantity expressed in mm for length, width, thickness; portion mass in g per pouch (including pouch material and filler) and in g per filler
- Micro Tests: Three to four replicates at 1g each (combined with chemistry tests) from at least two pouches

Division of Product Science scientists reviewed the analysis provided by SRL and evaluation of the sample testing did not raise any concerns.

Clinical Microbiology

Product stability (including moisture content, pH, water activity, bacterial counts and validation parameters), heat treatment process, additives, fermentation, storage and microbial concerns were evaluated. The clinical microbiology content of the submission was considered adequate as:

- Descriptions of manufacturing steps and quality control measurements were established and followed.
- A written testing program designed to assess the stability characteristics of the tobacco products was established and followed.
- Sample size and test intervals were determined based on statistical criteria for each attribute examined to assure valid estimates of stability.
- Evaluation of stability was made using the same container-closure systems in which the tobacco products are intended to be marketed.
- Expiration dates were related to storage conditions stated on the labeling, as determined by stability studies.
- Written procedures, designed to prevent the growth of objectionable microorganisms (including the mycotoxin ochratoxin A and aflatoxins B1, B2, G1 and G2) were established and followed.
- Written procedures designed to determine the physical and chemical attributes that affect microbial activity and/or are susceptible to change during product storage were established and followed for pH, moisture content, and water content. Written procedures for sampling and testing parameters were established, described, and followed including method of sampling and the number of batches tested.
- Validation protocols showing the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the applicant were established and documented.
- Statistical quality control criteria including appropriate acceptance levels and/or appropriate rejection levels were established and followed.

Shelf Life

The applicant recommended retail shelf lives of 14 weeks for loose snus, 20 weeks for pouched snus (White and Original) and 30 weeks for "dry" pouched snus. These shelf lives are supported by the provided data.

Manufacturing, Processing, and Controls

The applicant has provided descriptions about tobacco procurement, grading method, countries of origin, curing method for each type of tobacco, tobacco storage conditions, criteria for choosing suppliers, and criteria for acceptance of raw tobacco based on chemical testing results and tolerance levels of certain constituents (see the discussion about the applicant's internal quality standard below). According to the applicant, the tobacco grade is based on the country of origin, curing process, and plant position.

Briefly, manufacture of these products includes grinding, blend processing, and packaging.

During the April 2015 FDA inspection, several issues were observed regarding manufacturing equipment (e.g., the scale for weighing tobacco flour was not calibrated; the calibration of the temperature probes for blenders was outdated). However, these issues are not expected to have a major impact on the quality of the new products because: 1) the applicant will not routinely manufacture the new products unless FDA issues the marketing authorization orders, and 2) the applicant responded that it would take corrective actions in a timely manner and the issues were noted by OCE reviewer to have been corrected on or before May 30, 2015. Furthermore, during the inspection, FDA reviewed the manufacturing processes that would be applied to the new products according to the applicant and found no significant deviations from the process described in the PMTAs.

The applicant states that it uses analytical methods, chemical quality control programs, brands testing programs, and agrochemical management programs according to its proprietary quality standard for snus products to ensure product quality. The principal components of this standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a "best before" date. The constituent standards set maximum levels that must not be exceeded for selected constituents in the finished products. Currently, the Swedish Match standard has limits for the following nine constituents:

- NDMA: (b) (4) ng/g (dry weight basis); (b) (4) ng/g (as is)
- Nitrite: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- BaP: (b) (4) ng/g (dry weight basis); (b) (4) ng/g (as is)
- Arsenic: (b) (4) ng/g (dry weight basis); (b) (4) ng/g (as is)
- Lead: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is);
- Cadmium: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- Chromium: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- Nickel: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- NNN+NNK: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)

In addition to the Swedish Match standard, the applicant states that the Swedish National Food Agency and the Swedish Medical Product Agency have also set regulatory limits for the following constituents:

- Lead: 3 mg/kg (as is)
- Propylene glycol: 40 g/kg (as is)
- Aflatoxins (sum of B1, B2, G1, and G2): 0.005 mg/kg (as is)
- Ethanol: 2.25% v/v (as is)

The applicant states that all snus products are analyzed three to four times a year in its Chemical Control Program. The applicant has provided the chemical testing data on all the products included in these from the 2011 Chemical Quality Control Program and the 2012 Brands Testing Program. All products have constituent levels below the Swedish Match limits and the Swedish national regulatory limits.

Additionally, the applicant states that their proprietary standard also includes Guidance Residue Limits (GRL) for agrochemical residues in raw tobacco and finished snus products. Testing of raw tobacco is performed and results are reviewed prior to the tobacco's release for

snus manufacturing (if results are acceptable). Testing of the finished products is performed annually. For all the products that are the subjects of these PMTAs, the applicant provided the 2011 testing results, and the levels of the agrochemical residues tested all fell below the applicant's GRL. The reported analyses and use of voluntary standards appear acceptable.

Inspections of Swedish Match Manufacturing Facilities and Laboratory

The Office of Regulatory Affairs (ORA), accompanied by Subject Matter Experts (SMEs) from the Division of Enforcement and Manufacturing (DEM) in the Office of Compliance and Enforcement (OCE) and the Office of Science (OS) within the Center for Tobacco Products (CTP), conducted an inspection of Swedish Match manufacturing and testing facilities from April 13, 2015 – April 17, 2015 (April 13-14 at two Gothenburg sites; April 15-16 at the Kungälv site; and April 17 at the Stockholm site). Manufacturing, product analysis, packaging, distribution, recalls and complaints, shipping, laboratory accreditation, validations, raw data, and procedures were evaluated at the different sites. DEM's review of both the application and the manufacturing facilities and laboratory inspection results did not identify any issues of concern for the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of the tobacco products for which the applications were submitted.

DEM inspectional review recommends classification as VAI (voluntary action indicated) for facilities inspected other than the Stockholm laboratory facility which was recommended as NAI (no action indicated).

4. Toxicological Risk (Nonclinical Science)

The applicant provided HPHC data for each of the eight snus products in the PMTA based on wet-weight (as is weight). The FDA converted the wet-weight levels into dry-weight levels using the product moisture levels provided by the applicant in the application in order to allow HPHC level comparisons to be made between the eight new snus products and other smokeless tobacco products on the market that reported the HPHC levels as dry-weight levels in the respective publications.

HPHC Levels Calculated on a Dry-weight Basis

Product	NNN	NNK	Acetaldehyde	Arsenic	BaP	Cadmium	Crotonaldehyde	Formaldehyde	Nicotine (total)	Nicotine (free)
	(b) (4)									
PM0000010										
PM0000011										
PM0000012										
PM0000013										
PM0000014										
PM0000015										
PM0000016										
PM0000017										
Average										

HPHCs, Excess Cancer Risk, Relative Risk of Specific Cancers

The PMTA products were compared to other ST products (including moist snuff, chewing tobacco, American snus, and dry snuff) and cigarette products currently on the US market. The eight new Swedish snus products have significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market. NNN and NNK are arguably the most concerning carcinogenic HPHCs in smokeless tobacco products. They showed strong dose response relationships with cancer development, are specific to tobacco products, and biomarkers of exposure are present in minimal to below levels of detection in most nonusers of tobacco products. Since NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers who use these products instead of other US smokeless products. Assuming tobacco product use pattern to be consistent, for an individual the use of PMTA products with low levels of NNN could decrease the excess cancer risk by 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of US-style snus, and 92% compared to use of dry snuff. Even further reductions in excess cancer risk could occur with the corresponding reductions in NNK; however, a quantitative contribution cannot be determined at this time due to the absence of a NNK cancer slope factor. The excess lifetime cancer risk is a toxicological tool to estimate the probability of cancer incidence in a population of individuals for a specific lifetime from projected intakes (and exposures) and dose-response data (i.e., slope factors) for a specific chemical, in this assessment, NNN.

Other HPHCs in these PMTA products, including arsenic, cadmium, acetaldehyde, crotonaldehyde, formaldehyde, and BaP exist at similar or lower levels than in the other types of ST products on US market. The estimated levels of exposure to these HPHCs are typically at or below dietary intake levels or the reference levels set by government agencies, and are therefore not considered to be a significant toxicological concern. Dietary intake levels are used as comparison as the “tobacco juice” generated when snus is consumed can be ingested similar to foods.

Data showed that ST use in general is associated with elevated risks of oral cancer in the US, *but not associated* with oral cancer in Nordic countries where Swedish snus with lower levels of NNN and NNK is used by Swedish ST users (Boffetta, 2008). This suggests that the lower levels of NNN and NNK in the Swedish snus may reduce the risk of oral cancer in US consumers who use a low NNN- and NNK-containing snus product as compared to other ST products.

Comparison to Cigarette Smoke

FDA’s established list of HPHCs includes over 40 more carcinogenic constituents in cigarette smoke than in ST products. Certain HPHCs -- such as acetaldehyde, cadmium, acrolein, and nickel have been identified as constituents of more toxic concern in the smoke of combusted products as compared to smokeless products. Direct comparisons of HPHC levels using urinary biomarker information and estimated absolute HPHC levels, which would allow a comparative risk assessment of the proposed Swedish snus products and cigarettes, is difficult. Inherent differences in the products -- such as combusted vs. non-combusted, route of HPHC exposure (oral vs. inhalation), and the complex mechanisms of target organ-specific toxicity

by each individual HPHC, as well as toxicity resulting from the complex mixture of HPHCs, make a direct comparison challenging in terms of nonclinical toxicological assessment. While smokeless tobacco is associated with many health problems, epidemiology studies discussed later in this review, provide evidence that smokeless tobacco users have much lower relative risk of developing oral cancers, respiratory diseases (COPD, emphysema and chronic bronchitis) and lung cancers as compared to smokers. Overall death rate is also lower in smokeless tobacco users as compared to smokers.

5. Abuse Liability, Exposure/Response, and Use Behavior (Clinical Pharmacology/Behavioral Pharmacology)

Abuse Liability

The applicant acknowledges the abuse liability (addictive and reinforcing effects) of its Swedish snus products given their nicotine content. Although the applicant did not submit formal abuse liability studies or predictions about uptake and use specific to the proposed snus products, the reinforcing and addictive effects of the proposed snus products are acknowledged and the abuse potential of the proposed products is understood to be within the range of similar marketed products. Also, the proposed snus products expose individuals to nicotine levels that are broadly similar to traditional combusted tobacco products (e.g., cigarettes). Data provided demonstrate that snus products produce reinforcing effects, as indicated by positive ratings of "liking" and "good effects." The behavioral pharmacology review focuses on the effects of Swedish snus products in general on tobacco use behaviors. This includes consideration of the expected rates of use of snus products by current tobacco users, use of the snus products in conjunction with other tobacco products, the potential for abuse and misuse of the snus products, the potential for experimenters to become addicted, and the impact on cessation rates.

Pharmacokinetics and Exposure/Response

The applicant submitted four clinical pharmacology studies. Three evaluated the nicotine pharmacokinetics after single and multiple administrations of Swedish snus. The nicotine maximum concentration (Cmax) values after use of a single snus portion ranged from about 10.8-29 ng/mL, with the highest Cmax values reported after use of "General" and "Catch" brands. Nicotine pharmacokinetics were dose proportional, a finding consistent with previous literature (Digard et al., 2013). Estimations of area under the curve (AUC) values are hampered by the use of varied time collection periods across studies and varied product use characteristics (e.g., amount and duration). The format of the products (i.e., loose or pouched) had little influence on the nicotine pharmacokinetic parameters. After overnight abstinence, time to maximum nicotine plasma concentration (Tmax) appeared to be dependent on product use time. Similarly, other studies examining Swedish snus reported Tmax values between 30 and 37 minutes (Holm et al., 1992; Lunell and Curvall, 2011; Lunell and Lunell, 2005). In comparison, after cigarette smoking, nicotine reaches peak venous concentrations within eight minutes and peak arterial plasma concentrations within five minutes (Arcavi and Benowitz, 2004; Benowitz et al., 2009; Gori et al., 1986; Lunell et al., 2000; Lunell and Curvall, 2011; Schaedeli et al., 2002). As used by consumers, the proposed snus products expose individuals to nicotine levels that are broadly similar to cigarettes and traditional ST products. Thus, from

a clinical pharmacology perspective, systemic exposure to nicotine following use of the proposed snus products is expected to produce reinforcing effects and have an abuse liability similar to traditional cigarettes and other ST products.

One study measured the pre- and post-use levels of lead, cadmium, nicotine, and TSNAs in Swedish snus products; however, systemic exposures were not assessed. The systemic exposures to TSNAs and other HPHCs after use of some snus products including Swedish snus are described in peer-reviewed literature (Hatsukami et al., 2004; Sarkar et al., 2012).

Summaries of the four clinical pharmacology studies submitted by the applicant are presented below.

SW WS 02: This study was an open-label, crossover study of nicotine plasma levels after the use of four types of snus and nicotine chewing gum. In the study, male snus users aged 18-23 were administered snus portions [General (8.8±0.4 mg nicotine/portion), Catch Licorice (7.0±0.1 mg nicotine/portion), Catch Mini (4.5±0.3 mg nicotine/portion), Catch Dry Mini (4.8±0.6 mg nicotine/portion)] or nicotine gum (Nicorette, 1.9±0.1 mg nicotine) once an hour for 11 hours (12 doses total). Subjects were instructed to keep the snus between the upper lip and gum for 30 minutes. In the Nicorette gum condition, subjects were administered 2 mg Nicorette chewing gum and instructed to chew each piece for 30 minutes. For each condition, serial venous blood samples, were drawn to assess nicotine levels. After multiple doses (12 doses over 11 hours) of the four types of snus or Nicorette gum, nicotine pharmacokinetic parameters were reported, but only after the last use (Cmax and AUC_{11-12}). The mean±SD nicotine amount extracted per dose was calculated as 2.74±0.80, 1.55±0.68, 2.00±0.56, 1.08±0.94 and 0.84±0.12 mg/portion for General, Catch Licorice, Catch Mini, Catch Dry Mini snus, and Nicorette gum, respectively.

After the multiple dosing regimen, nicotine plasma concentrations reached the following mean±SD Cmax values (ng/mL) for the snus products: General, 29.00± 8.53; Catch Licorice, 23.79± 8.60; Catch Mini 20.95 ±6.90; Catch Dry Mini, 10.85 ±5.65; and nicotine gum, 12.75± 4.67. For the first three snus products, nicotine Cmax values were similar to Cmax values observed in smokers (Benowitz et al., 1982;Benowitz, 2008;Kotlyar et al., 2007). Mean±SD AUC values (ng·h/mL) following the last dosing interval reached the following values for the snus products: General, 26.2 ± 3.4; Catch Licorice, 21.6 ± 8.8; Catch Mini, 19.0 ± 6.7; Catch Dry Mini, 9.8 ± 5.1; and Nicorette, 11.6 ± 4.5. Mean Cmax and AUC_{11-12} values were dose proportional, with R^2 values of 0.82 and 0.81, respectively. Thus, from the comparison of these parameters, the nicotine pharmacokinetics did not differ across all products.

SW WS 06: This study was an open label, single center, three-way cross-over study, designed to examine the nicotine plasma concentrations and subjective effects of a single dose (1 g) of General Onyx and General White portion snus relative to Nicorette chewing gum (4 mg). The study involved male and female subjects aged 18-50 years who smoked more than seven cigarettes per day. After baseline measurements and dosing, plasma nicotine concentrations were monitored for eight hours. Subjective effects assessments were performed using visual analog scale (VAS) assessments. Following the use of Nicorette gum, the extracted dose of nicotine was about 2.56 mg compared to 2.12 and 2.18 mg for Onyx portion snus and General

White snus, respectively. Mean Cmax values for Onyx portion snus and General White snus were 14.76 and 13.72 ng/mL, respectively, both higher than Nicorette gum (12.77 ng/mL). Tmax was reached about 30 minutes after snus use, faster than the 45 min Tmax observed following Nicorette administration. The faster absorption of nicotine following snus administration was reflected in higher VAS ratings of "head rush" following snus use relative to nicotine gum. The applicant concluded that snus provides a higher Cmax in a shorter amount of time (e.g., decreased Tmax) relative to Nicorette, and that the faster onset may account for the increased ratings of "head rush" compared to the gum. However, despite the lower Cmax of Nicorette relative to the snus comparators, Nicorette had a larger AUC, which is consistent with the increased amount of extracted nicotine. This study was limited to single dose administrations, which may not reflect actual use.

SM WS 12: This study compared the nicotine pharmacokinetics and subjective effects of single doses of sublingual nicotine (Nicorette Microtab, 6 mg) to Swedish snus. The study was an open-label, five-way, crossover study involving 18 healthy snus users. The goal of the study was to examine the interaction between nicotine amount and portion size; the study involved four snus products with two nicotine concentrations. Four Swedish snus products with different nicotine concentrations were administered in different portion sizes: 8 mg nicotine in a 1 g portion; 8 mg nicotine in a 0.5 g portion; 16 mg nicotine in a 1 g portion; and 16 mg nicotine in a 2 g portion (composed of two 1 g portions of 8 mg each). Blood plasma samples were taken over a six-hour time period and VAS assessments were performed. For the four snus products, the extracted nicotine doses were 1.56 ±0.95 mg, 1.90±0.82 mg, 3.0 ±1.65 mg, and 3.0 ±1.35 mg, respectively. Nicotine was absorbed more slowly from Nicorette Microtab tablets, but systemic exposure was within the range of the snus products. All products increased "head rush" and reduced craving over the first 30 minutes. The effects were strongest for the portioned snus (i.e., two 1 g portions of 8 mg each), although the effects were not statistically significant from Nicorette Microtab. According to the applicant, the similar nicotine absorption for both 16mg conditions indicates that absorption kinetics were dependent on total nicotine extraction (i.e., dose) rather than mode of administration (i.e., portioned or single dose). Both 16 mg conditions displayed similar pharmacokinetic (e.g., AUC values) and pharmacodynamic effects (e.g., VAS scores) compared to 6 mg Nicorette Microtab sublingual tablets. This study was limited to single dose administration.

SM WS 03: This study examined the in-vivo extraction of cadmium, lead, and TSNAs from four brands of Swedish snus [General Large (1 g), Catch White Licorice Large (1 g), Catch Licorice Mini (0.5 g), and Catch Licorice Dry Mini (0.3 g)] in regular snus users. The study was an open-label, randomized, four-way, single dose study in 32 males. Snus portions were administered once every hour (four administrations/brand) and were kept between the upper lip and the gum for 30 minutes. The received dose of cadmium (Cd), lead (Pb), and TSNAs was calculated by comparing pre- and post-use levels of constituents in used and unused snus products. Systemic exposures to Cd, Pb, and TSNAs were not examined. In this study, the mean±SD extracted amounts of Cd from General Large, Catch White Licorice Large, Catch Licorice Mini, and Catch Licorice Dry Mini were (b) (4), and (b) (4) ng/portion, respectively. The mean extracted amount of Pb was negative for all products and the applicant has not explained this finding, the impact of this to the study as a whole is

unknown. The mean±SD sum of extracted TSNAs from the four brands was calculated as (b) (4) (b) (4), and (b) (4) ng TSNA/portion, respectively.

In summary, the studies focused on nicotine pharmacokinetics and nicotine exposures and found that Swedish snus products were similar to other marketed ST products. None of the submitted studies evaluated exposure-response relationships (i.e., changes in biomarkers and clinical outcomes related to systemic exposures to HPHCs). The health impacts (influence on the disease development and endpoints) of the new tobacco products were not specifically assessed in these sponsored clinical pharmacology studies. Prospectively-designed clinical pharmacology studies that compare systemic toxicant exposures following the use of the proposed Swedish snus products relative to other tobacco products would provide more data to evaluate actual exposure and response differences. However, substantial epidemiological data is submitted by the applicant evaluating health impact of similar Swedish snus products informing anticipated health impact from use of these products.

Use Behavior

ST products are usually chewed, placed in the oral cavity between the cheek and gum, or inhaled or snorted through the nose. The applicant provides a description of data relating to the frequency, amount, duration, and overall use profile of snus products. While the applicant describes general use of the proposed products, the proposed labels do not include a description of "intended use". With traditional ST, topography measures include: self-reported measures of tobacco use such as ST tins used per week, total dips per day, total daily dip duration, and total daily dipping time (time from first to last dip of the day) (Lemmonds et al., 2005). According to the applicant, the most common method of snus use is to place 1-2 grams of product (loose or pouched) in the vestibular area inside the upper lip. Survey data of Swedish snus users suggest that this is the manner of use for 96% of pouched users and 99% of loose snus users, although movement of the product inside the mouth is common (Digard et al., 2009). In a telephone survey of 2,914 Swedish snus users (359 females and 2555 males), pouch snus use was much more common among females (92.8%) than males (42.1%). The survey also indicated that average "loose" snus consumption per day was approximately equal for both genders (29.3 g for men and 29.0 g for women). Similarly, total consumption of portioned/pouched snus was similar for men (32.1 g/day) and women (33.8 g/day). However, men used snus portions for a longer duration (69.6 min vs. 56.1 min for women). These data are broadly similar to values reported in the Norwegian Tobacco report, which found that snus users reported about 9.5 "pinches" of snus per day, with each "pinch" weighing about 2.5 g for a total use of 23.75 g/day.

Snus products are generally placed in the oral cavity but there are some differences in oral placement among users as US studies indicate that American ST users typically place ST between lower lip and gum. Whether the same snus product is placed near upper lip or lower lip, the health impacts from these products are expected to be similar given oral exposures to the product itself. Total snus consumption per day by Swedish users while informative may not be directly transferrable to the US experience.

Acceptability

Receptivity to snus use in Indianapolis, Indiana and Dallas/Fort Worth Texas (two cities with the greatest exposure to the major snus brands) was examined in a telephone and mail survey

conducted in 2011 and 2012 (Biener et al., 2014). More than 5000 adults completed surveys assessing trial, ever use, current use, and reasons for using or quitting snus after the trial. Among male smokers, 29.9% had ever tried snus (95% CI [confidence interval]=22.7-38.1) and 4.2% were current users (CI=1.6-10.7). Among female smokers, 8.5% had tried snus (CI=4.4-15.7) and current use was unknown. Current use was low among former smokers and never smokers. Conventional ST use was a major predictor of any snus use. Those who tried and gave up snus cited curiosity (41.3%) and the fact that it was available at low or no cost (30%). Reasons for not continuing snus use included preferring another form of tobacco (75.1%) and disliking the mouth feel (34.6%). Almost all current snus users indicated that they were trying to cut down on cigarettes, but few (3.9%) were using snus to quit smoking entirely. Low acceptability of snus use has been found elsewhere in the US (Hatsukami et al., 2011; Hatsukami et al., 2013; O'Connor et al., 2011; O'Connor et al., 2014). The low rate of snus adoption suggests that any adverse effects conferred on the population as a whole will be minimal especially given that the proposed snus products have lower NNN, NNK and other HPHC levels compared to other US smokeless tobacco products currently on the market.

Flavors

Of the eight snus products that are the subjects of these PMTAs, one contains mint and the ingredients (b) (4) One product includes (b) (4) (b) (4) is a major chemical component of (b) (4) (World Health Organization, 2002). These ingredients (e.g., (b) (4)) can give the new products a characterizing mint flavor that is distinct from other Swedish Match Snus products described in the published literature and in the submitted studies. Furthermore, the two products (General Mint Portion White Large 0.9 oz. [24g] and General Nordic Mint Portion White Large .38 oz. [10.8g]) may be sweeter than other Swedish Match Snus products because they contain the artificial sweetener (b) (4) (. A recent study (Choi et al., 2012) reported that young adults view new ST products (including snus) favorably because these products are available in flavors.

It is possible that introducing the products with new flavor ingredients may make the products more appealing to consumers. It has been suggested that flavored products have a unique and important role with respect to initiation and maintenance of tobacco-use patterns, particularly among young adults (Kenny et al., 1996;Lisnerski et al., 1991;Villanti et al., 2012). There is also evidence to suggest smokeless tobacco users typically initiate with a flavored product and that brand switching from a non-flavored to flavored product can occur (Hatsukami et al., 2007; Oliver et al., 2013b).

Access and utilization of ST remains a public health issue among American middle and high school students, with more than 25 different types of smokeless tobacco (ST) available in the United States (Bromberg et al., 2012). Analyzing data from Legacy's Young Adult Cohort Study, a nationally representative sample collected in January 2012, Villanti et al. (Villanti et al., 2013) sought to determine the prevalence of flavored tobacco use, dual use of flavored and menthol tobacco products, and sociodemographic predictors of flavored tobacco product use in young adults aged 18-34 years (n=4196). Overall, 18.5% of tobacco users report using flavored products, and dual use of menthol and flavored product use ranged from 1% (nicotine products) to 72% (chewing tobacco products). In a multivariable model controlling for menthol use, younger adults were more likely to use flavored tobacco products (OR=1.89,

95% CI=1.14, 3.11), and those with a high school education had decreased use of flavored products (OR=0.56; 95% CI=0.32, 0.97). The authors concluded that individuals most likely to use flavored products are also those most at risk of developing established tobacco-use patterns that may persist through their lifetime.

The proposed products are reported to have flavors such as mint, wintergreen, or tobacco character with citrus. While flavored smokeless tobacco products are a potential concern of youth initiation, these proposed flavors are consistent with traditionally available ST flavors and are not novel flavors that likely increase appeal to youth. Overall uptake of snus products including among youth in the US is low even with such flavors available in currently marketed products and unexpected to dramatically increase with the marketing of the PMTA products at this time. Postmarket data describing sales of these proposed snus products may be informative in better understanding appeal and use of newly marketed flavored products.

6. Health Impact (Medical/Epidemiology/Statistics)

Health Risks of Swedish Snus

The Applicant cites data spanning several decades, derived from numerous cohort, case-control, and cross-sectional studies, to describe the impact of snus use on health risks in Scandinavian countries. In particular, the Applicant discusses the health risks of Swedish snus compared with cigarette smokers and nonusers, and the health risks of dual use and switching from cigarette smoking to Swedish snus use compared with quitting completely and nicotine replacement therapy (NRT) use.

Comparison to Smoking and Nonuse

There is no evidence that snus causes lung cancer and COPD, which together are estimated to account for over 50% of smoking-attributable mortality in the US (CDC, 2008). This alone suggests a difference between cigarette smoking and snus in overall risks to health. Use of snus is not associated with significant 'second-hand' exposure which, in this respect, decreases risk for both users and nonusers. With regards to the risk of oral cancer, the literature[12] indicates that the risk from snus is significantly less than the risk from smoking cigarettes. However, the literature presented does not support use of snus as having no effect on dental health. Gingival recession was noted at increased frequency in several studies, even with younger subjects exposed for shorter periods of time. Snuff-induced lesions (SIL) were found to be almost universal among snuff users in Scandinavia. The long-term health implications of these lesions are unknown. The incidence of oral cancer in Sweden is low and the use of oral snuff is high indicating that malignant transformation of the lesions is uncommon. The prevalence of SIL is lower in the United States but it is not clear whether this is related to the product, patterns of use, differences in diet or dental care, or exposure to other agents. In general, the published literature presented confirms the health risks of snus for the individual user are less, or at least no greater, than those associated with cigarette smoking.

[12] Note that the volume of published literature addressing the risk of oral cancer with snus use is much lower than that for the risk of oral cancer associated with cigarette smoking.

While the available evidence suggests that there are likely to be differences in health risks between snus and cigarettes for some endpoints, the magnitude of these differences appears to vary considerably by endpoint. For example, the available evidence suggests that risks to the fetus due to snus use and cigarette smoking during pregnancy may not be very different. The applicant notes that pregnant or lactating women should not use products containing nicotine, including Swedish snus. Maternal snus use has been reported to be associated with increased rates of stillbirth. The fetal and neonatal effects related to cigarette smoking are well known. NRTs are considered a "safer alternative" but use during pregnancy is discouraged. In addition to adverse pregnancy outcomes, multiple studies have reported associations between Swedish snus use and increased risk of fatal cardiovascular events, pancreatic cancer, diabetes, and all-cause mortality. Finally, the applicant does not address the potentially negative effect of nicotine on the developing brain in youth, however, this is a universal concern of all nicotine containing products. Given that the nitrosamines in snus are still elevated and that there are suggestive associations between snus and a number of diseases, it is unlikely that switching to snus is comparable to quitting tobacco completely with or without using NRTs.

Thus, while the proposed snus products may be a less toxic product compared to cigarettes, the proposed snus products are not risk-free. Nonusers never starting tobacco use and current users quitting tobacco completely are still the optimal outcomes.

Impact on Cessation
Use behavior is described in the above section. Understanding use patterns is important because using the product frequently, using larger portions, or increasing deposition time in the mouth are behaviors known to affect nicotine exposure (Hatsukami et al., 1988; Hatsukami et al., 1991; Hatsukami et al., 2004). Snus appears to increase cigarette smoking cessation rates in some studies (Rutqvist 2012) but the Swedish population appears to be more homogenous, have a higher socioeconomic status, and greater access to healthcare services including dental care relative to individuals in the US. Swedish Match conducted two clinical trials designed to examine if Swedish snus use could decrease smoking. The subjects recruited for these studies were motivated to quit smoking and the product was provided free of charge; however, the success rate for smoking cessation was low. Of note, the placebo group used a snus product with no nicotine, making the placebo an "active control". Neither study demonstrated that current cigarette smokers are likely to use snus as a smoking cessation aid. Thus, although snus was not associated with certain significant health risks for the users, the studies did not provide evidence that US smokers will use snus to reduce or replace cigarettes. It is unlikely that we can expect to see a large migration of cigarette smokers to switch completely to use of these snus products and decrease individual risk, however, some switching behavior may occur.

SM 07 01: This was a randomized, placebo-controlled, double blind study in Serbia designed to examine whether *ad libitum* snus use could affect smoking relative to placebo. Subjects (n=319) could choose between two pouch sizes (0.5 and 1.0 g) and two flavors of snus. Placebo pouches were identical to the "active" pouches in size and appearance, including flavoring, pH, and other sensory characteristics. Subjects were young adults aged 20-65 who had smoked daily for more than one year and who were motivated to quit. This study involved a smoking reduction stage (weeks 1 to 24 post-randomization) and a smoking cessation stage

(weeks 25 to 48). The primary outcome measure was smoking reduction at week 24. At the week 24 visit, the snus and placebo groups did not differ in the proportion of subjects who achieved the protocol definition of a >50% smoking reduction. However, a higher proportion of participants in the snus group (9.5% vs. 2.5%, $p<0.01$) reported >75% reduction in average number of smoked cigarettes per day compared to baseline, particularly during the first six months of the trial. Fagerström dependence scores were similar in both groups. ST is not available in Serbia; therefore, experience with ST was limited in this population. Because participants were motivated to quit and counseling was offered during the study, the results may not be applicable to the general snus user population; however, the data suggest that some individuals may switch from smoking combusted cigarettes to snus.

SM 08 01: This study was a multi-center, randomized, double-blind, placebo controlled trial in the US comparing snus vs. placebo to examine whether snus use increases quit rates among cigarette smokers aged 25-65 (n=152) who wished to stop smoking. Snus in 0.5 or 1.0 g sachets or matching placebo (without tobacco or nicotine) was used *ad libitum*. The study consisted of four phases: pre-randomization screening (up to two weeks), a study product test period (four weeks), an intervention phase (12 weeks), and a follow-up phase (12 weeks). The primary outcome measure was complete abstention during weeks 6 to 28. This was a smoking cessation trial with participants who were motivated to quit, and study counseling was offered as part of study participation. During the test period, participants were instructed to use the study product when they had an urge to smoke, without requiring complete abstention from cigarettes; instructions were the same during the intervention phase, but participants were encouraged to completely stop smoking. Biologically verified (e.g., expired air carbon monoxide (CO) $\leq$ 8 ppm), continuous abstinence rates during weeks 6 to -28 were 4.0% for snus and 1.6% for placebo. Minnesota Withdrawal Scale scores for craving were not statistically significant between the groups. Nearly two-thirds of the participants had tried other pharmaceutical smoking cessation aids. Given US and Swedish population differences, the results may not be generalizable to the US population.

In the two clinical trials conducted by SMNA, the studies were performed in generally healthy subjects. Reported adverse events (AEs) were generally mild and non-serious and were not unexpected reactions to these products; most reported AEs were either related or possibly related to the study product. In the US study, 616 AEs were reported by 200 subjects (350 in the snus group and 266 in the placebo group). No deaths occurred. Overall, the most common AEs reported were gastrointestinal disorders (45%; gingival pain, dyspepsia, nausea, toothache, diarrhea, dry mouth, gingivitis, salivary hypersecretion, abdominal pain, and sensitivity of teeth), infections and infestations (34%; viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, pharyngitis, bronchitis, otitis media, and viral infection), nervous system disorders (20%; headache, dizziness, and dysgeusia), respiratory, thoracic, and mediastinal disorders (17%; cough, hiccups, oropharyngeal pain, nasal congestion, and rhinorrhea), musculoskeletal and connective tissue disorders (13%; back pain, arthralgia, and myalgia), injury, poisoning, and procedural complications (10%; skin laceration, back injury, and joint sprain), psychiatric disorders (10%; insomnia, anxiety, and mood alterations), general disorders and administration site conditions (6%; irritability), and skin and subcutaneous tissue disorders (6%; acne). The most frequently reported AEs were gingival pain, headache, dyspepsia, and nausea.

Six subjects discontinued study participation due to AEs (5 from snus group, 1 from placebo group). The AEs leading to discontinuation from the snus group were mild gingival pain (definitely product related), severe vaginal bleeding (unlikely related), glossitis and pharyngitis (probably related), pregnancy (not related), and dyspepsia, diarrhea, and acne vulgaris (unlikely related). A total of five serious AEs were reported in the study, however, none were reported to be related to the study product.

Bioresearch Monitoring (BIMO) Inspection
In March and April 2015, FDA conducted inspections at clinical study sites (Indianapolis, IN and Serbia), manufacturing sites (Sweden) and an SMNA laboratory facility (Sweden). The clinical site inspections included the review of paper and electronic source data, electronic case report forms, and administrative files. Documents were reviewed for issues such as: protocol adherence, randomization, informed consent, eligibility, investigational product dispensing, study endpoints, adverse events and subject final status. Overall, the inspection teams report that while there were some missing and inconsistent data, there was no overt fraud reported. The limited missing and inconsistent data are not considered substantive to prevent product authorization.

During one of the manufacturing inspection visits, the inspection team noted that 256 consumer complaints were received by SMNA during the period from January 2013 to April 2015, and only two of these were health-related complaints (burning of mouth/throat and esophagus).

7. Population Health (Epidemiology/Social Science/Behavioral Pharmacology)

Initiation
In Sweden and Norway, snus initiation is more prevalent among former cigarette smokers than among nonusers. Generally, in these populations, tobacco initiation is gender-dependent; males are more likely to initiate snus and females are more likely to initiate cigarette smoking. Adolescent males initiate snus use at a median age of 15 while females who used snus usually started by age 18. In the US, tobacco users (male and female) are more likely to initiate with cigarettes, but no specific data compare the likelihood of initiation with snus versus cigarettes.

In 2014 according to the National Survey on Drug Use and Health, 3.3% of the US population aged 12 or older used ST in the past month (SAMHSA, 2015). National estimates of ST use have been reported by a variety of sources and provide relatively consistent results. For example, across several representative surveys, ST use rates were reported as follows: National Adult Tobacco Survey 3.9%; National Health and Nutrition Examination Survey, 2.3%; Tobacco Use Supplement, Current Population Survey, 1.6%; and National Health Information Survey, 2.8% (Agaku et al., 2015). More specifically, overall prevalence of current daily snus use in the US adult population was reported to be 1.8% from National Adult Tobacco Survey data (CDC, 2014). These data indicate that the adoption and initiation of ST product use in the US is relatively low and therefore, overall initiation of the proposed snus products would be expected to be quite low given Swedish snus are a low percentage of the US ST market.

SMNA conducted a US consumer perception study ((b) (4)) in February 2015 and submitted findings (b) (4) on March 6, 2015 (b) (4) (b) (4)

Due to methodological and data reporting limitations, the data from this study do not offer firm conclusions about consumer perceptions evaluated. However, studies from the US literature indicate low acceptability of snus use has been found, as discussed earlier, and it does not appear there would be significant shift in these snus product use by nonusers or current tobacco users; although current ST users may be more inclined to consider these snus products use. Other General brand snus products are currently available on the market in round and square cans with disposal compartment.

Transition from Snus to Smoking

According to the applicant, there is little evidence that snus use leads to future cigarette smoking and that longitudinal and cross-sectional studies conducted on snus use in Sweden and other Scandinavian countries suggest that snus use is associated with a reduced risk of becoming (or continuing to be) a regular smoker. These longitudinal studies suggest that users will transition from cigarettes to snus, rather than switching from snus to cigarettes. The applicant summarizes studies examining the transitioning of snus users to combusted cigarettes.

Researchers (Tam et al., 2015) conducted a review of published estimates of the proportion of US adults and adolescents transitioning between ST and cigarettes. Six studies of US populations were published since 2000 with longitudinal data on some or all of the transitions between ST and cigarette use. There was considerable heterogeneity across studies in design and tobacco use definitions. Despite these differences, the existing data fairly consistently indicated that switching behaviors from exclusive smoking to exclusive ST use are limited (adults: 0-1.4%, adolescents: 0.8-3.8%) but switching from ST use to smoking may be more common (adults: 0.9-26.6%, adolescents: 16.6-25.5%). Among adults, exclusive cigarette smoking was generally stable and consistent (79.7-87.6%) during follow-up across studies but less stable in adolescents (46.8-78.7%). Exclusive ST use was less stable than exclusive cigarette smoking over time (adults: 59.4-76.6%, adolescents: 26.2-44.8%). A potential limitation of this study is that the data were collected more than a decade ago. Available US data do not address snus specifically and are inconclusive regarding whether prior ST use is associated with or leads to subsequent cigarette smoking in adults. Researchers (Meier et al., 2015) also examined the use of various nicotine-containing products on a tobacco-free college campus and whether the first product tried predicts subsequent tobacco use. The authors

concluded that uptake of emerging tobacco products (including snus) was poor, and does not appear to lead to use of cigarettes and traditional ST products.

In sum, existing data indicate that switching behaviors from exclusive smoking to exclusive smokeless tobacco use are limited. Findings from Tam et al. indicate that in the US, switching from ST use to smoking is more common than switching from smoking to ST use. Nevertheless, limited data suggest overall that the adoption of snus use in the US is low and therefore, unlikely to lead to use of other tobacco products. Thus, it is anticipated that the marketing of these products, as described in the PMTAs, is unlikely to lead to significant increases in initiation of tobacco product use.

Likelihood of Cessation

Cessation is discussed in the Health Impact section above. In addition, the SMNA MRTP Warning Label Evaluation study presented data on the likelihood of quitting or reducing use of different tobacco products. More than 13,000 subjects were enrolled and six warning labels were tested in this online experimental study. Due to study limitations, it is difficult to draw concrete conclusions and implications from the data. Nevertheless, one pattern evident across the different harm measures was that a portion of participants (about 25%) reported not knowing the risks of snus or snus use risks compared to those of other tobacco products. Also, 18% of tobacco users ages 18 to 24 believed that there was little or no risk from using snus. Risk perceptions are often related to use behavior; however, it is unclear from the data presented how risk perceptions will influence use behavior. One caveat is that studies have found that perceptions of relative harm of snus depend on how the question is framed. Preliminary data from the Population Assessment of Tobacco and Health (PATH) Study indicate that nearly 40% of adults and 43% of youth who are current tobacco users use more than one tobacco product. The significant proportion of tobacco users who use multiple products was not accounted for in the MRTP Warning Label Evaluation study. Product labels with appropriate warning labels and educational campaigns to increase awareness of various tobacco product health impacts are important tools to utilize in increasing likelihood of cessation of tobacco products. These proposed product labels do include mandated warnings.

Dual Use

The availability of snus may result in dual use. While relatively uncommon in Sweden, dual use may be more likely in the US. SMNA provided a summary of available scientific evidence addressing snus use and behavior patterns; however, most studies were conducted in Sweden and other Scandinavian countries. Limited data related to US snus use are available, and most relevant studies include the broader category of ST products and are not specific for snus products.

The 2014 NYTS reports that 24.6% of high school students report using tobacco products and more specifically, 1.9% use snus products (prevalence of middle school student snus use is 0.5%). Given the historically low and stable rates of ST use in the US, there is no compelling reason to believe the marketing these products, as described in the PMTAs, that concomitant use of snus and cigarettes will exceed concomitant use of traditional ST products and cigarettes. However, it is possible that a market authorization order may increase dual use due to the perceived favorable profile associated with an “FDA authorization” marketing order which could lead to benefit if tobacco users who use multiple tobacco products then transition

to exclusive use of less toxic tobacco products and then ultimately quit all tobacco products. Conversely, there could be harm if the perceived favorable profile discourages transition to exclusive use of less toxic tobacco products and cessation.

According to the applicant, the Swedish National Tobacco Survey indicates that the prevalence of daily snus and cigarette smoking (i.e., dual use) has remained stable at 2% since 2004. Norway and Sweden have reported roughly similar results with the percentage of dual users ranging from 2-10%. In the MONICA cohort study (representative of Northern Sweden from 1986-1999), dual use was reported to be around 2-5% (Rodu et al., 2002; Stegmayr et al., 2005). In the Norway Tobacco Statistics survey, 7% of individuals reported dual use of snus and cigarettes. In a study of Norwegian youth, dual use was reported to be10%. Overall, the applicant concluded that males and individuals with low educational background were more likely to be dual users of cigarettes and snus. The applicant also notes that data suggests slightly lower overall tobacco use among dual tobacco users.

Concomitant use of two tobacco products may increase the risk of adverse health consequences relative to use of a single tobacco product. Few representative US national data sets on the prevalence of concomitant smoking and ST use exist. The few data sets available suggest that 25% or more of current adult ST users also smoke cigarettes, whereas 2.5-5% of adult smokers also use ST (CDC, 1993; CDC, 2000; SAMHSA, 2001). Using data from the Working Well Trial, a large cancer prevention study that tested the effectiveness of worksite health promotion interventions in reducing cancer risk behavior, researchers (Wetter et al., 2002) examined correlates of concomitant smoking and ST use. The researchers found that the prevalence of concomitant smoking and ST use exists among males (5%) but is nonexistent among females. The characteristics of dual users were relatively distinct from those of exclusive smokers and exclusive ST users (e.g., more likely to live with a smoker, younger, less educated), and indicators of nicotine dependence predicted tobacco cessation for both smokers and ST users but were unrelated to tobacco cessation for dual users. Swedish studies indicate low prevalence of dual use is possible. While this is not the situation in the US, further understanding of factors leading to high rates of multiple tobacco use in the US is important in being able to decrease rates of multiple tobacco use in US with the goal of decreasing risk of adverse health consequences. The most effective way to decrease morbidity and mortality from tobacco use remains to never start or to quit tobacco product use as early in life as possible.

Likelihood Product Used as Designed

The proposed label does not include statement of “intended use”. In particular, as noted in section 2.4, differences in the manner of use between traditional US ST products and Swedish snus include the placement of the product in the mouth and expectoration. Given these differences and the lack of instructions, it is likely that individuals in the US will use the products which are the subject of these applications in a manner that may be different than users of snus in Sweden. It is unknown if and how these different use patterns would impact the health effects associated with these products; however, while discrepancies may be possible, overall, similar health impacts are expected from these snus products given oral exposure whether it is placed near upper lip versus lower lip.

Population Modeling

The applicant describes the implementation of a Dynamic Population Model to track population-based tobacco use and harm and presents results from analyses conducted with the model to assess the hypothetical effects of cigarette and snus use in the US population in a variety of scenarios. (b) (4)

The model and analyses provide for a range of tobacco use behaviors including initiation and cessation of snus and cigarettes, switching between the products, and, to some extent, dual use. In general, it is difficult to determine from these population model results what effect, if any, the marketing and sale of the proposed PMTA products would have on tobacco product use and health effects in the US (b) (4)

In general, it would have been useful if the applicant had provided a clearer description of the model and its use, including detailed explanations of how all data inputs were derived from the original data sources and a complete listing of all tobacco use behaviors that were used in the model along with their transition probabilities. It also would have been helpful if the applicant had provided additional information to aid in the interpretation of model analyses and results, including cigarette and snus use prevalence estimates for each model scenario, in order to facilitate an evaluation of the plausibility and relevance of these scenarios for the U.S. population. However, given the particular situation that these PMTAs offer epidemiologic data on Swedish snus use and health impact ("The Swedish Experience"), as well as experience from sales of similar Swedish snus products in the US, CTP reviewers can develop a reasonable understanding of potential impact from marketing of the proposed products as discussed in their reviews.

III. Tobacco Product Science Advisory Committee Meeting

On April 9-10, 2015, the Tobacco Product Scientific Advisory Committee (TPSAC) met to discuss MRTPAs submitted by SMNA for 10 General brand snus tobacco products, of which eight were submitted for PMTA consideration. SMNA submitted MRTPAs seeking risk modification orders under Section 911(g)(1) of the FD&C Act specifically requesting certain modifications to the health warnings currently required by the Comprehensive Smokeless Tobacco Health Education Act for smokeless tobacco products:

- Remove "WARNING: This product can cause gum disease and tooth loss."
- Remove "WARNING: This product can cause mouth cancer."
- Revise "WARNING: This product is not a safe alternative to cigarettes" to "WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes."

The FDA identified several topics for discussion for which TPSAC recommendations were sought with respect to the relative health risks to individual users of the snus tobacco products that are subject to the proposed MRTPAs:

1. The relative health risks to individual users of the snus tobacco products that are subject to the proposed MRTPAs, particularly with respect to gum disease, tooth loss, and oral cancer, and a comparison to risks of cigarette smoking

2. The behavioral aspects of snus use, particularly as they relate to:
    - The likelihood that existing users of tobacco products who would otherwise stop using those products will switch to the snus tobacco products that are subject to the proposed MRTPAs
    - The likelihood that persons who do not use tobacco products will start using the snus tobacco products that are subject to the proposed MRTPAs
3. Comprehension of the modified risk information and perception of the product in the context of total health
4. Postmarket surveillance and studies

As per section 911(f)(1), any MRTPAs must be referred to TPSAC for discussion. In the case of PMTAs, the FDA or the applicant may refer applications to TPSAC for discussion but no requirement exists [section 910 (b)(2)(A&B)]. Many of the issues for TPSAC discussion regarding the MRTPAs for the General brand snus products overlap with potential issues related to premarket authorization consideration, such as considerations of health impact from these snus products. FDA determined that there were no issues specific to the PMTAs that would require a second TPSAC meeting to discuss these same products.

TPSAC members generally agreed that Swedish snus products when used exclusively confer lower health risks than cigarettes in terms of respiratory and cardiovascular diseases; however, for other disease end points, the situation is not as definitive that there is lower health risks as compared to cigarette use.

IV. Labeling (DPAL/Social Science)

Labeling for each of the eight snus products without any proposed claims (as compared to those submitted for the respective MRTPAs) were evaluated by reviewers from Social Science Branch and Division of Product Advertising and Labeling (DPAL, Office of Compliance and Enforcement). The MRTP Warning Label Evaluation study included questions about warning claim believability and intention to use based on warning claim; these data have limited applicability to the PMTAs as they focused on the warning label and not the labeling as a whole. This was primarily a test of modified warning labels. While no studies were conducted to evaluate consumer perceptions of the entire labeling, the FDA reviewers concluded that the labeling does not appear to be false or misleading.

Of note, the labeling for General Classic Blend Portion White Large – 12ct (PM0000013) and General Nordic Mint Portion White Large -12 ct (PM0000015) indicates that a disposal compartment is included in the packaging for these two products in particular. The February 2015 (b) (4) Study as discussed earlier in this review (b) (4) Due to methodology and design limitations of the study, no firm conclusions can be drawn from the study. However, other General brand snus products are currently available with disposal compartment. Thus, this feature does not raise new questions that these products may have increased appeal for users or nonusers.

Instructions for Use

Instructions for use are not included with the actual products. The applicant does state in the PMTAs that a pouched snus or a pinch of loose snus is typically placed between the gum and the upper lip at the front of the oral cavity; furthermore, the pouch may be pre-wet on the tongue before being placed in the mouth and is most often worked on orally during use. The applicant states that none of the proposed products "require specific instructions for use or storage to get the proposed reduction in risk… or on how to avoid using the products in a way that could reduce or eliminate the potential benefit or increase the risk of use the products." The applicant refers to the population-based telephone survey of 2,914 randomly selected respondents in Sweden investigating snus use patterns and behaviors (Digard et al., 2009). It found that the typical usage time for one portion snus pouch is 60-70 minutes, and the total usage time is 10-12.5 hours per day. The study further found that the typical usage time is approximately the same among users of loose snus products and users of pouched snus products.

ST products including very similar products to these proposed products have been marketed for many years and the reviewers are unaware of reports of serious adverse experiences from unexpected uses of snus products. Nonetheless, it is recommended that with marketing authorization that the applicant provides with the proposed products any appropriate instructions for use.

V. Conclusions and Recommendation

Section 910(c)(4) of the FD&C Act specifies that FDA deny a PMTA where it finds that, among other things, a new tobacco product is not "appropriate for the protection of public health." One of FDA's goals is to decrease morbidity and mortality from tobacco use and to change the status quo so that nearly half a million Americans no longer die every year from tobacco use. Therefore, the broad overall objective of authorizing new tobacco products to be marketed through the PMTA process is to reduce the morbidity and mortality from tobacco use. In evaluating how marketing authorization for these eight Swedish snus products impact the current market, FDA considered it is possible that a PMTA order may increase use and initiation of snus due to its perceived favorable profile. Given this possibility, the products' impact on health, impact on smoking cessation, impact on snus initiation and uptake, and impact on current ST users must be considered.

Impact on health: SMNA provided a comprehensive review of published literature on the health effects related to Swedish Match snus use and specific disease states. In general, the literature presented confirms that individual snus user health risks are lower, or at least no greater, than those associated with cigarette smoking. The applications provide evidence that use of the products which are the subject of these applications is not likely to be associated with lung cancer, COPD, or chronic respiratory disease. Data are insufficient to support a lack of association between product use of these products and the other disease endpoints specified in the applications (e.g., stomach, pancreatic cancers, CVD, stroke, all-cause mortality). Use of these products is not associated with significant "second-hand" exposure, which decreases disease risks for the general population.

With regard to oral cancer risk, the scientific evidence provided in this application suggests that the *risk from these proposed Swedish snus products* is lower than the risk from smoking cigarettes or use of other smokeless tobacco products. However, the literature presented indicates that Swedish snus use does have a negative effect on dental health. Gingival recession was noted at increased frequency in several studies, even in younger subjects exposed for shorter periods of time. SIL were found to be almost universal among snuff users in Scandinavia. The long-term health implications of these lesions are unknown. Of note, the lesions typically reverse when the user quits using ST. At least one long-term study involving 1,115 individuals with SIL followed for > 25 years (Roosaar et al., 2006) found no cases of oral cancer at the site of snuff placement. The incidence of oral cancer in Sweden is low and the use of oral snuff is high, indicating that malignant transformation of the lesions is uncommon. But, overall the evidence supports that the use of the products which are the subject of these applications has a lower risk of disease for the individual user than the use of other smokeless tobacco products.

Where we may see the greatest impact is among current users of ST products. Given that (1) the full characterization, manufacturing, processing, and labeling of the eight snus products are considered to be acceptable and (2) their toxicological risk is considered to be significantly lower than that of similar products on the market, for current smokeless tobacco users it is likely appropriate to allow access to these tobacco products. Otherwise, available options would be limited to the existing grandfathered products and similar products.

Impact on smoking cessation: SM**NA** provided data from two clinical studies, one of which was conducted in the United States. Both studies were small and subject discontinuation rates were high (~40%). Although study subjects were motivated to quit smoking and the Swedish snus test products were provided free of charge, the success rate for smoking cessation was low. Stated alternatively, neither study demonstrated that current cigarette smokers are likely to use snus as a smoking cessation aid. The studies' analyses of health effects, including AEs and other information related to product use, showed no significant unexpected concerns for individual users.

In contrast, considerable data in the Scandinavian literature support the use of snus to facilitate smoking cessation; this would clearly benefit the individual user as well as the population as a whole due to reduced tobacco smoke exposure. Swedish longitudinal studies indicate that snus use is associated with a reduced risk of becoming or continuing to be a regular cigarette user.

Additionally, studies of Swedish adolescents show that snus use is neither a precursor to exclusive cigarette smoking nor a predictor of future cigarette smoking. Similar data for the US is unavailable. But, given the evidence as described in the PMTAs, it is reasonable to conclude that the marketing of these products which are the subject of these applications will not significantly reduce smoking but some smokers may switch to use of these products and quit smoking.

Impact on snus initiation and uptake: The applicant does not provide U.S. product use data demonstrating that the proposed Swedish Match snus products will be used similarly to traditional American ST products; however, since snus and traditional ST products are broadly similar, use behaviors are not expected to differ. Snus products are a small minority of tobacco products sold in the US and epidemiological data indicate that use rates remain relatively low; thus, there is no compelling reason to consider the marketing of these products, as described in the PMTAs, would result in uptake and initiation of these proposed products will exceed that of traditional ST products. Furthermore, the marketing of snus (including very similar General brand snus) does not appear to have increased overall ST use rates. It is unlikely that a significant portion of US cigarette smokers will switch exclusively to these Swedish Match snus products, given cultural and population differences as discussed in numerous FDA scientific discipline reviews evaluating these PMTAs. It is also expected that uptake of these products by nonusers is also likely to be very low, given that other very similar Swedish snus products currently exist and no increase in these product use has been reported.

In general, the availability of a product with abuse potential might lead to a number of consumers who sustain their addiction to nicotine or individuals who initiate use of the new product; therefore, it is important to understand how different characteristics such as nicotine dose delivered, nicotine delivery pharmacokinetics, and nonpharmacologic factors such as taste and other sensory aspects affect a product's abuse liability (Carter et al., 2009; Fant et al., 1999; Kotlyar et al., 2007). The proposed Swedish snus tobacco products have nicotine content that are considered to have abuse potential. However, several similar Swedish Match snus products are currently marketed in the US, and widespread use of snus has not been reported. A clinical study conducted in five US locations showed no evidence of smokers beginning to use snus along with their cigarettes (i.e., dual use). Several studies have reported low acceptability of snus in the US (Biener et al., 2014; Hatsukami et al., 2011; Hatsukami et al., 2013; O'Connor et al., 2011; O'Connor et al., 2014). Current low snus adoption rates suggest that, any detrimental effects to the US population from marketing these products are likely to be minimal. Overall, it is anticipated that unless use patterns change in unfavorable ways (increased youth initiation, delayed/decreased cessation), the products which are the subject of these applications may decrease the individual risk among current ST user due to their favorable toxicological profile (see below) without posing increased risk to the general population.

Top-line reasons for granting authorization for the proposed eight products include the following:

- Produced with a voluntary, proprietary manufacturing process that distinguishes Swedish snus from other types of ST, including snus-like products sold in the US market. The proprietary standard for Swedish snus products was developed to ensure product quality.

The principal components of this standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a "best before" date. The constituent standards set maximum levels that must not be exceeded for selected constituents in the finished products.

The proposed products have significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market. Since NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers. Assuming that the only users of these products are persons who would have used other ST products currently on the US market, individuals using these products with lower NNN levels could decrease their excess cancer risk by 90% compared use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share:15%), 38% compared to use of US-style snus, and 92% compared to use of dry snuff.

- Levels of other HPHCs (including As, Cd, acetaldehyde, crotonaldehyde, formaldehyde, and BaP) are similar to or lower than levels of ST products currently on the US market. Certain HPHCs (such as acetaldehyde, cadmium, acrolein, and nickel) have been identified as constituents of more toxic concern in the smoke of combusted products as compared to smokeless products.

- When used exclusively instead of other US market smokeless tobacco products or cigarettes, offer potential for reductions in oral cancer.

- When used exclusively instead of cigarettes, offer lower risk of developing respiratory diseases (i.e., COPD, emphysema, chronic bronchitis) and certain cancers (such as oral, esophageal, and lung).

- It is anticipated that the marketing of the proposed products, as described in the PMTAs, there is a low likelihood of nonuser uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

The most effective way to decrease morbidity and mortality from tobacco use remains to never start or to quit tobacco product use as early in life as possible. However, given the reasons described above, **authorization of these products is recommended** so that current ST product users who chose to continue using tobacco products will have additional options for less toxic smokeless tobacco products, thereby potentially decreasing the negative health impact from tobacco product use.

Environmental Decision

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on October 8, 2015. The FONSI was supported by an environmental assessment prepared by FDA on October 8, 2015.

Required Postmarketing Reports

1. **Serious and Unexpected Adverse Experience Reporting**

- Report to the FDA all serious and unexpected adverse experiences associated with the tobacco product that have been reported to you **within 15 calendar days** after the report is received by you. These experiences may become known to you through a response to a customer complain, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure reported to you; or identified in the literature/media.

2. **Manufacturing Deviations**

- Promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. For products that have been distributed, if there is a potential for that deviation to impact public health, promptly identify and report to your regional FDA Office of Regulatory Affairs.

3. **Periodic Reporting**

On an annual basis, beginning October 2016, provide the following postmarketing reports:

- A cover letter listing the PMTA submission tracking number, tobacco product name(s), company name, date of report, reporting period, and worldwide marketing authorization status.
- A summary of how the tobacco product continues to be appropriate for the protection of the public health.
- If you have not already submitted specimens of all final printed labeling (actual labeling distributed with the product) including labels, insert/onserts, instructions and other accompanying information or materials for this product as a result of this authorization, include the labeling in your first annual report. Also include descriptions of all labeling changes.
- A description of all changes made to the manufacturing, facilities, or controls during the reporting period, including:
    i. A comparison of each change to what was described in the PMTA
    ii. The rationale for making each change
    iii. A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of the tobacco product;
    iv. The basis for concluding that each change did not result in any modification to the final product
- A summary of all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution and indicate a deviation that may affect the characteristics of the final product.
- An inventory of ongoing and completed studies about the tobacco product conducted by, or on behalf of, the applicant.

- A summary of reports on scientific investigations and full articles from literature about the tobacco product and significant findings from publications not previously reported. Any new scientific data (published or otherwise) should also be reported on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults.
- A list of each, and a summary analysis of all, adverse experiences associated with the tobacco product that have been reported to the applicant, accompanied by a statement of any changes to the reference risk information and a summary of important risks, including the nature, frequency, and potential risk factors.
- A summary of sales and distribution of the tobacco product: Total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold (e.g. convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops);
- Data on current product users. Data should be collected about new users, current users, those who have switched tobacco products, and multiple product users. The results should be broken down by key demographic variables including age, gender, and race/ethnicity. Also, any change in the intended target market for the product should be reported. The data described above may include sales data and postmarketing analysis.
- Full-color copies of all advertising for the tobacco product that has not been previously submitted, along with the original date the materials were first disseminated and the date when their dissemination was completely terminated.

Recommended Action

Instructions for use are not included for the proposed products. We recommend that you add consumer instructions for product use and disposal.

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APPENDICES
Full Characterization of Products

1.1. Appendix A

The following information is applicable to PM0000010, General Loose:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/g		
Tobacco (b) (4)	Ingredient	mg/g		
Tobacco (b) (4)	Ingredient	mg/g		
(b) (4)	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[13]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		

13 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to (b) (4).

Performance Criteria

Phase	Test	Method[14]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			

14 QEMS: Swedish Match's proprietary Quality and Environmental Management System

TPL Review for: PM0000010-PM0000017

1.2. Appendix B

The following information is applicable to PM0000011, General Dry Mint Portion Original Mint:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[15]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
Pouch Paper Wicking[17]		
Pouch Paper Caliper (µm)		

15 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4).
16 The range limits for the portion mass in MR0000021 are what the applicant defines as acceptance criteria. FDA's definition for range limits matches the applicant's definition for acceptance criteria.
17 In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[18]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			

18 QEMS: Swedish Match's proprietary Quality and Environmental Management System

1.3.Appendix C

The following information is applicable to PM0000012, General Portion Original Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[19]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
Pouch Paper Wicking[20]		
Pouch Paper Caliper (µm)		

19 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4).

20 In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[21]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			

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1.4. Appendix D

The following information is applicable to PM0000013, General Classic Blend Portion White Large – 12 ct:

Chemistry Product Specifications

	Category	Unit of Measure	Target	Range
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[22]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
Pouch Paper Wicking[23]		
Pouch Paper Caliper (µm)		

22 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4)

23 In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[24]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

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1.5. Appendix E

The following information is applicable to PM0000014, General Mint Portion White Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[25]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
Pouch Paper Wicking[26]		
Pouch Paper Caliper (µm)		

25 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom (b) (4).

26 In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[27]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

27 QEMS: Swedish Match's proprietary Quality and Environmental Management System

TPL Review for: PM0000010-PM0000017

1.6. Appendix F

The following information is applicable to PM0000015, General Nordic Mint Portion White Large – 12 ct:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[28]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
Pouch Paper Wicking[29]		
Pouch Paper Caliper (µm)		

28 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom (b) (4).

29 In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[30]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

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1.7.Appendix G

The following information is applicable to PM0000016, General Portion White Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[31]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
Pouch Paper Wicking[32]		
Pouch Paper Caliper (µm)		

31 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom (b) (4)

32 In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[33]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

33 QEMS: Swedish Match's proprietary Quality and Environmental Management System

1.8. Appendix H

The following information is applicable to PM0000017, General Wintergreen Portion White Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[34]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
Pouch Paper Wicking[35]		
Pouch Paper Caliper (µm)		

34 The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4)

35 In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[36]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

36 QEMS: Swedish Match's proprietary Quality and Environmental Management System

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF TIMOTHY B. PHILLIPS

I, Timothy B. Phillips, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. I am the General Counsel of the American Cancer Society Cancer Action Network ("ACS CAN").

2. The information set forth in this affidavit is based on my personal knowledge.

3. Created in 2001, ACS CAN is the nonpartisan affiliate of the American Cancer Society, Inc. and is incorporated separately under section 501(c)(4) of the Internal Revenue Code. ACS CAN is a nonprofit organization incorporated in the District of Columbia, with its principal place of business in Washington, D.C.

4. ACS CAN is a membership organization, with approximately 32,000 members nationwide.

5. ACS CAN is the nation's leading voice advocating for public policies that are helping to defeat cancer. ACS CAN works to defeat cancer by helping protect and increase public investment in groundbreaking medical research, and by improving access nationwide to

the latest prevention and early detection measures, treatments, and follow-up care that are proven to save lives.

6. Because tobacco usage is a leading cause of lung and other forms of cancer, ACS CAN has, since its founding, been a leader in educating the public about the dangers of using tobacco products and advocating for policies and programs that discourage initiation of tobacco use and encourage cessation. ACS CAN advocates for effective tobacco control at every level of government, including reasonable regulation of cigars and e-cigarettes.

7. ACS CAN has been an active participant in FDA rulemaking proceedings related to tobacco products since the Food and Drug Administration ("FDA") was given regulatory authority in 2009, including submitting detailed comments to the proposed deeming rule both individually and as part of a broader coalition in August 2014. ACS CAN and its members have frequently filed comments with FDA on proposed rules, guidances, and draft guidances concerning the regulation of tobacco products.

8. ACS CAN and its members devote substantial resources to educating the public about the dangers of tobacco products. ACS CAN has mobilized staff and volunteers nationwide to advocate for regulation and taxation of tobacco products at the federal, state, and local levels.

9. To inform and strengthen its advocacy on cancer- and tobacco-related issues, ACS CAN reviews and synthesizes the latest scientific knowledge. In particular, ACS CAN relies on scientific data published by FDA through the premarket review process to focus its efforts on effective interventions and to educate policymakers and the American public.

10. For example, in November 2015, FDA issued a scientific review of certain smokeless tobacco products submitted by Swedish Match for premarket review. This review concluded that Swedish Match's products offered the potential to reduce oral cancer risk

compared to other smokeless tobacco products or cigarettes, due in significant part to the low levels of N-nitrosononicotine ("NNN") in Swedish Match's products.

11. FDA's Swedish Match premarket review provided valuable information to ACS CAN, allowing it to identify a specific product standard to advocate for. Based on the content of FDA's premarket review, ACS CAN advocated for FDA to establish an upper limit on the level of NNN in smokeless tobacco products. It used FDA's published review to show that lower levels of NNN were not only associated with a lower risk of oral cancer but feasible to impose on smokeless tobacco products. ACS CAN incorporated the information derived from the Swedish Match premarket review into comments it made in support of the proposed rule.

12. When FDA does not conduct premarket review, it is far more difficult for ACS CAN to advocate effectively for its members. Scientific data on the contents of novel tobacco products and their physiological consequences are crucial to ACS CAN's ability to identify effective and feasible product standards. Without such data, designing and proposing a product standard is akin to building a highway without knowing how to make asphalt. And such data largely comes from FDA, because tobacco manufacturers typically release as little information about their products' specific contents and interactions as possible.

13. For example, JUUL, currently one of the most popular e-cigarettes among school-aged youth, has not gone through the premarket review process. If it did, it would have to provide information to FDA about its contents and their effects, and FDA would make that information public if it approved JUUL. Having that information would allow ACS CAN to determine whether there were specific aspects of JUUL that were troublingly carcinogenic and determine whether there are product standards that would minimize the carcinogenic effects of all e-cigarettes. Without premarket review, however, that information is simply unavailable.

14. While other portions of the Deeming Rule do require *some* disclosure of ingredients for e-cigarettes and cigars, these disclosures are far less fulsome than the results of premarket review. The Deeming Rule's ingredient disclosure requirements require manufacturers to disclose the harmful and potentially harmful ingredients in a product, but not to disclose their quantities, their specific source and form, or other facts that affect the scope and magnitude of risk to consumers of the product.

15. Moreover, FDA's failure to perform premarket review increases the sheer number of potentially dangerous products on the market, thereby significantly increasing the costs to ACS CAN of monitoring the marketplace for such products, identifying viable policy proposals, and advocating for their adoption. Without a prohibition on marketing newly deemed products until review is complete, hundreds of products in thousands of flavors are currently being sold without a decision from FDA on those products' effect on public health. This situation forces ACS CAN to invest considerably more resources in monitoring the market and the products in the market so that we can determine where the greatest risks to public health are arising. This work hinders ACS CAN from working on other priorities in our evidence-based tobacco prevention and control efforts. Because of the ever-changing nature of these products and the lack of information about them, ACS CAN cannot target its proposals at specific products or design characteristics. Instead, it can only focus on the sale and use of those products in a broader, blunter, and less focused way. These efforts must occur at not only a nationwide level but in states and municipalities, making them vastly more expensive and onerous solutions.

16. If these products could not be marketed without surviving premarket review, ACS CAN would be able to reduce its spending on these patchwork efforts and focus instead on the products that were most harmful and the regulatory solutions that are most direct. This would be

a far more cost-effective way of pursuing ACS CAN's mission but will not be possible as long as FDA defers premarket review and allows unreviewed products to remain on the market.

Signed under the pains and penalties of perjury this 24th day of August 2018

Timothy B. Phillips
General Counsel
American Cancer Society Cancer Action Network

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF MARK A. SCHOEBERL

I, Mark A. Schoeberl, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am the Executive Vice President for Advocacy for the American Heart Association, Inc. ("AHA").

3. AHA is a nonprofit organization incorporated under Section 501(c)(3) of the Internal Revenue Code.

4. AHA works with local health care providers, church leaders, employers, and school administrators to provide education and counseling in hospitals, churches, and schools to help prevent youth initiation of tobacco use, including e-cigarette and cigar use, and to encourage tobacco users to quit. This involves contact with individuals about the consequences of tobacco and nicotine use. One of the principal goals of AHA's programs is to ensure that the individuals who receive counseling fully understand the consequences of tobacco use.

5. The proliferation of e-cigarettes and cigars that have not gone through premarket review impedes these efforts in numerous ways. When FDA approves a product through

premarket review, it publishes a substantial amount of information about the contents and health impacts of that product. It also requires manufacturers to sell the approved product as it was submitted for review, standardizing the contents of that product.

6. As a result, premarket review provides an extraordinary amount of information to AHA about the contents and health impacts of particular products and of e-cigarettes or cigars more broadly. If FDA published such information, AHA could and would use that information to further its mission, by analyzing and synthesizing it to educate the public, improve its guidelines for health care providers, and advocate for science-based regulatory measures.

7. For example, when FDA approved Swedish Match's application for premarket review for its smokeless tobacco, it published a review of those products that discussed their specific toxicology in considerable detail. This allowed us to identify certain smokeless tobacco attributes that could reduce some of the health risks of smokeless tobacco, such as the feasibility of lowering levels of N-Nitrosonornicotine, which enabled us to advocate to the FDA for a product standard for smokeless tobacco products.

8. Without the information provided by premarket review, AHA has little if any ability to provide medically accurate, evidence-based information about specific products and limited ability to provide authoritative information about product categories. This harms AHA's mission and its day-to-day activities in numerous ways.

9. One of the key components of AHA's work is its "Get With the Guidelines" quality improvement program, which seeks to ensure that hospitals and other health care providers are providing the most effective screening for tobacco use among patients and providing cessation resources when needed. The Get with the Guidelines program seeks to

ensure that health care providers are treating patients in ways that comply with the most up-to-date clinical practice guidelines.

10. This includes providing assistance and information about screening and counseling patients for tobacco use, including patient education materials and clinician training. These efforts have reached more than 700,000 patients since 2003, providing best-practices counseling that might not otherwise be available.

11. To fund the Get With the Guidelines program, AHA charges hospitals for AHA's materials and support. To the extent AHA is unable to provide up-to-date, evidence-based, medically accurate, useful material, hospitals are less likely to purchase Get With the Guidelines reducing AHA's revenues from the program and decreasing its resources for maintaining and improving the program.

12. The proliferation of unregulated, unapproved e-cigarettes and cigar products has this exact effect, impeding AHA from offering authoritative, medically accurate material on the diverse products that health care providers encounter and their most effective treatments.

13. In addition to the Get With the Guidelines program, AHA offers continuing education programs to individual clinicians. These programs hone in on specific areas of interest, such as health impacts of and treatment modalities for tobacco use. Clinicians pay by the session or access the programs as part of their paid professional membership. Because e-cigarettes and cigar products are not subject to premarket review and therefore are not accompanied by the scientific literature necessary to withstand premarket review, AHA cannot obtain concrete information on those products and is therefore severely restricted in the programming it can offer clinicians. If such information did exist, AHA could study it and convert it into practical educational programs that it would offer as part of this series.

14. AHA also convenes CEOs from many of the country's top businesses in a CEO Roundtable, whose goal is to foster worksite health promotion that improves cardiovascular health. As part of that initiative, AHA has developed resources for employers around tobacco policy and ways that employers can address tobacco use and provide cessation support to their employees. These efforts are similarly impeded by AHA's inability to provide authoritative information about e-cigarettes and cigars.

15. In lieu of premarket review, AHA must do its own research and review published research on e-cigarettes and cigars. But due to the paucity of published information, the variable contents of the unregulated products, and the sheer number of products on the market, this endeavor is not only a completely inadequate substitute for premarket review, but also expensive.

16. Similarly, AHA develops resources for individuals, including its 40 million volunteers and supporters. It is currently developing or updating materials on topics such as resources to help quit smoking, whether vaping is safer than smoking, common products such as JUUL, and the public health implications of e-cigarettes. All of this material is more costly to develop—and less complete—due to the absence of premarket review and the information it would provide, as well as the immense diversity of products in the absence of premarket review.

17. AHA also published a Policy Statement on e-cigarettes in 2014.[1] Given the rampant proliferation of new products, AHA is already updating this statement, a significant endeavor that entails significant research time and other financial and staff resources. Because of the FDA's decision to allow products to remain on the market indefinitely pending premarket

[1] The Policy Statement can be found at https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000107.

review, the AHA must invest substantial resources into covering the waterfront of products that are available but is simultaneously unable to make the most up-to-date recommendations between product categories or for particular product standards, as it would otherwise do.

Signed under the pains and penalties of perjury this 24 day of August, 2018

Mark A. Schoeberl
Executive Vice President
American Heart Association

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF HAROLD P. WIMMER

I, Harold P. Wimmer, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am the National President and CEO of the American Lung Association ("ALA").

3. ALA is a nonprofit voluntary health organization incorporated under Section 503(c)(3) of the Internal Revenue Code.

4. ALA's mission is to save lives by promoting lung health and preventing lung disease. The prevention and cessation of the use of tobacco products is an integral part of this mission.

5. Providing effective assistance to tobacco users who are trying to quit is one of ALA's top priorities. ALA expends substantial resources to support its highly acclaimed Freedom From Smoking program, which has in-person, online, self-help, and telephonic options to help tobacco users quit. All Freedom From Smoking participants also have access to certified tobacco treatment specialists at our Lung Helpline by telephone, through email, and via an online

chat function. ALA also offers Freedom from Smoking Plus, a nine-session online cessation course.

6. These efforts are made substantially more complicated, more expensive, and less effective because of the proliferation of unregulated tobacco products such as e-cigarettes.

7. With traditional cigarettes, users tend to have a relatively high level of background knowledge about their harms, along with a personal desire to quit. Moreover, the scientific literature on traditional cigarettes (and their cessation) is extensive, allowing ALA to provide authoritative, science-based information and evidence-based treatment methods.

8. With e-cigarettes, however, both users and ALA are in a far worse situation. There is a significant amount of misinformation and consumer confusion about e-cigarettes, including whether they even are tobacco products, whether they contain nicotine and how their nicotine levels compare to traditional cigarettes, what other chemicals they contain, and what health risks they pose. In reality, however, the vast majority if not all e-cigarettes contain numerous chemicals that can cause lung injury, and many provide at least as much nicotine as traditional cigarettes and are similarly addictive.

9. Because most consumers' baseline understanding of the risks of nicotine addiction and lung injury from e-cigarettes is nowhere close to that of traditional cigarettes, our counseling efforts must spend a significant amount of time simply providing that initial level of understanding so that e-cigarette users understand the risks they face. Unlike cigarette counseling, where clients typically have at least a general understanding that smoking cigarettes leads to well-known diseases like lung cancer and COPD, we need to explain the connection between e-cigarette use, lung injury and bronchitis, and explain less commonly known conditions like bronchiolitis obliterans ("popcorn lung"). That effort entails a substantial use of

our counseling resources, taking up time and money that would otherwise be used to reach more users and innovate to improve our offerings.

10. Moreover, our counseling is seriously compromised by our own inability to obtain factual information about these products. For many e-cigarettes, there is no public information about the contents, much less the quantities and specific forms of potentially injurious chemicals. And because manufacturers do not need to standardize their products, we cannot even confidently say that the same brand bought on different days or from different stores will have the same contents. It is thus often impossible to describe authoritatively the contents or risks of a given e-cigarette, or a given e-cigarette user's consumption habits.

11. There is also a lack of public understanding about the health harms of cigar use. According to the National Cancer Institute, cigar smoking causes lung cancer. Daily cigar smokers, particularly those who inhale, have an increased risk of chronic obstructive pulmonary disease (COPD). Cigar sales increased by 29 percent during 2012-2016 and can be expected to further increase in part because of FDA's failure to fully implement the deeming rule. The incidence of lung disease caused by cigar use will likely continue at its current level or even increase over time because of FDA's failure to properly implement the deeming rule. This will require additional resources from the Lung Association to provide patient support services.

12. In order to best serve our constituents, we expend significant resources to study the products that are on the market. Because of the vast diversity of products that are available even though they have not gone through premarket review by the FDA, this requires a substantial amount of time and money. But as already said, many products lack any definitive information, leaving us powerless to update our information and counseling materials. The proliferation of unregulated products makes it more expensive for us to stay current and provide up-to-date

information to our clients—as well as to the many researchers, journalists, public health experts, and policymakers who look to ALA for expertise in this field.

13. The increased availability of these unapproved products also drains ALA's resources in another way. By allowing unregulated e-cigarette and cigar products to remain on the market, many of them marketed at young, first-time smokers, the absence of premarket review increases the number of smokers in the United States. This will produce a higher incidence of lung disease, asthma attacks, nicotine addiction, and other conditions at the core of ALA's mission. That requires us to devote more resources to addressing addiction and harm, and fewer resources to air pollution, climate change, influenza, or numerous other core ALA interests that affect the lung health of the American public.

14. For example, we are currently devoting a substantial amount of time and financial resources to studying and understanding current research on the health impact of e-cigarettes so that we can provide resources to our counseling program, the general public, academics, journalists, public health practitioners, and policymakers. If there were fewer e-cigarettes and flavored cigars on the market, this report might not be necessary at all—or, at a minimum, would be substantially less expensive. But until the FDA restrains companies from marketing e-cigarettes and modern cigars that have not been approved through premarket review, this expenditure will be necessary to fulfill ALA's mission and will drain our resources accordingly.

15. In addition to reducing the variety of e-cigarettes and cigars that are on the market without FDA approval, premarket review would provide invaluable information about the contents and effects of each e-cigarette and cigar product. As noted above, there is little concrete information—and substantial misinformation—about most e-cigarette and modern cigar products. Premarket review would provide detailed scientific evidence about the contents,

toxicological effects, and other attributes of specific products. Analyzing these data would allow us to hone our cessation support for individuals, our educational products for the public, and our advocacy efforts for evidence-based regulation.

16. As an example, we were able to use the premarket review conclusions that FDA published for Swedish Match's smokeless tobacco products to identify a product standard for smokeless tobacco products that would substantially reduce certain cancer risks from smokeless tobacco, which helped us advocate for that standard before the FDA. If FDA conducted premarket review for e-cigarettes and cigars, we would be able to undertake similar analyses and identify information that could substantially benefit public health, both for individual smokers, public health practitioners, and federal regulators.

Signed under the pains and penalties of perjury this 27 day of August, 2018

Harold P. Wimmer
National President and CEO
American Lung Association

EXHIBIT E

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF ROBERT N. FALK

I, Robert N. Falk, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am the General Counsel and Corporate Secretary for the Truth Initiative Foundation, d/b/a/ Truth Initiative ("Truth Initiative").

3. Truth Initiative is a non-profit corporation created in 1999 out of the 1998 Master Settlement Agreement ("MSA") resolving litigation brought by 46 states, five U.S. territories, and the District of Columbia against the major U.S. cigarette companies. It was formerly known as the American Legacy Foundation. Truth Initiative is a nonprofit organization incorporated under Section 503(c)(3) of the Internal Revenue Code.

4. Truth Initiative's purposes are to study and support programs in the United States to reduce youth tobacco use and to prevent diseases associated with tobacco use. Truth Initiative supports innovative and highly successful programming to educate young people about all forms of tobacco so they can make informed choices about its use encourage and assist smokers to quit.

5. For example, Truth Initiative's nationally recognized **truth**® campaign has reached hundreds of millions of teens and young adults through television, radio, and print advertisements, social media, the internet, earned media, and in-person events, with information about the health effects and social costs of tobacco in order to enable young people to make informed decisions about tobacco use.

6. Recognizing the popularity of e-cigarettes, little cigars, and cigarillos among youth, along with the widespread lack of understanding that they can be as dangerous and addictive as cigarettes, **truth** has addressed them in advertisements, on its website, and on social media.

7. In particular, Truth Initiative is in the process of launching a new public campaign on e-cigarettes, to inform teen users (and other e-cigarette users) of the contents and risks of e-cigarettes. This has entailed a tremendous amount of research into popular e-cigarette products such as JUUL, as well as many of the less common e-cigarette products that have proliferated in the absence of premarket review. For example, Truth Initiative has researched patent applications, chemical components, and known risks as part of this substantial expenditure of resources.

8. Even so, Truth Initiative's new campaign is impeded by the lack of information about the products on the market. Premarket review requires standardization of a product and results in the publishing of an invaluable set of information on the product's contents and impacts. Were FDA performing premarket review, Truth Initiative would use that information in its public education and outreach efforts. Without it, Truth Initiative is severely limited in the information it can provide to teen users and other members of the public.

9. As an example, Truth Initiative used the output from FDA's premarket review of smokeless tobacco products to educate the public about the link between nicotine and cancer. The Truth Initiative's research branch, the Steven A. Schroeder National Institute for Tobacco Research and Policy Studies, analyzed the FDA's premarket review report for Swedish Snus products sponsored by Swedish Match as part of an examination of the link between nicotine and cancer, finding that the evidence shows that nicotine on its own "does not measurably cause or promote cancer in humans." *See* https://truthinitiative.org/sites/default/files/ReThinking-Nicotine.pdf at 9-10. This not only allowed Truth Initiative to more accurately inform the public about the risks of products containing nicotine—and the potential public health benefits of products that contain nicotine but not other carcinogens—it helped Truth Initiative advocate for a new product standard for smokeless tobacco products, which FDA subsequently incorporated into a proposed rule.

10. By contrast, the absence of premarket review prevents Truth Initiative from helping users make decisions regarding e-cigarettes, including making informed choices between e-cigarettes. Truth Initiative is committed to harm reduction and would identify products that appeared to carry the least risks in its materials, but simply cannot do so without data from FDA. Nor can they say which e-cigarette products are the worst of the worst and emphasize the importance of avoiding those products.

11. This dearth of information also severely impacts Truth Initiative's cessation intervention programs, BecomeAnEX® and the EX Program®.

12. BecomeAnEX is a free, evidence-based, online smoking cessation intervention that aims to help people stop smoking. It has reached more than 800,000 persons in the decade since Truth Initiative created it. As part of BecomeAnEX, Truth Initiative educates users about

nicotine replacement therapies such as the gum, lozenge, and patch. But many people view e-cigarettes as a safer alternative to cigarettes, on par with such replacement therapies. Without information about the actual contents and risk profiles of *particular products*, Truth Initiative cannot provide evidence-based information to these clients—neither to explain why traditional replacement therapies are a safer choice, nor to recommend them as a potentially effective therapeutic alternative.

13. The EX Program is a business-to-business service providing a comprehensive digital smoking cessation platform to corporations, launched in 2017 in collaboration with the Mayo Clinic. It offers cessation support and nicotine replacement therapy to employees and health plan members, and is intended to ultimately be a self-sustaining, revenue-generating program.

14. As part of the EX Program, Truth Initiative purchases and provides replacement therapies for individual smokers. Once FDA evaluates individual e-cigarette products through premarket review and other assessments, some e-cigarettes could ultimately serve as replacement therapies, either as frontline treatments or as fallback treatments for individuals who do not find success with traditional replacement therapies such as gums and patches. Such products would increase the effectiveness of the EX Program and therefore increase its appeal to commercial entities.

15. Even if no e-cigarette products are ever identified as viable cessation aids, merely having the information provided by premarket review, and having unapproved products off the market, would improve the efficacy of the EX Program and its appeal to employers. As part of the EX Program, Truth Initiative offers one-on-one digital coaching via live chat to users, which includes providing information about products and offering cessation assistance. The

proliferation of diverse products with inconsistent contents and scant public information makes this task far harder and far less effective, decreasing Truth Initiative's ability to pursue its mission and the EX Program's appeal to the employers who pay for it.

16. In addition to these programs, Truth Initiative conducts research into both e-cigarettes and cigars, which is more expensive than it would be if premarket review were providing information and limiting the offerings on the market.

17. Truth Initiative's research arm, the Schroeder Institute, conducts epidemiological and population health research, studying topics such as prevalence, patterns of use, and the impact of national public education efforts on behavior. The proliferation of unregulated products makes such studies significantly more expensive due to the longer survey instruments needed to collect the appropriate data across numerous products. Most recently, studies examining the new vape product, JUUL, use of which is perceived by many consumers as a unique behavior separate and apart from vaping, now require repeated surveys given the rapid uptake of this product and the changes in nicotine concentration accessories. In fact, in the past fiscal year alone, Truth Initiative has spent significant sums to incorporate JUUL-specific questions in its research surveys—more than we spent to conduct research on any other brand-specific tobacco product, including both cigarettes and e-cigarettes. Similarly, the Schroeder Institute's efforts to examine the effect of flavored cigars on youth uptake has been thwarted by the frequency of changing names, releasing new products, and altering flavors across various flavored cigar manufacturers.

Signed under the pains and penalties of perjury this 22nd day of August, 2018

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Robert N. Falk

General Counsel and Corporate Secretary
Truth Initiative Foundation dba Truth Initiative

EXHIBIT F

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF V. FAN TAIT, MD, FAAP

I, V. Fan Tait, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am a pediatric neurologist and the Chief Medical Officer for the American Academy of Pediatrics ("AAP"). In this capacity, I oversee the Julius B. Richmond Center of Excellence, discussed below, as well as our Continuing Medical Education programs, Division of Innovation, and disaster preparedness activities. Prior to becoming Chief Medical Officer, I directed AAP's Department of Child Health and Wellness.

3. AAP is a professional membership organization of 67,000 pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists.

4. AAP is operated exclusively for charitable and educational purposes under section 501(c)(3) of the Internal Revenue Code.

5. AAP's mission is to attain optimal physical, mental and social health and well-being for all infants, children, adolescents and young adults.

6. Each of our state chapters, including the Maryland chapter, is incorporated as its own non-profit organization and shares AAP's mission of supporting pediatricians in the promotion of optimal health for their state's children and adolescents.

7. To accomplish this goal, AAP's pediatrician members actively screen their patients for use of tobacco and provide counseling to their patients and patients' parents about the health hazards of tobacco use, in an effort to prevent tobacco initiation.

8. AAP dedicates a substantial amount of staff time and financial resources to researching tobacco products, educating its members about tobacco use and treatment, and creating resources that members can use in their practice.

9. Over the past few years, a substantial portion of this work has focused on e-cigarettes,[1] due to the exponential increase in the prevalence of e-cigarette use, the number and variety of products on the market, and the lack of concrete, medically useful information about these products. If FDA required all e-cigarette products to be the subject of an approved premarket review report to be marketed, much of this work would not have been necessary.

10. After FDA issued the Deeming Rule, we eagerly anticipated the arrival of premarket review. Under the premarket review process laid out in the Deeming Rule, each product would need to be off the market no later than August 2019 (one year after the deadline for submitting premarket review applications) or be the subject of a premarket review report that provides extensive scientific and medical information about its content, use, and effects.

11. Because of FDA's Guidance delaying premarket review, AAP will not have the benefit of premarket review until 2022—and in practice, until even later, because the Guidance allows products to stay on the market indefinitely while FDA evaluates premarket applications.

[1] I use "e-cigarettes" to refer to the full range of electronic nicotine delivery systems ("ENDS").

This means AAP will be dealing with the vast proliferation of products for years to come, so that it will have to continue all of these efforts—with all of their costs—for several years. All of the work discussed below will need to continue, or even intensify. This will force AAP to incur costs beyond its normal operating expenses, and prevent AAP from engaging in other projects by draining its resources.

12. Below I will provide an overview of the work that AAP performs related to e-cigarettes.

1. The Julius B. Richmond Center of Excellence

13. The centerpiece of AAP's Division of Tobacco Control is the Julius B. Richmond Center of Excellence (the "Richmond Center"), which provides education and tools to help AAP's pediatrician members effectively intervene to protect children from the harmful effects of tobacco and secondhand smoke. In order to provide this assistance, we conduct our own research to understand the products in the market, create numerous documents spelling out our findings and the best practices for pediatricians, and conduct trainings and other programs for clinicians and AAP chapters.

14. The Richmond Center's work is performed by five full-time staff and dozens of pediatrician leaders, all overseen by AAP's Chief Medical Officer and our Director of the Division of Tobacco Control. The pediatrician leaders comprise more than two dozen pediatricians, scientists, and researchers undertaking research into pediatric tobacco issues at all levels, from basic scientific research and randomized control trials to broad research into prevention and cessation strategies. We also work with approximately 400 pediatricians interested in tobacco control and prevention to develop and implement our physician education and clinical resources.

15. Since FDA issued the Guidance, our full-time staff has spent approximately 2000 hours on e-cigarette work, the equivalent of an entire staff member's full-time work for a year. As discussed further below, this has impeded our ability to perform numerous activities that are ordinarily part of the Richmond Center's regular activities. It also required us to hire a full-time temp worker to manage our necessary work for a significant portion of 2018, the only time in years that we've needed to bring on a temp worker for any purpose.

2. In-Person Training on E-Cigarettes

16. One of the most important tasks that AAP undertakes is providing in-person trainings for our pediatrician members. This includes a two-day in-person tobacco training called "Asking the Right Questions: Physicians and Tobacco Control in the Clinical Encounter."

17. Each session of "Asking the Right Questions" costs AAP approximately $25,000-$30,000, and requires a full-time staff manager and full-time staff coordinator to each devote 50% of their time to the project for approximately four months, along with substantial amounts of volunteer work contributed in-kind by 7 pediatrician faculty members to develop and deliver the training curriculum.

18. Asking the Right Questions was first developed in 2014 and then implemented successfully a few times over the next two and a half years with minimal updating needed.

19. Since August 2016, however, we have had to offer Asking the Right Questions more frequently—6 times so far—due to increased member demand related to e-cigarettes. We have also had to undertake major updates before each session to ensure that it is reasonably up-to-date. These updates require dozens of hours of staff time, not to mention all the work contributed by our pediatrician faculty members.

20. Today, approximately 30% of the content in Asking the Right Questions focuses exclusively on understanding and addressing e-cigarettes and emerging tobacco products in clinical settings.

21. Updating Asking the Right Questions takes significant effort on the part of pediatrician faculty members and AAP's staff. The significant, rapid changes in the e-cigarette market—including shifts between popular products, changes within individual products due to the lack of product standardization, and changes in uptake by youth populations—require us to continually update the training curriculum to cover newly popular varieties or brands of e-cigarettes, the health impacts of their flavoring constituents, device components, and teen usage-trends of new products.

22. Even with the updates we undertake before each session, the significant, rapid changes in the e-cigarette product market that come from the widespread availability of thousands of products make much of the content presented in each training outdated within months, making the trainings less useful for the pediatrician members who attend them and having a negative impact on the care they deliver to their patients.

23. If fewer e-cigarette products were on the market and those that were on the market were standardized and accompanied by the scientific information provided in premarket review reports, all of this information would have been easier and cheaper to assemble, more long-lasting, and more useful to our pediatrician members.

24. Our faculty members also purchase e-cigarette tobacco products for each training, to conduct a hands-on learning segment where pediatricians can become familiar with specific products. These products run anywhere from $10 to over $100, adding up to a large collective expense across the several trainings. If FDA allowed the premarket review requirement to come

into effect, we would not need to purchase as many products because many would leave the market pending review, and each approved product would be standardized so that we could use products purchased for one session at subsequent sessions.

25. Moreover, our members attending training sessions generally must take at least two days off work to attend. Their need for training on e-cigarettes, caused in significant part by the availability of so many products without accompanying scientific and clinically useful information, thus directly reduces their income and ability to perform their duties to all patients.

3. Technical Assistance to AAP Chapters

26. The Richmond Center also provides technical assistance to AAP chapters who are looking to educate their members about addressing tobacco in pediatric practice. This typically includes the development and implementation of webinars and/or in-person trainings for AAP members.

27. In the past two years, the most common requests for technical assistance have been related to e-cigarettes. This year alone, we have conducted an in-person training and eight webinars, with another webinar under development.

28. With most other technical assistance topics, the Richmond Center has a standard curriculum that remains stable for years at a time. Because of the wide variety of e-cigarette products and the rapid change in the market in the absence of premarket review, our existing curricula go out-of-date quickly, so that we have needed to create new curricula each time a chapter requests technical assistance. This requires AAP staff, chapter staff, and AAP faculty members to conduct significant background research and create new educational content for each chapter to help its members identify, understand and address e-cigarettes as they are used among that chapter's patients.

29. If fewer e-cigarette products were on the market and those that were on the market were standardized and accompanied by the scientific information provided in premarket review reports, all of this information would have been easier and cheaper to assemble, more long-lasting, and more useful to our pediatrician members.

4. Tobacco Resources and Educational Materials

30. In addition to our trainings and chapter assistance, we create educational curricula and clinical resources related to tobacco issues, both for presentation at national meetings and professional conferences and for individual members to use with their patients and provide to parents.

31. Because of the proliferation of products on the market with little information and the rapid uptake among youth, our pediatrician members are highly interested in, concerned with, and uninformed about these products and their impact on child health. As the market expands and evolves, and as e-cigarettes consume more and more of our members' times, we have had to create multiple new curricula and resources in order to ensure our members are equipped to address these products in practice.

32. Just since FDA announced the Guidance delaying premarket review, we have issued numerous new factsheets and online articles regarding e-cigarettes, including "Vaping: Dangerous, Available and Addicting" (January 2018), "Talking to Teens About Tobacco" (March 2018), "JUULing: What Pediatricians and Families Need to Know" (April 2018), and "4 Things Parents Need to Know About JUUL and Nicotine Addiction" (August 2018). We have also conducted five educational sessions at the national meetings or conferences since the Guidance, including "No ENDS in Sight: Addressing E-Cigarettes and Vaping in Your Practice" (AAP National Conference and Exhibition plenary session), "Let's Talk About the New Cigs on

the Block" (AAP National Conference and Exhibition presentation), "Electronic Cigarettes and Vaping: What You and Your Patients Don't Know Can Hurt Them" (Pediatric Academic Societies Conference workshop), "Vaping, Dripping and Hookah Use: Counseling Parents and Teens About the Evolving Nicotine Landscape" (AAP National Conference and Exhibition plenary session), and "JUUL, Vaping and Electronic Cigarettes: A Public Health Crisis" (AAP National Conference and Exhibition plenary session).

33. For each of these items, AAP staff and AAP faculty members conduct literature reviews and create new educational content to help AAP members and the general public identify, understand, and address e-cigarettes.

34. All of these clinical resources and educational presentations would have been less expensive and less time-consuming to create if premarket review were required, because there would be scientific information about each product on the market and its impact on consumers, and products without that scientific information would not be available.

5. Policy Statement

35. AAP also issues Policy Statements on a number of subjects, which offer evidence-based guidance to pediatric healthcare professionals, thereby improving the health of all children.

36. Before publication, these Policy Statements are written by pediatrician leaders of AAP Sections, Committees, and Councils; peer-reviewed by experts across AAP; and approved by AAP's Executive Staff and Board of Directors.

37. AAP's standard practice is to update or reaffirm each Policy Statement every five years. More frequent changes are a burden not only for AAP staff and for policy authors, but for pediatrician members, because they must relearn the recommendations in each update.

38. AAP's current e-cigarette Policy Statement, "Electronic Nicotine Delivery Systems," was published in November 2015. Under our standard practice, it would not be reviewed and updated until 2020. However, due to the increased prevalence of e-cigarettes, the complexity of the problems they present for pediatricians, and the lack of evidence-based information from FDA, we have already begun updating the Policy Statement, years ahead of schedule, so that we can publish a new statement entitled "E-Cigarettes and Similar Devices" in 2019.

39. This has entailed a comprehensive literature review by AAP staff and pediatrician authors, reviewing the variety of e-cigarettes in the field, the constituents and components of each type and brand, and the health risks associated with these products. This allowed our authors and staff to draft the new Policy Statement and submit it for peer review by AAP expert groups, who provided extensive comments that required reconciliation in a new draft.

40. The current draft is currently in copy-editing, and then will be presented to AAP Executive Staff and the Board of Directors for approval.

41. All told, the process will take nearly two years and considerable work from the Richmond Center staff, the full Board of Directors, the Board's Committee on Policy, and dozens of members. It has consumed more than 1000 hours of staff time alone, not counting the time spent by AAP members, the Board, and the Committee on Policy.

42. Under the Deeming Rule and its original deadline for premarket review applications (along with its requirement that products be taken on the market one year after the deadline, if the application is not approved by then), all products would have to either be taken off the market or accompanied by a substantial amount of scientific, medically useful evidence no later than August 2019. We likely would not need to issue our Policy Statement years ahead

of schedule, because the urgent professional and public health crisis that e-cigarettes present for our members would be substantially reduced and the FDA's review of each product would have obviated the need for our staff and authors to engage in their own arduous, comprehensive review.

43. Moreover, portions of the new Policy Statement will likely be outdated soon after we release it, due to the ongoing, explosive growth of e-cigarette use among pediatric patients and FDA's decision to allow thousands of products to remain on the market without scientific evidence indefinitely. If premarket review had come into effect as per the Deeming Rule, many of these products would likely come off the market next August, simplifying the e-cigarette landscape. Products that remained on the market would be accompanied by a wealth of scientific evidence, allowing for presentation of clinical guidance without AAP needing to undertake two years of its own work.

44. Instead, with premarket review postponed until 2022—and manufacturers allowed to keep products on the market indefinitely after submitting their applications—we will quite likely need to update our e-cigarette Policy Statement ahead of our usual five-year schedule again, with all of the burden described above. This will impose a substantial drain on our resources, using up hundreds or thousands of hours of staff time and countless hours from the members who are donating their time to help us assist their fellow pediatricians.

6. Inability to Carry Out Normal Activities Due to E-Cigarette Work

45. The massive increase in time that we have had to spend on e-cigarette work in light of the proliferation of products without premarket review has prevented the Richmond Center from engaging in numerous activities that would otherwise be at the core of our mission.

46. One of the Richmond Center staff's most important activities is identifying grant opportunities for funding for physician education and research programs. Most if not all of our continuing education and research efforts rely on outside grant funding. The time spent on designing and providing e-cigarette training, updating e-cigarette resources and policy materials, researching e-cigarettes, and responding to member inquiries has come directly out of the time our staff spends on identifying and applying for available grants. Due to our staff being over-committed with the activities outlined above, we have not had sufficient time to search for new grant opportunities, seek out new funders, and develop applications for funding. As a result, we have been unable to secure new funding for some of our programs as their previous grants have expired. This directly decreases the Richmond Center's and AAP's resources and reduces the amount of programming and professional assistance our members receive.

47. We have reduced staffing on the Richmond Center's "Building the Field" program, which provides small grants to early-career researchers engaged in tobacco control research and develops Visiting Lectureship programs at AAP chapters and health systems to jumpstart their tobacco initiatives. While we previously had a program manager and coordinator who spent more than a third of their time to this work, we have had to retask them to split their time across e-cigarette initiative (particularly the in-person training and chapter technical assistance discussed above), which has significantly delayed the Building the Field program's operations.

48. We have similarly had to downgrade our involvement in the Adolescent Health Consortium, a project uniting four major medical organizations (AAP, American Academy of Family Physicians, Society for Adolescent Health and Medicine, and American College of Obstetricians and Gynecologists) to collaborate on improving confidential adolescent health

services for teens and young adults. Prior to the emergence of the e-cigarette issue, this was a near-daily part of the work of the Director of our Division of Tobacco Control, which has been impossible due to the urgent e-cigarette work.

49. The Richmond Center's global tobacco project has also been significantly impacted. The Director of the Division of Tobacco Control was also the primary staff for this program until 2017, but has been unable to participate in it in a significant way since that time. We have had to bring in a program manager from outside the Richmond Center to cover this project, which in turn has decreased AAP's ability to work on the global child health initiatives that the project manager focuses on for the core of her job.

50. We have also postponed several initiatives altogether, directly due to the time staff and leaders have had to dedicate to e-cigarettes. These initiatives include the development and implementation of a webinar on how to engage physicians in encouraging smoke-free homes; the writing of an AAP Clinical Report on Health Disparities and Tobacco; and plans to create two Chapter Liaison positions to assist chapters in tobacco control initiatives such as physician education.

51. Moreover, as noted above, we have had to expend significant amounts of money on e-cigarette related efforts that would be less frequent and less intensive if premarket review were required for all products on the market. We have spent more than $150,000 on six in-person tobacco trainings, which would have been significantly less expensive if we did not need to overhaul our trainings to keep up with the rapid change in the marketplace brought about by the proliferation of products. Our faculty members have spent thousands of dollars purchasing e-cigarette products to enable hands-on learning in our training sessions, which would not be necessary if there were fewer products on the market and if they remained the same from session

to session. We would otherwise dedicate these resources to supporting other initiatives, such as training pediatricians on other crucial clinical issues.

7. Effect on AAP's Members

52. The effects that I have described above principally fall on AAP as an organization and on the many AAP members who contribute their time to working on AAP initiatives. The proliferation of e-cigarette products without clinically useful, evidence-based information has had equally significant effects on our 67,000 members.

53. We have received requests from countless members for resources to educate them and their patients about e-cigarettes. Our members have encountered dozens if not hundreds of different e-cigarette products in treating patients. They must research these products, the effects of e-cigarette use, and treatment modalities to provide competent treatment and counseling.

54. For many AAP members, this consumes a substantial amount of their professional time, reducing the amount of time they can see other patients or the amount of time they can spend with their patients on other issues.

Signed under the pains and penalties of perjury this 27th day of August, 2018

V. Fan Tait
Chief Medical Officer
American Academy of Pediatrics

EXHIBIT G

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF SHARON LEVY, MD, MPH

I, Sharon Levy, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am a board-certified Developmental-Behavioral Pediatrician and Addiction Medicine specialist.

3. I am an Associate Professor of Pediatrics at Harvard Medical School and the Director of the Adolescent Substance Use and Addiction Program in the Division of Developmental Medicine at Boston Children's Hospital.

4. I am also a member of the American Academy of Pediatrics ("AAP") and a former member of its Committee on Substance Use and Prevention.

5. I have evaluated and treated thousands of adolescents with substance use disorders, and have taught national curricula and published extensively on the outpatient management of substance use disorders in adolescents, including screening and counseling for tobacco use for both primary care physicians and specialists.

6. My practice primarily focuses on children and adolescents who are suspected of having a substance use disorder.

7. As long as I've been practicing, cigarettes were a factor with the patients who had the most severe addictions, who typically had comorbid use of multiple substances. But before the introduction of electronic cigarettes, use of tobacco products was far less common among patients who used fewer substances (for example, just marijuana).

8. Over the last several years, however, use of electronic cigarettes, often referred to as "vaping", has become nearly universal among my patients. Nearly every child I treat or assess uses some form of e-cigarette product.

9. This increase has added significant complications to my practice, inhibiting my ability to assist my patients and decreasing their chances for leading a substance-free life.

10. First, it means that nearly every patient I see is using multiple substances. Treating patients with co-use of multiple substances requires more treatment, necessitating longer appointments and more intensive clinical work.

11. For example, many of my patients voluntarily opt into a drug testing program that helps their clinicians and parents monitor them and provides important feedback for self-monitoring. We have had to add testing for nicotine and cotinine (a metabolite of nicotine) to the drug testing panels, given the increase in use across the patients we see. This also makes it harder, and at times less accurate, to interpret drug test results and determine how best to counsel patients and advise parents.

12. Second, the ready availability of e-cigarettes harms my patients' health, both endangering their welfare and necessitating a substantial investment of time and clinical resources. If FDA were prohibiting these products from being sold until they receive premarket

approval, my patients could not use them and therefore far fewer of my patients would be experiencing nicotine addiction, and other harmful consequences such as alterations of the brain that increase the risk of addiction to other substances. All of these conditions require significant treatment, which reduces the amount of time I can spend either with other patients or on other issues. This treatment is also often costly and time-consuming, but does not increase my income for several types of appointments.

13. Third, the proliferation of e-cigarettes has required me to spend a significant amount of time tracking down information about the products my patients use. In order to have credibility and authority with my patients, it is essential for me to know what I'm talking about. If an adolescent patient concludes that I am uninformed about e-cigarettes, it becomes extremely difficult to convince them to take my advice and efforts to assist them seriously.

14. Accordingly, when I learn that a patient is using a product with which I'm unfamiliar, I immediately seek out as much information as I can about the product, trying to learn, for example, how manipulable the device is; the nicotine content and other chemical contents of the manufacturers' pods; whether the pods it comes with can be refilled, and what they might be refilled with; and the appearance and layout of the device. This information is sometimes available—but often is not. Much of the time, the best that I can do is find pictures, general descriptions, and advertisements on the internet.

15. The vast diversity of products on the market thus requires me to spend a significant amount of time researching new products just to be able to perform my duties as a medical professional. And the dearth of information about those products means that I often have difficulty providing precise information that would be most helpful to them. In many cases, the best I can do is talk in general terms and inform them that we don't definitively know the effects

of the products that they're using, which often makes them less receptive to efforts to reduce use. But the fact that the information isn't available doesn't mean these products are safe; it just means that I can't help my patients to the same extent that I can with cigarettes and other better-studied and better-regulated substances.

16. I run into similar problems with cigarillos and other cigar-family products. The most common use of cigars among my patients is as a delivery system for marijuana, commonly called blunts. This combination has all the problems of dual exposure and multiple-use that I mentioned above.

17. On top of the problems of comorbid substance use, many of my patients report that they don't use tobacco products even though they smoke blunts. They don't recognize this type of use as tobacco use per se. I therefore need to spend more time probing my patients who use marijuana to determine whether they are also using tobacco, and then engage in all of the counseling and treatment that that entails if so. This also means that many youth may not receive treatment for tobacco use even though they are using tobacco products, simply because they do not think of this type of use as "tobacco use."

18. In addition to my clinical practice, I conduct research on substance use at Boston Children's Hospital. Much of my research entails survey questions to adolescents about e-cigarettes, other tobacco products.

19. The diversity of products and adolescents' lack of information—or even affirmative misunderstandings—about these products hinders my research by making it more time-consuming to write questions that accurately capture participant behaviors of interest, more costly to perform and process surveys, and less effective. Our surveys often need to be significantly longer so that we can determine exactly what products a survey respondent is using,

how they are using them, and what they contain. They require substantial research both beforehand and after to determine what questions should be asked about different products, so that the results can be used at all. And our interpretation of the surveys is limited by the proliferation of products and the unregulated nature of their contents, which hampers our ability to reach generalizable conclusions and publish meaningful results.

Signed under the pains and penalties of perjury this 23rd day of August, 2018

Sharon Levy MD, MPH

Sharon Levy MD, MPH
Adolescent Substance Use and Addiction Program
Boston Children's Hospital

Associate Professor of Pediatrics
Harvard Medical School

EXHIBIT H

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF DEEPA R. CAMENGA, MD, MHS

I, Deepa R. Camenga, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am a pediatrician who is board certified in both pediatrics and preventive medicine, with a subspecialty in addiction medicine.

3. I am an Assistant Professor of Emergency Medicine, Section of Research at Yale School of Medicine and practice medicine at Yale New Haven Hospital and the APT Foundation, a community-based substance use treatment organization.

4. I am also a member of the American Academy of Pediatrics ("AAP") and its Committee on Substance Use and Prevention, as well as its Section on Tobacco Control.

5. My research focuses on improving practices around the identification and treatment of drug and tobacco use disorders in adolescents and young adults, understanding adolescent nicotine dependence and its co-occurrence with substance use, and understanding youth behaviors around emerging tobacco products. I have authored peer-reviewed articles such as:

Camenga DR, Tindle HA. Weighing the Risks and Benefits of Electronic Cigarette Use in High-Risk Populations. Med Clin North Am. 2018 Jul;102(4):765-779.

Camenga DR, Fiellin LE, Pendergrass T, Miller E, Pentz MA, Hieftje K. Adolescents' perceptions of flavored tobacco products, including E-cigarettes: A qualitative study to inform FDA tobacco education efforts through videogames. Addict Behav. 2018 Jul;82:189-194.

Camenga DR, Kong G, Cavallo DA, Krishnan-Sarin S.Current and Former Smokers' Use of Electronic Cigarettes for Quitting Smoking: An Exploratory Study of Adolescents and Young Adults. Nicotine Tob Res. 2017 Nov 7;19(12):1531-1535.

6. My practice focuses on adolescent medicine. I provide primary care and substance use care to children as young as 13 years old.

7. I screen every patient who I see for a well child exam for use of tobacco products, and address use of tobacco products in every visit.

8. Over the last four years—and especially over the last two years—the rate of e-cigarette use among my patients has increased significantly. In particular, many of my 13- to 16-year-old patients now report using e-cigarettes, which was not the case at all a decade ago.

9. There is a significant difference between cigarette and e-cigarette treatment and counseling I can provide to patients. When patients use traditional cigarettes, counseling is relatively straightforward. There is an extensive array of research literature, professional training, and useful practical aids that can be used to teach kids about the health risks of cigarettes or to reinforce their background understanding that cigarettes are harmful.

10. The fact that the health risks of cigarettes are well-studied and broadly recognized among youth makes it easier to connect with and educate patients about the long-term and short-term harms of smoking than vaping. There are several well-studied treatment modalities for cigarette smoking cessation, such as cognitive behavioral therapy and motivational enhancement therapy, that have been proven to be effective in research and are often effective in my practical experience. For example, it is often possible to counsel adolescents about the risks of smoking by

discussing people in a patient's family who have been affected by the diseases caused by smoking, recognizing age-relevant cigarette-related consequences (e.g., breathing problems, odors) that can be reduced by quitting smoking, or identifying positive goals through motivational interviewing.

11. For youth using e-cigarettes, treatment and counseling are far more difficult. Many of my patients have strong beliefs that e-cigarettes are harmless, safe, and fun. At best, they may know that the product they use contains nicotine, but their background understanding of the harms of e-cigarettes is typically low to non-existent.

12. Unlike traditional cigarettes, however, I and other pediatricians lack the information we need to provide basic education about the risks of e-cigarettes, let alone the particular e-cigarette products a given patient uses. I can counsel my patients about the risks of nicotine use and addiction, and can inform them that we don't know the long-term effects of e-cigarette use, but I don't the same conclusive scientific evidence to concretely demonstrate the risks like I do with cigarettes. This lack of definitive evidence often makes it far harder for me to connect with my patients about the dangers of the e-cigarette products they are using.

13. In particular, my counseling and treatment is inhibited because there is so much variety among e-cigarette products, so little information about the contents of any given product, and so much variability even within a given product.

14. When I learn that a patient is using e-cigarettes, I ask what they use and how regularly they use it, and ask them to describe their use habits. Sometimes they can tell me, particularly with the most common products like JUUL. But many of my patients use their friends' devices or e-liquids, and cannot say with any specificity what they're using or what's in the e-cigarette device.

15. If patients can identify the product they use, I can sometimes—but not always—identify some of the chemicals and talk about their potential effects. But much of the time I can't even do that, either because there is insufficient information available about the product, the product is too variable to speak about authoritatively, or the patient doesn't know the product's specifics. Even when I am able to identify the product and some of its contents, my ability to counsel about its use is limited because of the scant information on the contents or their long-term effects.

16. Similarly, the lack of counseling tools related to e-cigarettes and other practice aids inhibits my ability to counsel and treat my patients. With cigarettes, pediatricians have access to numerous tools to use with patients, which can provide detailed information to help with patients' specific situations. While the AAP has guidelines and some other resources to aid pediatricians in treating patients who use e-cigarettes, they cannot provide the same kind of scientifically supported and detailed information and therefore provide far less help with individual patients.

17. As a result, it is far more difficult to provide information that can help patients change e-cigarette behavior, or even provide basic education.

18. Moreover, the proliferation of unapproved, kid-friendly products harms my patients' health, thus requiring more time and resources to treat. Nicotine addiction, respiratory ailments, and other consequences of e-cigarette use are often difficult conditions to treat, requiring significant time and expensive clinical resources.

19. As I noted above, I conduct research in the area of substance use and prevention, in addition to my practice. Here, too, the massive proliferation of different products and the lack

of standardization within a given product directly impedes my ability to perform my research work.

20. FDA regulation of cigarettes means that every cigarette marketed as a certain product will be pharmacologically identical, with few exceptions. Therefore, it is possible to study a product and reach definitive conclusions about its contents, use patterns, and susceptibility to various treatment modalities, or to compare one product against another.

21. With e-cigarettes, however, that is difficult if not impossible to study the product and reach definitive conclusions about how its use will impact the health of patients. Because manufacturers do not need to submit their products to the FDA for premarket review, they do not need to standardize them to ensure that their contents are consistent. Thus, two research subjects using the same product might be exposed to significantly different levels of nicotine or chemical contents. As a researcher, therefore, I cannot reach any definitive conclusions about the impacts of a given product, nor can I definitively compare different products. Any attempt to do so would be subject to critique from peer reviewers and industry.

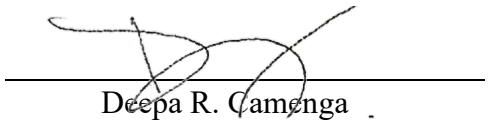
22. This feeds back into the problems in counseling and treating that I discussed above. Because we can't adequately study e-cigarettes, we can't answer patients' questions or translate research results into practice.

23. These problems are all magnified for patients who have co-occurring substance use disorders. Many of my patients also use alcohol or other drugs. We have extensive literature and practical aids regarding the interaction between cigarettes and other substances, but far less with regard to e-cigarettes. In particular, there is virtually no literature that we can rely on about the co-use of e-cigarettes and alcohol.

24. I encounter a similar problem with cigars. Some of my patients use cigarillos, particularly in conjunction with marijuana. The wide variety of cigarillos makes it much more difficult to counsel patients about the risks of the products that they are using, and to connect their use habits to their background knowledge of the dangers of cigarettes. Some of my patients associate cigarillos first with their flavors, and much less with nicotine or tobacco. The risks of nicotine addiction and tobacco consumption are far less salient, in part because the products they use seem so close to candy or other innocuous substances.

25. There is fairly little scientific literature or FDA-published information about these flavored products, and my patients often do not know what products they use within the vast array of products available to them. This makes it far harder to counsel them about the risks of their consumption, to treat comorbid substance use issues, or to provide information for which they look to me as a medical professional.

Signed under the pains and penalties of perjury this _27__ day of August, 2018



Deepa R. Camenga

EXHIBIT I

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF JONATHAN WINICKOFF, MD

I, Jonathan Winickoff, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am a board-certified pediatrician and a Professor at Harvard Medical School, where I serve as the Director of Pediatric Research in the Tobacco Research and Treatment Center. I have received numerous awards for my work in pediatrics, including the Department of Health and Human Services' Secretary's Award for Distinguished Service and the 2011 Academic Pediatric Association Health Policy Award.

3. I am also a member of the American Academy of Pediatrics ("AAP"). From 2003 to 2010, I served as the Chair of AAP's Julius Richmond Center of Excellence Tobacco Consortium, a national group of researchers who take a family-centered approach to tobacco control issues that affect children. I currently serve as the Director of Translational Research for the Richmond Center.

4. I practice medicine at Mass General Hospital in a pediatric group practice. In this practice, I treat patients from birth through age 22, seeing patients from all socioeconomic classes.

Impact of Electronic Cigarettes on My Practice

5. The proliferation of hundreds of varieties of e-cigarette products, the absence of the definitive information that would be provided as a result of premarket review, and the ready availability of e-cigarette products to my patients has had a substantial impact on my ability to carry out my professional obligations, requiring me to spend a significant amount of time on e-cigarette counseling and education—to the detriment of other patients, my e-cigarette–using patients' health, and my practice's income and expenses. FDA's failure to keep e-cigarettes off the market until they are approved through premarket review thus harms both my patients' physical health and (less importantly, but no less certainly) my practice's financial health.

6. Many of my patients are teenagers. In the past six months, not a visit with a teenager has gone by where we haven't talked about e-cigarettes. Every one of my teenage patients (and many of my preteen patients) either uses e-cigarettes or has friends who use them.

7. This been a complete change from my practice in prior years. In Massachusetts, rates of nicotine addiction had been very low for several years, in large part thanks to steady declines in the use of cigarettes. Accordingly, counseling on tobacco and nicotine was, for most patients, relatively simple: I asked common screening questions about tobacco use, and then could either move forward to other matters or use well-established treatment modalities to help my patients combat their use of or addiction to nicotine. Because my patients almost universally had a background understanding of the dangers of cigarettes, the doctor-patient relationship

could build on a basic recognition that they would be better off not smoking, which allowed for a therapeutic alliance to identify ways to change behavior.

8. Counseling teens and preteens on e-cigarette use starts from a completely different and far more challenging point. Unlike with traditional cigarettes, which kids know to be harmful, many of my patients hold unsubstantiated or simply incorrect beliefs about e-cigarettes. In the absence of clear governmental and public health messages about e-cigarettes, my patients cite the widespread availability of e-cigarettes—along with the youth-focused marketing of e-cigarettes, the proliferation of kid-friendly favors, and pro-vaping messages from e-cigarette makers—as the basis for inaccurate beliefs that e-cigarettes involve harmless water vapor or that nicotine isn't dangerous. Indeed, I have had to educate patients that e-cigarettes do not have the same positive health benefits as the fruits whose flavors they copy—for example, that using a mango-flavored e-liquid does not have the same beneficial properties as eating a mango.

9. As a result, counseling patients on e-cigarette use is significantly more difficult. I not only start from square one in terms of a patient's knowledge about nicotine addiction and the other health impacts of e-cigarette use (discussed further below), I often need to push back on strongly held but inaccurate beliefs. This effort takes far more time than reinforcing the scientifically based messages most patients have already received and internalized regarding traditional cigarettes.

10. The difficult task of counseling patients on e-cigarette use often consumes as much as a third of a visit. This either takes the place of time I can counsel my patients on other important health issues, such as exercise or STD protection, or lengthens my sessions so that I

can see fewer patients—with a corresponding effect on both my patients' health and my practice's income.

11. In addition to the time I spend directly counseling patients on e-cigarette use, I need to treat the health effects that come with nicotine addiction and e-cigarette consumption. My patients who use e-cigarettes may have asthma, exhibit nicotine addiction, or suffer from other diagnosable chronic conditions, all of which require time and attention. The comorbidity of these conditions often makes treatment substantially more challenging and expensive.

12. Similarly, e-cigarette use often comes with behavioral corollaries. Nicotine addiction is not cheap for a child; e-liquid pods often cost $4-5, and some of my patients go through a pod a day. As a result, some of my patients deal e-liquids or e-cigarette products to friends who do not have a reliable way to obtain them themselves, shoplift them, or steal money from their parents to purchase them. For a pediatrician, these are crucial behavioral issues to discuss and deal with, both with patients and with their families.

13. The rise in e-cigarette use has also required me to spend a huge amount of time outside individual sessions. For one thing, I spend a substantial amount of time trying to find suitable cognitive-behavioral therapists for my patients. Cognitive-behavioral therapy is one of the leading forms of treatment for nicotine addiction, but there is a shortage of providers compared to the current need. I often stay late after I finish my appointments trying to identify or arrange a viable referral for my patients.

14. I also spend a large amount of time outside my appointments educating myself about the newest e-cigarette products. To competently counsel a patient and have a successful therapeutic relationship, I need a substantial amount of information on the product he or she is using. In most cases, if a teenage patient believes that they know more about the product that

they are using than I do, they will not trust my opinion on the product and will put little stock in the advice I give on its use. Based on what my teenage patients tell me about the products they use and how they choose them, I have learned that many kids are constantly looking for the newest and trendiest products—not to mention products that their teachers and parents won't recognize. With the wide variety of products and the frequent release of new products, this means that I spend several hours a month—sometimes several hours a week—attempting to find information on the latest product.

15. Because the government does not put out information on specific products, as it would if products had to go through premarket review, I must rely on incomplete medical literature and the scant, often unreliable information made available online by manufacturers just to piece together the chemistry of what's happening in each product and the implications for my patients who use it. The process of getting educated on these hundreds of products has been a necessary and tremendous burden, and has impacted my life both outside my practice (by taking up personal time) and inside my practice (by taking time away from other patients).

Impact of Cigarillos and Other Cigar Products on My Practice

16. Much of what I said above is equally true of flavored cigars, cigarillos, and other products in the cigar family.

17. While my patients' use of cigar products is less pervasive than their use of e-cigarettes, if is still significantly higher than their use of cigarettes. In particular, many of my patients smoke flavored cigarillos, which are nearly identical to flavored cigarettes (indeed, *cigarillo* is simply the Spanish word for cigarette), or use blunt wraps (that is, tobacco leaves) to smoke marijuana.

18. My patients report the same misunderstandings for cigarillos as they do for e-cigarettes. Cigarillos are inexpensive, marketed in kid-friendly flavors and packaging. They are also often sold within kids' reach at convenience-store counters, making them easy to obtain. The inexpensiveness, widespread availability, and appealing flavors of cigarillos all combine to give kids the illusion that they are a safer product—a fun thing to try, not a serious health risk. To paraphrase what many patients have said to me, "If they were so harmful, why would the government allow them to be sold? Cigarettes don't have these flavors and aren't sold like this, so these must be ok."

19. Counseling and treatment of kids who use cigarillos thus has many of the same challenges as counseling and treatment of e-cigarette use, discussed above. I need to fight against a false sense of security that has been fostered by the government's refusal to take these products off the market until they have gone through premarket review.

20. Flavored blunt wraps pose similar, and often even more severe, problems. Blunt wraps are essentially the tobacco-leaf wrapping of a cigar sold without the tobacco filling, which users can fill themselves with a combustible substance of their choosing (most often, marijuana). They serve the same function as traditional cigarette rolling papers or other marijuana delivery devices such as bowls or pipes—but unlike those products, blunt wraps are made from tobacco and thus carry the same health risks as other tobacco products, including nicotine addiction and exposure to carcinogens.

21. Here again, many of my patients do not realize that blunt wraps carry these health risks, and their widespread availability leads many patients to believe that they are perfectly healthy, simply a wrapper that tastes like strawberries or candy. Few of them realize that they are

developing nicotine addiction and otherwise exposing themselves to health impacts at least as significant as the marijuana itself.

22. In addition to all of the implications for my practice that I discussed above (e.g., greater time spent with patients using blunt wraps, the need for treatment of associated conditions, and the need to research these products to understand what they are made of and how kids are using them), this also leads to many of my patients having dual addictions. Dual addictions are more complicated to explain and far more complicated to treat, creating difficulties both for me as a clinician and, more importantly, for my patients' health

Impact of Adults' Use of E-Cigarettes on My Practice

23. In addition to treating preteens and teenagers themselves, much of my practice and research is focused on familial factors and, in particular, parental use of tobacco products.

24. Over the past few decades, Americans have become far more aware of the dangers and harms of secondhand and thirdhand smoke, both societally and in their own families. "Secondhand smoke" generally refers to the plume released by smoking combusted tobacco; "thirdhand smoke" generally refers to the gases and residue left behind after a tobacco product is smoked. Both secondhand and thirdhand smoke create significant exposure to nicotine and carcinogenic substances, through inhalation, ingestion, dermal exposure, and other forms of contact. I have devoted much of my career to studying and reducing secondhand and thirdhand smoke, including developing the Clinical Effort Against Secondhand Smoke Exposure ("CEASE") program to help clinicians address familial tobacco use as a way of improving the health of entire families.

25. While the work that the medical community has put into increasing awareness and reducing incidence of secondhand and thirdhand smoke has had tremendous successes, the

proliferation of e-cigarettes without accompanying scientific information and the widespread misconceptions about them has led to major setbacks in these efforts.

26. Many parents share the same misconceptions as teenagers regarding e-cigarettes. Even for those who understand that they contain nicotine and may contain other harmful substances, there is a widespread perception that they do not produce secondhand and thirdhand smoke. Unlike traditional cigarettes, e-cigarettes create no ash and little if any visible plume, producing instead a scented and often invisible gas. Many people—including a large share of the parents I counsel—assume that this has no health impacts for people other than the e-cigarette smoker. Accordingly, my patients' parents and others smoke e-cigarettes in places and situations they would never smoke a cigarette: in their cars, in their homes, and around their children.

27. The assumption that e-cigarettes do not have deleterious secondhand and thirdhand effects is wrong. The gases produced by using e-cigarettes may appear harmless or even invisible, but they contain aerosols and toxins, typically including both nicotine and class-one carcinogens.

28. Nicotine and tobacco toxin exposure can create symptomatic conditions in patients of all ages. Indeed, for very young children, the consequences of secondhand and thirdhand exposure may be even more significant than what teenagers are experiencing, because of the heightened vulnerability of infants and toddlers. Babies exposed to nicotine have higher rates of SIDS; children of all ages are more susceptible to ear infections, pneumonia, and influenza; and school-aged children exposed to nicotine exhibit higher rates of ADHD.

29. The increased symptomology of children whose family members use e-cigarettes requires a significant amount of time and resources from my practice. ADHD is one of the most difficult issues for pediatricians, one of the conditions that takes the most time to treat, and one

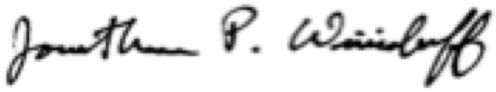
of the costliest pediatric diseases from both a payor's and a clinician's perspective. The increase in ADHD that comes from tobacco product exposure increases these costs for me and my practice.

30. The increase of secondhand and thirdhand smoke also requires extensive counseling of parents who use e-cigarettes (or who have other household members who use them), both to help them alter their behavior and to come off tobacco products altogether. Counseling and treatment of parents is a fraught and time-consuming issue for pediatricians, which has to be handled sensitively and over a long period of time if it is to be successful in protecting children. When it goes wrong, it can seriously harm the therapeutic alliance and create significant barriers to providing medical care to the child.

31. Moreover, the programs that we developed through CEASE and that others have developed were designed for traditional cigarettes, not for e-cigarettes. The differences, and the diversity of e-cigarette products, require extensive work to refine the programs to address families' e-cigarette use. Even then, the thorough research that has gone into developing and evaluating cessation products does not exist, and it is largely unknown what alterations are most effective for e-cigarettes in general (let alone any particular e-cigarette product).

32. Accordingly, the problem of adult use of e-cigarettes exacerbates the problems I explained above for my time, my patients' health, and my practice's income manyfold because many parents are using these products—and they can be parents of any aged child. Young children see the pediatrician over ten times in the first two years of life. The necessity of having e-cigarette discussions with parents thus multiplies the number of conversations I need to have manyfold.

Signed under the pains and penalties of perjury this 24th day of August, 2018



Jonathan Winickoff

EXHIBIT J

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF LEAH BRASCH, MD

I, Leah Brasch, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I have been a board-certified pediatrician since 1985. I am a partner and owner of Friendship Pediatrics in Chevy Chase. I am also a member of the American Academy of Pediatrics ("AAP") and a member of the AAP's Maryland chapter.

3. Since about 2014, I have asked my patients about e-cigarette use in my standard screening. As a result, I have learned that some of my teenage patients use e-cigarettes, some infrequently and some on a regular basis.

4. When I learn that a patient is using e-cigarettes, I talk to them about the risks of nicotine addiction. But I don't have much more information than that to tell them. We need good quality research on the effects of e-cigarettes on youth, both short term and long term. I have been unable to find clinically useful information from the sources I would normally turn to for practical information about the medical and public health issues my patients encounter.

5. This inhibits my ability to provide counseling and treatment to my patients in multiple ways. I don't have the kind of information I usually provide to help kids deal with sociologically complicated issues, such as traditional smoking or sexual activity. For example, I use evidence-based handouts on obesity in helping patients improve their nutrition, reinforcing the counseling I provide during our appointments. Such information does not exist with e-cigarettes, making it far harder to provide meaningful care to my patients.

6. I am also at a disadvantage because there seem to be many different products that I simply can't advise my patients on. For example, I have had patients tell me they use "low-percentage nicotine" vaping liquid. I don't know what that means and have been unable to find specific, medically useful information on these products, and can't counsel them on whether that actually does reduce their risk of nicotine addiction or other side effects. I am thus seriously limited in the counseling I can provide my patients and my ability to be an authoritative source of medical information, limiting my ability to carry out my responsibilities to them as their physician.

7. My co-partner in Friendship Pediatrics, Linda Goldstein, is also a plaintiff in this case. I am familiar with her practice by virtue of my co-ownership of the practice and our regular clinical discussions of our patients' care and practice business. She encounters the same obstacles I do in providing care to patients who use e-cigarettes, with similar effects on her practice and her ability to carry out her responsibilities as a physician.

Signed under the pains and penalties of perjury this 27 day of August, 2018

Leah Brasch

EXHIBIT K

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF CYNTHIA FISHMAN, MD

I, Cynthia Fishman, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am a board-certified pediatrician and have practiced pediatric medicine in Montgomery County for more than 20 years.

3. I am a partner in and owner of a pediatric practice with offices in Silver Spring and Rockville. My practice covers a wide range of ages, ethnicities, and insurance payors.

4. I am also a fellow of the American Academy of Pediatrics ("AAP"), a member of the AAP's Maryland chapter, and a fellow of the Montgomery County Medical Society.

5. Until the last two or three years, neither e-cigarettes nor traditional tobacco products were a notable presence in my practice. I asked screening questions about cigarettes, but very few of my patients smoked any tobacco products and all seemed to understand that it was a risky, undesirable behavior.

6. Around two years ago, my daughter—at the time a freshman in high school—told me kids were vaping in her classes at school. At first, it sounded impossible that teachers

wouldn't see and stop it. But she explained that they were easy to hide, could look like anything, and didn't produce tobacco odors or smoke—and even smelled like cotton candy or apple juice.

7. After learning about vaping from my daughter, I began including e-cigarette questions in my routine tobacco screening. I was shocked at how many of my patients said they had tried e-cigarettes or regularly vaped.

8. The number of patients who use e-cigarettes has only increased in the two years that I've been asking about e-cigarette use. At this point, I would estimate that about one-third of my high school–age patients report using or trying e-cigarettes. This includes many kids who say they would never smoke cigarettes or marijuana.

9. Counseling patients on e-cigarette use now takes up a significant amount of time in my practice. My appointments are typically 15-20 minutes long, during which I have to prioritize all of the medical and sociological issues my patients are dealing with, from acute illnesses to ongoing topics like anxiety, nutrition, or risk behaviors. When I learn that a patient is vaping, I need to spend some of my limited time counseling them on their nicotine use and the possible consequences of nicotine addiction. This reduces the amount of time I can spend on other issues, often preventing me from working with them on health and safety issues such as diet or sexual activity. This inhibits my ability to have a long-term positive effect on a range of issues that are essential for healthy adolescent development.

10. I have also found counseling teenagers on e-cigarette use to be significantly more challenging than counseling them about traditional cigarettes, for a number of reasons.

11. First, I don't have nearly the same level of information or material to use with patients. I look to the AAP and other national medical organizations and resources for information to use in my practice, but that information is noticeably lacking for e-cigarettes.

Indeed, I have had to rely on my teenage daughter for information about how e-cigarettes work and how they're used as much as I've been able to rely on the professional sources I turn for most other issues.

12. Second, many of my patients don't know that vaping involves nicotine or tobacco, and believe that it is largely safe and non-addictive. It often takes significant discussion to convince a kid that vaping has negative consequences, even if they say they would never smoke a cigarette. So unlike my few patients who smoke cigarettes, my many patients who vape require substantial remedial education before we can even begin discussing motivations for quitting or otherwise seek to reduce risk behaviors.

13. Third, the materials that I do have for helping teens quit smoking have generally been ineffective with vaping. For example, I recently had a patient who developed asthma late in adolescence, after vaping every day. Unlike most of my patients, this patient did recognize that vaping was harming him (in part because the patient was older and thus had better-developed higher-order thinking than younger teens) and was trying to cut down. But the available tobacco cessation materials focus on cigarettes, not vaping, and don't translate very well to the particular needs of patients who vape.

14. Fourth, the great diversity of products makes it hard to understand my patients' use and connect with my patients. Some of my patients will say "no" when I ask them if they vape, but "yes" if I specifically ask them about JUUL or another name-brand product. The more specific I can be about the product a patient uses—its cartridge system, its aesthetic design, etc.—the more the patient listens and the more productive our conversation tends to be. But because I can't keep pace with the new and different products my patients are using, I am often at a disadvantage in my appointments and my attempts to reach my patients.

15. Finally, I have to spend time educating parents, as well as their children. Most parents don't know what vaping and don't know what to look for. I frequently spend a couple minutes educating my high-school patients' parents about vaping before or after an appointment, but the same information gaps and diversity of products inhibits these conversations as well.

16. In all, the widespread availability of a diverse array of vaping products without high-quality medical information significantly impedes my ability to assist my patients and improve their health outcomes, and has been one of the biggest challenges in my medical practice over the last two years.

Signed under the pains and penalties of perjury this 27th day of August, 2018

/s/ Cynthia Fishman
Cynthia Fishman

EXHIBIT L

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF STEVEN HIRSCH, MD

I, Steven Hirsch, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am a board-certified pediatrician and am the owner and founder of Hirsch Pediatrics, a solo pediatric practice in Rockville that I began in 2007.

3. I am also a fellow of the American Academy of Pediatrics ("AAP"), a member of the AAP's Maryland chapter, past president of the Montgomery County Pediatric Society, and an Assistant Clinical Professor of Pediatrics at George Washington University.

4. The majority of my patients are young children, but I see over 100 teenage patients as well.

5. Until recently, I didn't ask about vaping in my standard screening. I asked about smoking cigarettes and marijuana, but virtually none of my patients used either.

6. Earlier this year, however, I learned from several patients that classmates were vaping in school. That led me to start asking my adolescent patients about vaping in addition to traditional tobacco products and other drug use.

7. Since I started asking, many of my patients have reported that they know kids who vape, including in the classroom, and some admit that they've tried vaping themselves.

8. I have little scientific evidence that I can provide to my patients to help educate them about the risks of vaping. When dealing with public health issues like sexual activity, safe driving, or tobacco use, I rely on sources like the Center for Disease Control, FDA, and AAP for extensive scientific evidence about the risk profile and health consequences of various behaviors, as well as for handouts and other practice aids to use with patients. But with vaping, I don't have the information I would have normally have. I haven't found significant scientific resources for educating patients about the risks of vaping.

9. This inhibits my ability to counsel my patients. Even though I know vaping exposes teenagers to risks for nicotine addiction and respiratory ailments, I don't have the authoritative, credible sources I would normally rely on to back up my advice. I'm also at a disadvantage because I don't know the specifics of many of the products they use, other than the most common one, JUUL. This significantly compromises my ability to carry out my professional responsibility to provide informed care for my patients.

Signed under the pains and penalties of perjury this 27th day of August, 2018

/s/ Steven Hirsch
Steven Hirsch

EXHIBIT M

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

DECLARATION OF DAVID MYLES, MD

I, David Myles, hereby state, under penalty of perjury, that the following information is true to my knowledge, information, and belief:

1. The information set forth in this affidavit is based on my personal knowledge.

2. I am a board-certified pediatrician. I work primarily as a general pediatrician in an Emergency Department in Westminster, Maryland, in addition to volunteering as a general pediatrician in an outpatient pediatric clinic in Germantown, Maryland, located in Montgomery County. I am also a member of the American Academy of Pediatrics ("AAP") and a member of the AAP's Maryland chapter.

3. Around early 2017, I added questions about e-cigarette use to my standard screening assessment. Since I began to ask about e-cigarettes, I have found that many more of my patients are using e-cigarettes than traditional cigarettes.

4. This has posed numerous problems for my counseling. When my patients use cigarettes, it's relatively easy to counsel them on their tobacco use, because they understand that smoking is dangerous. With e-cigarettes, though, many of my patients don't view e-cigarettes as having serious health impacts.

5. To make any headway with my patients, I have to explain to them that e-cigarettes contain nicotine, which is addictive and harmful. But I don't have the kind of evidence-based, empirical knowledge that I can use with cigarettes and other risk behaviors, so much of the message I can give them is that I simply don't know the specific health risks of their e-cigarette use. This prevents me from making cogent recommendations, and reveals a lack of knowledge that makes my advice far less effective.

6. For example, when I see a patient who smokes cigarettes, I will employ cessation support techniques such as motivational interviewing, where we discuss their goals and help them understand how their habits make them harder to achieve. This is most effective when I can concretely explain the medical link between smoking and the adverse health impact. If a patient wants to play in the NBA, for example, my ability to explain in an evidence-based way that smoking decreases lung capacity and function helps me lead them to see why smoking interferes with their objectives. With e-cigarettes, I don't have the evidence-based scientific information I need to perform the same professional role.

7. My work is also impeded by the range of products on the market. I don't know the difference between devices or the specifics of most products, so I don't know how to talk about their products in a credible, well-informed fashion. This inhibits my ability to connect with them as a clinician and to carry out my professional obligations as a physician.

Signed under the pains and penalties of perjury this 24th day of August, 2018

David Myles