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December 16, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting That FDA Take Certain Actions With Respect to Electronic Nicotine Delivery Systems to Curtail Youth Initiation and Use and to Encourage the Development and Adoption of Nicotine Products With Lower Health Risks

Dear Sir or Madam:

On behalf of Respira Technologies, Inc. ("Respira"),[1] the undersigned hereby submits this Citizen Petition pursuant to sections 901, 902, 903, 904, 906, 907, 910, and 915 of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. §§ 387a, 387b, 387c, 387d, 387f, 387g, 387j, 387o) and 21 C.F.R. §§ 10.25 and 10.30 to request the Commissioner of Food and Drugs to take certain actions with respect to electronic nicotine delivery systems ("ENDS") to curtail youth initiation and use of nicotine products, particularly ENDS products, and to encourage the development and adoption of innovative nicotine products with lower health risks.

The United States is grappling with *another* public health crisis fueled by the tobacco industry – this one related to electronic cigarettes ("e-cigarettes") and vaping. In the past few years, the use of e-cigarettes by middle and high school students has surged to "epidemic proportions," ***with more than 5 million youth using e-cigarettes in 2019***. This epidemic of youth usage has coincided with an unexpected and unexplained outbreak of serious lung injuries associated with the use of ENDS products, referred to by the Centers for Disease Control ("CDC") as "e-cigarette, or vaping, product use associated lung injury," or "EVALI." As of December 3, 2019, the CDC had received reports of ***nearly 2,300 cases of EVALI, including forty-eight (48) deaths.*** Moreover, the scope of this public health crisis is broad, with reports coming from all fifty states in the U.S., the District of Columbia, and two U.S. territories (Puerto Rico and the U.S. Virgin Islands).

[1] Respira Technologies is a healthcare platform technology company focused on delivering safe and effective inhalation experiences across nicotine, cannabis and medical drug delivery. Our technology platforms are unique because our IP protected devices and liquid formulations create aerosol without heat and harmful and potentially harmful constituents. Respira has a strong interest in supporting government policies that encourage the development and adoption of nicotine products with lower health risks and that are less appealing to youth.

The growing epidemic of youth usage of ENDS products and the outbreak of serious lung injury cases across the United States, including several deaths, demand swift, decisive and targeted regulatory action by the Food and Drug Administration ("FDA") to protect the public health. FDA was granted authority to regulate tobacco products in 2009, but the Agency has focused most of its attention on combustible products such as cigarettes and, thus far, has left non-combustible tobacco products like ENDS largely unregulated. Indeed, the Agency repeatedly has extended the compliance period for manufacturers of ENDS products to submit Pre-Market Tobacco Product Applications ("PMTA"), effectively allowing them to remain on the market without FDA review for years. Unfortunately, this "hands off" approach has not been effective and instead has contributed to an explosion in youth usage of e-cigarettes, an unexplained outbreak of serious lung injury cases across the United States, and an environment where the public is quickly losing faith in FDA's ability to drive tobacco harm reduction. As a result, many states are stepping into the perceived regulatory vacuum by enacting sweeping laws, such as banning flavored e-cigarettes, to safeguard the public health.

FDA, however, is the only governmental agency with the expertise and authority to offer a comprehensive, nation-wide solution to the dual public health crises facing the United States. To address these public health crises, Respira agrees with Dr. Stephen Hahn, the newly confirmed FDA Commissioner, that FDA must take "bold action." This petition therefore requests FDA to exercise federal leadership over this health crisis by adopting a comprehensive, targeted, and balanced strategy to stop the epidemic of youth tobacco usage and to drive the development of innovative tobacco products with lower health risks. More specifically, FDA should immediately develop new regulations and policies that impose stricter controls over ENDS products and heated tobacco products but that do not drive tobacco use toward more dangerous combustible products, such as cigarettes. These controls, which are described in more detail below, should:

- Prohibit products with nicotine formulations that appeal to youth and/or facilitate youth addiction;

- Impose stricter marketing limits to prevent exposure to youth and eliminate youth access;

- Promote innovation and incentives for industry to drive down risk to the lowest possible levels, including by imposing limits on harmful or potentially harmful constituents ("HPHCs");

- Impose packaging and labeling requirements designed to provide consumers with accurate information about a product's known or suspected health risks; and

- Align industry, FDA and public health priorities.

These regulatory actions are necessary because, although ENDS products generally are regarded as less harmful than combustible cigarettes, they are far from safe, and many of the short- and long-term risks associated with their use still are unknown. All currently available ENDS products operate by heating a liquid to create an aerosol that the user inhales. This heating process creates numerous toxic and/or carcinogenic chemicals, such as formaldehyde, acetaldehyde, and

volatile constituents, such as benzene. Moreover, the heating element itself, which usually consists of a metal coil or ceramic, can pollute the aerosol with metallic nanoparticles, such as nickel and hexavalent chromium. Because aerosol microparticles can penetrate deeply into the respiratory system, the toxic chemicals contained in ENDS aerosol created by heating may pose a risk for diseases not usually seen in smokers.

These risks, however, can be minimized. Indeed, there is evidence that the epidemic of youth usage is fueled by how current ENDS products are designed, manufactured, and marketed. Dr. David Kessler, a former Commissioner of FDA, summed it up nicely in a recent speech on tobacco regulation where he stated: "Make no mistake, the design, whether intentional or not, of a vast number of these products (ENDS), their chemical makeup, facilitates initiation. It is why at the end of the day I don't see how you could possibly get to that standard of appropriate for the protection of public health."[2]

Accordingly, Respira believes that more aggressive and comprehensive regulatory oversight over how ENDS products are designed, manufactured and marketed is necessary to protect the public health. FDA, however, cannot wait any longer to exercise its authority. Given the dual public health crises described above – the growing epidemic of ENDS usage among America's youth and the outbreak of serious and unexplained lung illnesses associated with ENDS usage throughout the country – the need for "bold action" and FDA leadership is urgent. Respira thus respectfully requests that FDA act swiftly to protect the public health by implementing the six regulatory actions requested below.

I. Actions Requested

For the reasons that follow, Respira respectfully requests the Commissioner to take the following regulatory actions and to refuse to approve any PMTA (or to rescind such approval) for an ENDS product that fails to satisfy the new requirements requested herein:

1. **Nicotine Standard**: Establish a nicotine standard for ENDS products that limits the amount of nicotine by percent weight while allowing for innovation to nicotine delivery that effectively switches smokers to new ENDS and other products further down the risk continuum.

2. **HPHC Standard**: Establish a product standard for all ENDS products that limits exposure to HPHCs and known toxins, such as formaldehyde and hexavalent chromium, to scientifically validated exposure limits. This standard should initially focus on a short list of constituents where there is strong scientific evidence (*e.g.*, formaldehyde), measured inhalation values, and safe EPA inhalation standards already in place. Over time, this standard should be expanded as inhalation science is deepened to eventually drive HPHCs to the lowest possible value, ensuring ENDS are appropriate for the protection of public health.

[2] Speech by David A. Kessler, "A Conversation with David A. Kessler on the Future of Youth e-Cigarette Use and Regulation David A. Kessler," FDLI Tobacco and Nicotine Products Regulation and Policy Conference (Oct. 25, 2019).

3. **Required HPHC Disclosures**: Establish standardized warnings and HPHC Fact Panels for all ENDS products and heated tobacco products to appropriately inform consumers of the absolute and relative risks of exposure to HPHCs posed by their use. Moreover, FDA should require all PMTA applications to provide science and evidence to create a product-specific warning that clearly states the intended use of the approved product and the absolute and relative risk, similar to the warning required on the recently approved IQOS product (*i.e.*, "Any use of this product other than exclusively switching from smoking, including first time use by a non-smoker, increases your risk of tobacco related disease.").

4. **Restrictions on Sale and Distribution**: Impose marketing restrictions on all ENDS products to prevent youth usage, including a requirement that ENDS products must be sold in a non-self-service format that requires not only age verification but also implementation of a purchase registry similar to pseudoephedrine sales, which was enacted to greatly restrict access/purchase to unintended audiences.

5. **Fast Track Pathway for Innovative Products**: Establish a voluntary, fast track pathway for the approval of ENDS products that deliver meaningful reductions in HPHCs versus currently marketed ENDS products; and

6. **Expanded Post-Market Reporting**: Require manufacturers of approved ENDS products to periodically submit post-market reports providing a detailed analysis whether the continued marketing of such ENDS products is still appropriate for the protection of the public health in light of the availability of newly approved ENDS products. Such reports should be required: (1) no later than six months after the approval of a new ENDS product that represents a significant improvement in risk profile versus currently available tobacco products (*e.g.*, delivers a meaningful reduction in HPHC levels); and (2) at least every three years after approval.

II. Statement of Grounds

A. Legal and Factual Background

1. FDA Authority to Regulate Tobacco Products

In 2009, with enactment of the Family Smoking Prevention and Tobacco Control Act ("Tobacco Control Act" or "the Act")), Pub. L. No. 111-21, 123 Stat. 1776 (2009), Congress granted FDA the authority to regulate tobacco products for the first time. The main purpose of the Tobacco Control Act was to provide FDA with regulatory tools to protect the public health and, most importantly, to reduce tobacco use by minors. Congress specifically found that "[t]he use of tobacco products by the Nation's children is a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults." Tobacco Control Act, Pub. L. No. 111-21, §2(1). The Tobacco Control Act thus was enacted, in large part, to end this epidemic of pediatric use of tobacco products. As then-Commissioner Scott Gottlieb explained in 2017, the Tobacco Control Act is "all about kids and families."[3]

[3] Speech by Scott Gottlieb, M.D., Protecting American Families: Comprehensive Approach to Nicotine and Tobacco (June 28, 2017), *available at* https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017 (last accessed Nov. 26, 2019).

The Tobacco Control Act grants FDA broad powers to regulate the manufacture, marketing, and distribution of tobacco products. For example, section 905 of the FFDCA, which was added by the Tobacco Control Act, requires all owners or operators of tobacco manufacturing facilities to register their establishments with FDA and provide a list of all tobacco products processed at those facilities for commercial distribution. 21 U.S.C. § 387e. Under section 904, each tobacco manufacturer or importer also is required to provide FDA (within certain time limits) with detailed information about (1) the ingredients in each tobacco product, and (2) the constituents, including smoke constituents, in each tobacco product that FDA has identified as harmful or potentially harmful to health.[4] *Id*. § 387d. And FDA is specifically authorized under section 915 to require manufacturers to test, report, and disclose tobacco product constituents, ingredients, and additives, including smoke constituents, that the Agency determines should be tested to protect the public health. *Id*. § 387o.

In addition, the Tobacco Control Act authorizes FDA to adopt a tobacco product standard if it determines such standard "is appropriate for the protection of the public health." *Id*. § 387g(a)(3)(A). In making such a determination, FDA must consider scientific evidence concerning: (1) the risks and benefits of the proposed standard to the population as a whole, including users and nonusers of tobacco products; (2) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (3) the increased or decreased likelihood that those who do not use tobacco products will start using such products. *Id*. § 387g(a)(3)(B)(i). Among other things, a product standard can include, where appropriate for the protection of the public health, provisions for the reduction or elimination of non-nicotine constituents, including smoke constituents, or other harmful components of the product. *Id*. § 387g(a)(4)(A)(ii).[5] Where appropriate, a product standard also should prescribe the form and content of labeling "for the proper use of the tobacco product." *Id*. § 387g(a)(4)(C). A tobacco product that fails to comply with an applicable tobacco product standard established under section 907 is considered to be "adulterated." *Id*. § 387b(5).

The Tobacco Control Act also provides FDA with broad authority to issue regulations establishing restrictions on the sale and distribution of tobacco products if FDA determines such regulations would be appropriate for the protection of the public health. *Id*. § 387f(d)(1). These restrictions may impose limitations on access to, or the advertising and promotion of, a tobacco product. *Id*. If restrictions on the sale and distribution of a tobacco product are imposed under this section, FDA may require the label of the tobacco product to bear "appropriate statements" describing the restrictions. *Id*. § 387f(d)(2).

Finally, section 910 of the FFDCA requires manufacturers to obtain premarket authorization from FDA before marketing a new tobacco product. *Id.* § 387j. A "new tobacco

[4] FDA established a preliminary list of 93 harmful and potentially harmful constituents ("HPHCs") in tobacco products in 2012. 77 Fed. Reg. 20034 (Apr. 3. 2012). FDA recently proposed to update this list to add 19 HPHCs to reflect the range of tobacco products subject to regulation under the Deeming Rule. 84 Fed. Reg. 38032 (Aug. 5, 2019).

[5] Last year, FDA proposed establishing a tobacco product standard under this authority to set the maximum nicotine level for combusted cigarettes. *See* 83 Fed. Reg. 11818 (March 16, 2018). Recently, however, there have been reports that FDA has dropped or delayed this proposal because it was not included on the Agency's Fall 2019 Unified Agenda of Regulatory and Deregulatory Actions released on November 20, 2019. *See* https://www.reginfo.gov/public/do/eAgendaMain.

product" is defined as any tobacco product that was not commercially marketed in the United States as of February 15, 2007 or any modification to a tobacco product after that date. *Id*. § 387j(a)(1). To obtain premarket authorization, a manufacturer must submit either: (1) a premarket tobacco application ("PMTA") demonstrating, *inter alia*, that the product would be "appropriate for the protection of the public health;" (2) a report establishing that the product is "substantially equivalent" to a predicate product; or (3) a request for an exemption from the substantial equivalence requirement. *Id*. §§ 387j(a)(2), (b). Generally, if a new tobacco product is marketed without either a PMTA, substantially equivalent marketing order ,or a finding of exemption from substantial equivalence, it is adulterated and misbranded under sections 902 and 903 of the FFDCA, respectively. *Id.* §§ 387b(6), 387c(6).

A PMTA must contain, among other things, full reports of investigations made to identify the health risks of the tobacco product and whether the tobacco product "presents less risk than other tobacco products." *Id*. § 387j(b)(1)(A). Given the focus on whether a new tobacco product is "appropriate for the protection of the public health," FDA has explained that the PMTA process is intended to "spur creative evolution and help to create a market where available products present a lower risk of user and population harm." 81 Fed. Reg. 28974, 29044 (May 10, 2016). In other words, the PMTA process is designed to drive innovation toward safer tobacco products and thereby create a tobacco marketplace that evolves over time to present less risk to tobacco users.

The engine of this innovation is the "appropriate for the protection of the public health" standard. New tobacco products generally will not be able to meet this standard, and thus cannot be approved, unless they demonstrate reduced safety risks versus currently marketed tobacco products. Moreover, tobacco products are subject to continuing scrutiny under this standard even after they are approved. This is because FDA has the authority to withdraw previously approved products from the market if, because of the approval of newer, safer tobacco products, the continued marketing of such older products no longer is "appropriate for the protection of the public health." 21 U.S.C. § 387j(d). To help FDA apply this standard to approved products, the Tobacco Control Act authorizes the Agency to require the submission of post-market reports to enable it to determine whether a PMTA should be withdrawn. *Id*. § 387j(f)(1). By requiring sponsors to periodically justify why the continued marketing of older tobacco products is "appropriate for the protection of the public health" in light of the evolving marketplace for tobacco products, the PMTA requirements foster the development of a safer marketplace for tobacco products.

2. FDA Actions to Regulate ENDS Products

The Tobacco Control Act applied immediately to all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco. *Id*. § 387a(b). For other tobacco products, the Tobacco Control Act authorized FDA to issue regulations "deeming" them to be subject to the new statutory requirements. *Id*. On May 10, 2016, FDA issued final regulations deeming all products meeting the statutory definition of "tobacco product" (except accessories) to be subject to the statutory requirements established by the Tobacco Control Act. 81 Fed. Reg. 28974 (May 10, 2016) ("Deeming Rule"). Pursuant to the final Deeming Rule, ENDS products are now subject to regulation as tobacco products under the FFDCA, including requirements pertaining to, *inter alia*,

registration and listing, adulteration and misbranding, ingredient and HPHC listing, tobacco product standards, labeling, advertising, promotion, and premarket approval.

Unlike the first wave of regulated tobacco products (*i.e.*, cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco), products that are "deemed" to be subject to regulation, such as ENDS products, were not granted any explicit grace period to come into compliance with the new statutory requirements, particularly the premarket approval requirements. Nevertheless, the Deeming Rule, which became effective on August 8, 2016, established compliance periods for most such requirements, including registration and listing, ingredient listing and reporting of HPHCs, and advertising and promotion. 81 Fed. Reg. at 29006. In the three years since the Deeming Rule took effect, many of those requirements have now become effective for ENDS products. For example, manufacturers of ENDS products are now required to comply with registration and listing requirements (since 2017), submission of ingredient information to FDA (since 2018), and advertising and labeling restrictions, such as the requirement to prominently display a nicotine addiction warning on ENDS products containing e-liquids (since 2018).[6]

The one major exception is the Tobacco Control Act's premarket approval requirement, which has not yet been fully implemented by FDA. In 2016, the Deeming Rule established staggered compliance periods for newly deemed tobacco products to allow them to stay on the market while manufacturers prepared, and FDA reviewed, newly required marketing applications. 81 Fed. Reg. at 28977-78. Specifically, FDA gave manufacturers 24 months to submit PMTAs; 18 months to submit substantial equivalence reports; and 12 months to submit requests for exemption from substantial equivalence – plus an additional 12 months to secure FDA approval.[7] 81 Fed. Reg. at 29011. FDA established these relatively short compliance periods because it "determined that exercising enforcement discretion indefinitely could put youth and young adults at risk for tobacco-related death and disease[,]" 81 Fed. Reg. at 28977, which would be contrary to the intent of the Tobacco Control Act.

In 2017, FDA announced a comprehensive plan to guide its future regulation of tobacco products by focusing on nicotine, and the issue of addiction, in combustible cigarettes. Under this new plan, the regulation of non-combustible tobacco products, such as ENDS products, was placed on a back burner to "afford the agency time to explore clear and meaningful measures to make tobacco products less toxic, appealing and addictive."[8] FDA thus announced that it was extending the compliance date for the submission of premarket applications for ENDS products until August 8, 2022.[9] Moreover, this compliance period would continue, without limitation, during FDA's

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[6] FDA, *Guidance for Industry: Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule (Revised),* pp. 5-14 (March 2019).

[7] The grace period only applied to new tobacco products that were on the market as of August 8, 2016. 81 Fed. Reg. at 29011.

[8] FDA News Release, *FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death* (July 27, 2017).

[9] FDA, *Guidance for Industry: Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule (Revised)*, p. 8 (Aug. 2017) ("August 2017 Guidance"). Again, this compliance policy applied only to products that were on the market as of August 8, 2016.

review of an application until the Agency either rendered a decision or the application was withdrawn.[10] Thus, FDA's revised policy greatly expanded the time period during which an ENDS product could remain on the market ***without*** submission of a PMTA and ***without*** any determination by FDA that its continued marketing would be "appropriate for the protection of the public health."

FDA's revised compliance dates were subsequently challenged in federal court by several public health and medical organizations focused on children's health issues, such as the Campaign for Tobacco-Free Kids and the American Academy of Pediatrics. These organizations argued that FDA acted illegally and contrary to the requirements of the Tobacco Control Act by allowing ENDS products to remain on the market (a) until 2022 without applying for FDA authorization, and (b) indefinitely thereafter during FDA review of an application.

On May 1, 2019, the federal court hearing the case agreed with the Plaintiffs and vacated FDA's new compliance dates. The court concluded that the delayed compliance dates had played a role in the skyrocketing youth use of e-cigarettes, contrary to the intent of Congress in passing the Tobacco Control Act. According to the court:

> Instead of addressing public health concerns associated with tobacco use by minors and others, the [extended compliance date] exacerbates the situation by stating, in essence, that manufacturers can continue to advertise and sell products that are addictive and that target a youth market, like the "Apple Juice" e-cigarette discussed in Plaintiffs' Complaint, at a time when minors' use of tobacco products like e-cigarettes is at an epidemic level and rising. Arguably, the five-year compliance safe-harbor has allowed the manufacturers enough time to attract new, young users and get them addicted to nicotine before any of their products, labels, or flavors are pulled from the market, at which time the youth are likely to switch to one of the other thousands of tobacco products that already are approved—results entirely contrary to the express purpose of the Tobacco Control Act.[11]

To combat the "epidemic-level rise in youth e-cigarette use," the court thus reset the compliance dates for ENDS products that were on the market as of August 8, 2016.[12] Under the new deadlines, such ENDS product now must submit a premarket application no later than May 11, 2020 – more than two years earlier than FDA's prior deadline. Moreover, if an application is submitted in a timely manner, such ENDS products may remain on the market for no more than one additional year from the submission date to allow FDA time to review the application. After expiration of those deadlines, however, all ENDS products that have not received premarket

[10] August 2017 Guidance, p. 3.

[11] *American Academy of Pediatrics v. FDA*, 379 F.Supp.3d 461, 492 (D. Md. 2019).

[12] *American Academy of Pediatrics v. FDA*, Case No. PWG-18-883, Memorandum Opinion and Order, p. 10 (D. Md. July 11, 2019).

authorization or approval under one of the three available pathways would become subject to FDA enforcement action (in FDA's discretion). FDA has appealed the district court decision.

3. ENDS Products and the Continuum of Risk

FDA recognizes that products that contain nicotine pose different levels of health risk to users based on, among other things, their method of delivery. FDA considers combustible products, such as cigarettes, to pose the highest health risk because the nicotine is delivered to the lungs through smoke particles, which contain a toxic mix of more than 7,000 chemicals, many of which are carcinogenic. Nicotine replacement therapies ("NRTs"), such as patches and lozenges, fall on the other end of this "continuum of risk" and are viewed by FDA as being the least harmful. Falling somewhere in the middle of this continuum are ENDS products, which delivery nicotine to the lungs but without combustion. FDA has stated that it believes "the inhalation of nicotine (*i.e.*, nicotine without the products of combustion) is of less risk to the user than the inhalation of nicotine delivered by smoke from combusted tobacco products." 81 Fed. Reg. at 28981.

ENDS products represent a broad category that includes, among other things, e-cigarettes, e-cigars, e-hookahs, vape pens, advanced refillable personal vaporizers, and electronic pipes. All ENDS products, however, share some common characteristics. For example, all are handheld electronic devices that typically are composed of a battery, a reservoir for holding a liquid mixture ("e-liquid") that contains nicotine, a heating element or atomizer, and a mouthpiece. The heating element usually consists of either a metal coil or ceramic. E-liquids typically use propylene glycol and/or vegetable glycerin as a solvent for the nicotine, and many e-liquids also contain flavoring agents that may appeal to children. Once the e-liquid is aerosolized through heating, the ENDS user inhales the aerosolized vapor in a manner similar to inhaling tobacco smoke.

Although ENDS products generally are considered by both FDA and the general public to be less harmful than combustible cigarettes, they are far from safe. This is because all currently available ENDS products operate by using a heating source to create an aerosol that the user inhales. This heating process, however, results in the creation of numerous HPHCs, such as formaldehyde, acetaldehyde, acrolein, and free radicals, many of which are toxic and/or carcinogenic. Moreover, newer ENDS devices that contain larger batteries are capable of heating the e-liquid to higher temperatures. This has the potential for releasing more nicotine (thereby increasing addictiveness), forming more or additional chemical toxicants, and creating larger clouds of particulate matter for inhalation.[13] The U.S. Surgeon general has warned that the e-liquids in ENDS products "produce chemical reactions that may result in the formation of new, harmful compounds. Carcinogens (e.g., formaldehyde, acetaldehyde, and acrolein) and toxic heavy metals (e.g., lead, tin, and cadmium) have been found in e-cigarette aerosols in laboratory tests conducted at temperatures within the range of most e-cigarette products."[14]

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[13] E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General, p. 13 (2016) ("Surgeon General's Report") (Exhibit 1), *available at* https://www.cdc.gov/tobacco/data_statistics/sgr/e-cigarettes/index.htm#report. In addition, FDA has noted that "Some research has found that there are some ENDS devices and some power levels of operating ENDS devices that deliver more formaldehyde than other ENDS products and conventional cigarettes." 81 Fed. Reg. at 29031.

[14] Surgeon General's Report, p. 119 (Exhibit 2).

Moreover, the heating element itself can be a source of dangerous or toxic chemicals in the aerosol of ENDS products. As noted above, the heating element in ENDS products usually consists of a metal coil or ceramic. Metal coils are responsible for releasing metallic nanoparticles, such as nickel, into the aerosol, while ceramic heating elements have been associated with the creation of hexavalent chromium, a carcinogen. Because of the significant health risks posed by hexavalent chromium, Respira recently asked FDA to add it to the official list of HPHCs.[15]

Significantly, many of the short- and long-term risks associated with use of ENDS products still are unknown. The Surgeon General has observed that "[t]he health effects and potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids, including solvents, flavorants, and toxicants, are not completely understood."[16] And FDA itself has acknowledged that "the long-term risks associated with chronic use of ENDS are unknown." 81 Fed. Reg. at 29038.

There are even concerns that ENDS products may pose different – and in some cases, more significant – risks than combustible tobacco products. For example, FDA itself has raised alarms about the ability of the "unique delivery systems" used by ENDS products to generate ultrafine aerosol particles for inhalation. According to FDA, "We know that aerosol exposure is a major health concern due to the ability of aerosol particles to penetrate deeply into the respiratory system. … That means some of the toxic chemicals and other substances contained in [heat-based ENDS] aerosols have the potential to go deep into the lungs and *may pose risk for disease not usually seen in smokers*."[17] In other words, FDA is concerned that the toxic chemicals contained in heat-based ENDS aerosol may pose a risk for disease that is different, and potentially greater, than the risks associated with smoke from combustible tobacco products because of the ability of these carcinogen-laden, ultrafine aerosol particles to penetrate more deeply into the lungs of users. FDA has indicated that this is one reason it is "so concerned about youth use of these products."[18]

4. Emerging Public Health Crises

FDA's concerns about the risks of ENDS products seem particularly warranted given the dual public health crises currently gripping the nation. First, public health officials recently identified an unexpected, multi-state outbreak of severe lung injuries associated with the use of ENDS products called "e-cigarette, or vaping, product use associated lung injury," or EVALI. As of December 3, 2019, nearly 2,300 cases of EVALI had been reported to the Centers for Disease

[15] Respira Therapeutics Comments to Docket No. FDA-2012-P-0143 (Oct. 3, 2019) (Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions, 84 Fed. Reg. 38032 (Aug. 5, 2019)), *available at* https://www.regulations.gov/document?D=FDA-2012-N-0143-0047.

[16] Surgeon General's Report, p. 125 (Exhibit 2).

[17] Scott Gottlieb, M.D., and Amy Abernethy, M.D., Ph.D., *Understanding the Health Impact and Dangers of Smoke and "Vapor"* (April 3, 2019) (emphasis added) (Exhibit 3), *available at* https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/understanding-health-impact-and-dangers-smoke-and-vapor.

[18] *Id*.

Control ("CDC"), ***including forty-eight (48) confirmed deaths***.[19] Moreover, the outbreak is widespread, with reports of EVALI cases coming from all fifty states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. A significant proportion of EVALI victims (16%) are reported to be youth under the age of 18, and more than 50% of EVALI patients are younger than 25 years old.[20] Thus, EVALI is having a particularly significant effect on youth and young adults.

Despite a comprehensive investigation by CDC, FDA, and state and local health officials, the specific cause of the outbreak is currently unknown. The CDC recently identified vitamin E acetate, which is sometimes used as an additive in THC-containing e-cigarettes, as a "chemical of concern" and stated that these findings "suggest products containing THC, particularly from informal sources like friends, or family, or in-person or online dealers, are linked to most of the cases and play a major role in the outbreak."[21] Nevertheless, these findings are only preliminary, and both CDC and FDA acknowledge that "the specific cause or causes of lung injury are not yet known."[22] Indeed, researchers at the Mayo Clinic have suggested that the lung injuries may be caused by one or more "inhaled toxic substances" in ENDS aerosol, "but the agents responsible remain unknown."[23] Moreover, 54% of EVALI patients reported using nicotine-containing ENDS products, and 12% reported using nicotine-containing ENDS products exclusively.[24] Consequently, the role of traditional nicotine-containing ENDS products in the EVALI epidemic cannot be excluded. CDC thus recommends that "the only way to assure that you are not at risk while the investigation continues is to consider refraining from use of all e-cigarette, or vaping, products."[25]

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[19] CDC, EVALI Outbreak Website, "Latest Outbreak Information," *available at* https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information (last accessed December 11, 2019).

[20] CDC, EVALI Outbreak Website, "Latest Outbreak Information," *available at* https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information (last accessed December 11, 2019).

[21] CDC, EVALI Outbreak Website, "What We Know," *available at* https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#what-we-know (last accessed December 11, 2019).

[22] CDC Press Release, *New CDC Report Provides First Analysis of Lung Injury Deaths Associated with Use of E-cigarette, or Vaping, Products* (Oct. 28, 2019), *available at* https://www.cdc.gov/media/releases/2019/p1028-first-analysis-lung-injury-deaths.html. FDA also has stated that "more information is needed to determine what is causing the respiratory illnesses." FDA, Lung Illnesses Associated with Use of Vaping Products, "Incident Overview" (Nov. 21, 2019), *available at* https://www.fda.gov/news-events/public-health-focus/lung-illnesses-associated-use-vaping-products (last accessed December 11, 2019).

[23] Letter to the Editor, Pathology of Vaping-Associated Lung Injury, New England Journal of Medicine (Oct. 2, 2019) (Exhibit 4), *available at* https://www.nejm.org/doi/full/10.1056/NEJMc1913069?query=featured_home.

[24] CDC, EVALI Outbreak Website, "Latest Outbreak Information," *available at* https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information (last accessed December 11, 2019).

[25] CDC, EVALI Outbreak Website, "What CDC Recommends," *available at* https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#what-cdc-recommends (emphasis added) (last accessed December 11, 2019).

Second, the EVALI outbreak has coincided with a troubling surge in ENDS usage by middle and high school students in the United States. According to the 2019 National Youth Tobacco Survey, current ENDS use has "increased dramatically" among young people. Indeed, ***more than 5 million youth used e-cigarettes in 2019.***[26] This represents nearly a 40% increase over 2018, when there were 3.6 million youth users. Currently, 27.5% of high school students and 10.5% of middle school students use ENDS products. Moreover, a large percentage of these young people are heavy users, with about 1.6 million youth using ENDS products on 20 or more days per month and nearly 1 million using ENDS product daily. This is, without question, an epidemic.[27] And it is an epidemic that has been raging, unchecked, for years.

The surge in youth usage of ENDS products is particularly troubling from a public health standpoint. The Surgeon General has warned that "the brain of youth and young adults is more vulnerable to the negative consequences of nicotine exposure" than older adults.[28] "The effects include addiction, priming for use of other addictive substances, reduced impulse control, deficits in attention and cognition, and mood disorders."[29] Indeed, the use of ENDS products, particularly those with high levels of nicotine, creates a significant risk that youth users will develop an addiction to nicotine, thereby increasing the likelihood of cigarette use in the future. As FDA has observed, "addiction to nicotine is often lifelong (Ref. 4), and youth and young adults 'generally underestimate the tenacity of nicotine addiction and overestimate their ability to stop smoking when they choose (Ref. 5)." 81 Fed. Reg. at 28981.

In addition, "[s]ubstantial evidence suggests that nicotine can negatively influence both adolescent and prenatal brain development."[30] Children who use nicotine are more likely to exhibit drug-seeking behaviors and are more susceptible to attention and cognition deficits and to mood disorders. Finally, youth who use ENDS products are exposed to the direct health effects of ENDS aerosols. As noted above, these aerosols can contain carcinogens, irritants, heavy metals, and volatile organic compounds and, because of the ability of ENDS products to generate ultrafine particles, these substances may travel more deeply into the lungs than combusted smoke. Consequently, ENDS products expose youth and young adults to the risk of severe lung injury, including, possibly, EVALI.

As a result of these dual public health crises, both Congress and state and local governments have shown intense interest in addressing the risks of ENDS products, particularly for teens and

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[26] FDA and CDC, 2019 National Youth Tobacco Survey (2019) (Exhibit 5), *available at* https://www.fda.gov/media/132299/download.

[27] Alex Azar & Scott Gottlieb, *Op-ed: We cannot let e-cigarettes become an on-ramp for teenage addiction*, Washington Post (Oct. 11, 2018), *available at* https://www.washingtonpost.com/opinions/we-cannot-let-e-cigarettes-become-an-on-ramp-for-teenage-addiction/2018/10/11/55ce424e-ccc6-11e8-a360-85875bac0b1f_story.html.

[28] Surgeon General's Report, p. vii (Exhibit 6).

[29] Surgeon General's Report, p. vii (Exhibit 6).

[30] Surgeon General's Report, p. 104 (Exhibit 2).

young adults. In the past few months, Congress has held several public hearings[31] and introduced legislation[32] designed to fight teen tobacco use, including by prohibiting remote retail sales and banning flavored e-cigarettes. In September, a bipartisan group of Senators asked FDA to "immediately remove all pod- and cartridge-based e-cigarettes from the market, unless or until they can prove that they benefit the public health."[33] Likewise, several state and local governments, including Michigan, Massachusetts, New York, Rhode Island, and Washington state, have passed emergency bans on flavored e-cigarettes, which are thought to be particularly attractive to teens and young adults and thus at least partially responsible for the epidemic of teen usage. While many of these bans have been delayed by court challenges,[34] they demonstrate the general view among state and local health officials that urgent action is necessary to address these public health crises caused by ENDS products.

B. Respira's Proposal for an Immediate, Multi-Pronged, and Balanced FDA Strategy to Address the Public Health Crises Caused by ENDS Products

Respira believes that FDA must play a leading role in addressing these public health crises by taking swift, decisive, and targeted action to more vigorously regulate the manufacture, marketing, and sale of ENDS products. While state and local action can be helpful, it also often results in piecemeal regulation that cannot effectively grapple with problems of national scope. This is due, in part, to the fact that state and local regulation creates uncertainty and unnecessary hardships on manufacturers, who must try to comply with an ever-changing web of fifty different regulatory requirements. In Respira's view, FDA is the only regulatory body with the expertise and authority to offer a comprehensive, nation-wide solution to the dual public health crises facing the United States. Unless FDA acts decisively, state and local governments will step in to fill this regulatory vacuum.

Thus far, FDA has focused most of its regulatory activity on combustible tobacco, not ENDS products. FDA explained in 2017 that these priorities were established to strike "an appropriate balance between regulation and encouraging development of innovative tobacco products that may be less dangerous than cigarettes."[35] Respira fully supports these policy goals,

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[31] *See* Hearing on "Legislation to Reverse the Youth Tobacco Epidemic," Subcommittee on Health of the House Committee on Energy and Commerce (Oct. 16, 2019), *available at* https://energycommerce.house.gov/committee-activity/hearings/hearing-on-legislation-to-reverse-the-youth-tobacco-epidemic; *see also* Hearing on E-cigarettes: An Emerging Threat to Public Health, House Committee on Appropriations (Oct. 16, 2019), *available at* https://appropriations.house.gov/events/hearings/e-cigarettes-an-emerging-threat-to-public-health.

[32] Reversing the Youth Tobacco Epidemic Act of 2019, H.R. 2339, 116th Cong., 1st Sess. (2019).

[33] Letter from Senators Durbin, Murkowski, Merkley and Blumenthal to FDA Commissioner Sharpless (Sept. 20, 2019) ("Bipartisan Senate Letter") (Exhibit 7), *available at* https://www.durbin.senate.gov/imo/media/doc/E-Cig%20Cartridge%20Letter%20to%20FDA.pdf.

[34] For example, a New York state court has temporarily stayed a rule to ban flavored e-cigarettes in the state of New York. Similar stays have been imposed in Michigan and Oregon.

[35] FDA News Release, *FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death* (July 27, 2017), *available at* https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death.

particularly the need to encourage the development of innovative tobacco products that pose fewer risks to users; however, we do not believe FDA's current strategy has been effective in achieving its stated goals.[36] Although FDA has sought to encourage innovation by delaying many of the regulatory requirements for ENDS products, Respira believes that *increased* regulation is necessary to drive innovation, particularly the vigorous application of the "appropriate for the protection of the public health" standard to currently marketed products. Respira further believes that this can be accomplished in a balanced manner that avoids driving tobacco use toward products higher on the risk continuum, such as combustible cigarettes.

Accordingly, Respira believes there is an urgent need for FDA to re-prioritize its regulatory oversight over ENDS products in order to (a) make such products less appealing to youth, and (b) drive the development of innovative ENDS products that pose fewer risks than existing technologies. Respira thus respectfully requests that FDA immediately take action to implement the following six regulatory policies.

1. Establish a Nicotine Standard for ENDS Products

It is undisputed that nicotine is highly addictive.[37] FDA, in fact, considers nicotine's addictiveness to be one of the primary causes of tobacco-related harms because it drives compulsive, long-term tobacco use, thereby repeatedly exposing users and non-users to thousands of toxic chemicals in tobacco smoke. Accordingly, FDA is considering taking action to reduce the level of nicotine in combusted cigarettes "so they are minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health." 83 Fed. Reg. 11818 (March 16, 2018). FDA believes this proposal could have significant health benefits by making it easier for addicted users to quit and by preventing experimenters – mainly youth – "from initiating regular use and becoming regular smokers." *Id*.

In order to stem the epidemic of youth usage of ENDS products – which likewise is fueled in large part by the addictiveness of nicotine – FDA should establish a similar nicotine standard for ENDS products pursuant to section 907(a) of the FFDCA, 21 U.S.C. § 387g(a) (granting FDA authority to establish tobacco product standards, including over "nicotine yields"). In particular, FDA should set a maximum nicotine level (by percent weight) in ENDS product so that they are minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health. Respira believes that such a standard should be developed as quickly as possible and can be expedited by relying, to the extent appropriate, on the data, information, and findings obtained as a result of FDA's Advance Notice of Proposed Rulemaking ("ANPRM") for combusted cigarettes.

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[36] Indeed, a bipartisan group of Senators recently attributed the increasing popularity of e-cigarettes with children primarily to "FDA's years-long refusal to regulate any e-cigarette devices or impose common-sense design standards preventing against adulteration, despite having the authority to do so." Bipartisan Senate Letter, p. 2 (Sept. 20, 2019) (Exhibit 7).

[37] Surgeon General's Report, p. 9 ("nicotine [is] similar in its addictive capability to other drugs of abuse, such as heroin and cocaine") (Exhibit 1); *see also* 81 Fed. Reg. at 28981 ("The Surgeon General has long recognized that the addictive nature of tobacco products is due to the presence of highly addictive nicotine that can be absorbed into the bloodstream").

The growing epidemic of youth usage of ENDS products highlights the urgent need to make such products less addictive. ENDS products have now become the main gateway for teens and young adults to become addicted to nicotine.[38] This addiction has long-term health consequences. First, adolescents are more susceptible to developing nicotine addiction than adults, and "addiction to nicotine is often lifelong." 83 Fed. Reg. at 11821. Once addicted, young people are more likely to migrate to tobacco products that are higher up the risk continuum, such as combusted cigarettes, or engage in dual use of such products. FDA has voiced "similar concerns that youth may initiate tobacco use with ENDS, become addicted, and then dual use or move on to traditional tobacco products." 81 Fed. Reg. at 29040.

Second, nicotine use by children and young adults can have negative long-term health effects. The evidence shows that early exposure to nicotine "can disrupt brain development and have long-term consequences for executive cognitive function (such as task-switching and planning) and for the risk of developing a substance abuse disorder and various mental health problems (particularly affective disorders such as anxiety and depression) as an adult." 83 Fed. Reg. at 11821. Moreover, FDA has acknowledged that early nicotine usage can result in "decreased attention performance and increased impulsivity" by youth and young adults. *Id.*

Given these significant risks of early exposure to nicotine, FDA should take immediate action to ensure that ENDS products, which are widely used by America's youth, are minimally addictive or nonaddictive. FDA has stated that it expects making combusted cigarettes minimally addictive or nonaddictive may have "significant benefits" for youth. *Id*. Respira believes that limiting the addictiveness of ENDS products by establishing a nicotine standard will have similar short- and long-term health benefits for America's youth and is a necessary prerequisite for reversing the troubling surge in youth usage of ENDS products.

2. Establish an HPHC Standard for ENDS Products

In addition to limiting the addictiveness of ENDS products via a nicotine standard, FDA should seek to reduce their risks by establishing a product standard that limits exposure to HPHCs and known toxins, such as formaldehyde and hexavalent chromium, to scientifically validated exposure limits. Although it is generally believed that ENDS aerosols contain fewer toxic chemicals than the smoke from combusted cigarettes, it is undisputed that all currently available ENDS products generate HPHCs and other toxins. This is because, as noted above, all currently available ENDS products operate by heating an e-liquid until it vaporizes, and this heating process necessarily results in the formation of various HPHCs. Moreover, given the wide variety of ENDS products and e-liquids available, with vastly different heating sources, voltages, solvents, and flavorings, HPHC levels can vary dramatically from product to product.

Currently, HPHC levels in ENDS products are completely unregulated. The recent outbreak of serious lung injuries (*i.e.*, EVALI), however, demonstrates that this "hands off" regulatory approach is no longer viable. In order to protect the public health – including the health and safety of children and young adults who are frequent users of ENDS products – FDA should establish standards for HPHCs that are appropriate for the protection of the public health. FDA is

[38] FDA and CDC, 2019 National Youth Tobacco Survey (2019) (Exhibit 5), *available at* https://www.fda.gov/media/132299/download.

specifically authorized to establish such standards pursuant to section 907(a)(4)(A)(ii) of the FFDCA, 21 U.S.C. § 387g(a)(4)(A)(ii), which provides that, where appropriate, tobacco product standards should include provisions "for the reduction or elimination of [non-nicotine] constituents, including smoke constituents, or harmful components of the product."

In this case, FDA should initially focus on a short list of constituents where there is strong scientific evidence, solid inhalation values, and safe EPA inhalation standards already in place. For example, Respira believes that formaldehyde should be a high priority for establishing a standard because it is a well-known carcinogen and toxicant[39] with low exposure thresholds[40] and is highly abundant in ENDS aerosols.[41] Respira believes that FDA's initial HPHC standard should consist of high priority chemicals similar to formaldehyde, such as acrolein and acetaldehyde, which are known to be present in ENDS aerosol and could present significant health risks if not limited to levels below established exposure thresholds.

Over time, FDA should expand the HPHC standard as inhalation science is deepened to include newly identified "high priority" chemicals and, subsequently, to medium and low priority HPHCs. For example, benzene could be classified as a low priority chemical because, even though it is a well-known toxicant and carcinogen, there are limited studies indicating it is present in ENDS aerosols.

Respira acknowledges that establishing an HPHC standard for ENDS products will be a major undertaking for FDA but believes its proposed stepwise approach is reasonable and feasible and, most importantly, necessary and appropriate for the protection of the public health. Moreover, Respira believes the HPHC standard should be viewed as a "living document" that will be updated as the science evolves, eventually driving HPHCs to the lowest possible value. In other words, while developing a comprehensive HPHC standard may be a long-term project, the current public health crises demand that FDA begin the process now by harvesting the low-hanging fruit, *i.e.*, the high-priority HPHCs, which will yield significant public health benefits in both the short- and long-term.

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[39] Formaldehyde is classified as a carcinogen by FDA, the Environmental Protection Agency ("EPA"), CDC, and the International Agency for Research on Cancer ("IARC"). *See, e.g.*, FDA, Established List of Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke (April 2012), *available at* https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list; *see also* CDC, NIOSH Table of IDLH Values for Formaldehyde (May 1994), *available at* https://www.cdc.gov/niosh/idlh/50000.html; IARC, List of Agents Classified by the IARC Monographs, Volumes 1-123, *available at* https://monographs.iarc.fr/wp-content/uploads/2018/09/ClassificationsAlphaOrder.pdf. FDA and EPA also classify it as a respiratory toxicant. *See, e.g.*, EPA, Formaldehyde Summary (Rev. Jan. 2000), *available at* https://www.epa.gov/sites/production/files/2016-09/documents/formaldehyde.pdf.

[40] The Occupational Safety and Health Administration ("OSHA") has established an exposure limit of 0.75 ppm, and National Institute for Occupational Safety and Health ("NIOSH") has established an exposure limit of 0.016 ppm. OSHA, Permissible Exposure Limits, Annotated Table Z-1, *available at* https://www.osha.gov/dsg/annotated-pels/tablez-1.html#niosh_rel. Both the CDC and NIOSH consider 30 ppm a lethal dose for humans.

[41] Respira has identified more than twenty-one (21) independent studies confirming the presence of formaldehyde in ENDS aerosol, four of which identify it as the most abundant carbonyl HPHC and five of which showed increasing formaldehyde levels associated with increasing ENDS power levels.

3. Establish Standardized Warnings and Fact Panels to Communicate HPHC Content for ENDS and Heated Tobacco Products

FDA should establish by regulation standardized informational disclosures, including warnings and Fact Panels, to appropriately inform consumers of the absolute and relative risks of exposure to HPHCs posed by use of ENDS and heated tobacco products. These disclosures should be required for all labeling and advertising used to promote ENDS and heated tobacco products to consumers. Moreover, the specific disclosures should be based on both (1) the general risks associated with specific product categories (*e.g.*, high risk, medium risk and low risk ENDS products); and (2) the specific risks associated with the individual tobacco product based upon FDA's review of the PMTA (*e.g.*, use of specific flavorants or ceramic heating elements).

Respira believes that HPHC disclosures are necessary to correct the widespread misunderstanding that non-combusted tobacco products, such as ENDS and heated tobacco products, are safe. Although ENDS products likely are "less hazardous for an individual user than continued smoking of traditional cigarettes," 81 Fed. Reg. at 29035, they are not safe, particularly for consumers who have never used a tobacco product and are initiating tobacco use for the first time with ENDS products. FDA adopted the Deeming Regulations, in part, to "help alleviate consumer misperceptions" about the safety of ENDS products. 81 Fed. Reg. at 29036. Respira believes that clear, conspicuous and consumer-friendly disclosures about the HPHC risks associated with ENDS and heated tobacco products are necessary to fully dispel these lingering misperceptions and to ensure that consumers who initiate tobacco use with ENDS or heated tobacco products do so with a complete understanding of the known and suspected health risks.

This is particularly important to help combat youth initiation and usage of ENDS products. Like adults, youth and young adults lack a complete understanding and appreciation of the health effects and risks associated with ENDS products, which may make them more likely to experiment with tobacco products (like ENDS) that they mistakenly believe to be "safe." Indeed, FDA has observed that adolescents who were exposed to "protobacco advertising at the point of sale and on the Internet" had "significantly higher odds of ever using e-cigarettes."[42] By providing clear and conspicuous warnings about HPHC risks in language they can understand, the requested HPHC disclosures may dissuade a significant proportion of teens from trying ENDS products in the first place by dispelling the misguided notion that they are "safe."

Respira believes that the required disclosures should be based, in part, on where a specific product falls along the continuum of risk. FDA should establish three general "risk categories" for ENDS products and heated tobacco products: (1) high risk, which should include all heated ENDS products; (2) medium risk, which should include heated tobacco products like the recently approved IQOS product; and (3) low risk, which should include all non-heated ENDS products (*i.e.*, ENDS products that generate aerosol without heat). Because the HPHC levels differ

[42] FDA, The Public Health Rationale for Recommended Restrictions on New Tobacco Product Labeling, Advertising, Marketing, and Promotion, p. 4 (April 29, 2019) ("FDA Public Health Rationale Memo") (Exhibit 8), *available at* https://www.fda.gov/media/124174/download.

markedly among these three categories, FDA should establish different standardized warnings and HPHC Fact Panel disclosures that would apply to specific products falling within each category.[43]

Moreover, FDA should require all PMTA applications to provide science and evidence to create a product specific warning that clearly states the intended use of the approved product and the absolute and relative risk, similar to the warning required on the recently approved IQOS product (*i.e.*, "Any use of this product other than exclusively switching from smoking, including first time use by a non-smoker increases your risk of tobacco related disease."). This may require product-specific warnings and disclosures in addition to the general warnings/disclosures noted above to account for product-specific risks. For example, if the e-liquid in an ENDS product contains a specific flavorant that is known to create HPHCs, or if the ENDS product heats the e-liquid to an unusually high temperature, additional product-specific disclosures may be necessary to fully inform users about relevant risks.

Although Respira acknowledges that FDA is required to publish a list of HPHCs in each tobacco product by brand and by quantity in each brand and subbrand, this publicly available list has not yet been created by FDA. 21 U.S.C. § 387d(d), (e). Moreover, even after it becomes publicly available at some future date, Respira does not believe it will be adequate to educate potential users – particularly children – about the HPHC risks posed by particular ENDS and heated tobacco products. Indeed, youth and young adults are especially unlikely to be aware of, or research and review, a list published on FDA's website (or otherwise) when making purchase and initiation decisions regarding tobacco products. Only a highly sophisticated, educated, and motivated user will take the time to research the HPHC content of specific products online. Consequently, to be even marginally effective, Respira believes that HPHC disclosures must be made at the point of sale and in all advertising, since this is when decisions about purchasing and/or initiating use with a new tobacco product will be made, particularly for young people.[44]

FDA has ample authority to impose these disclosure requirements either by regulation or in a PMTA approval order for a specific tobacco product. For example, section 915 of the FFDCA authorizes FDA to promulgate regulations requiring tobacco product manufacturers, packagers or importers to make disclosures in labeling or advertising regarding the results of testing of, *inter alia*, "smoke constituents" that FDA determines should be disclosed to the public to protect the public health. 21 U.S.C. § 387o(b)(2). Likewise, section 906 of the FFDCA authorizes FDA to issue regulations restricting the sale and distribution of tobacco products, including the advertisement, promotion and labeling of tobacco products, if FDA determines such restrictions would be appropriate for the protection of the public health (including the likelihood that those

[43] The use of these required standardized warnings, however, should not be viewed as grounds for considering an ENDS product to be a "modified-risk tobacco product" under section 911 of the FFDCA (21 U.S.C. § 387k).

[44] FDA has noted that "an analysis of the 2011 National Youth Tobacco Survey (NYTS) found that 'adolescents who reported frequent exposure to protobacco advertising at the point of sale and on the Internet (e.g., seeing ads most of the time or always) had significantly higher odds of ever using e-cigarettes, and there was a dose-response association between the number of marketing channels to which they were exposed and ever use' (HHS 2016; Agaku & Ayo-Yusuf 2014)." FDA Public Health Rationale Memo, p. 4 (Exhibit 8).

who do not use tobacco products will start using such products). *Id*. § 387e(d)(1), (2).[45] Finally, a PMTA approval order can impose restrictions on the sale and distribution of a tobacco product to the same extent as permitted under section 906, which (as noted above) may impose restrictions on the labeling, advertising and promotion of a tobacco product. *Id*. § 387j(c)(1)(B).

Respira requests that FDA immediately move forward with promulgating a regulation requiring the labeling and advertising disclosures discussed above. Since such a regulation likely cannot be finalized for several years for administrative reasons, Respira requests that FDA, in the interim, require such disclosures in all PMTA approval orders for ENDS products and heated tobacco products. FDA should refuse to approve any PMTA that does not include such disclosures as a required condition of approval.

4. Impose Marketing Restrictions on ENDS Products to Help Prevent Youth Usage

In addition to requiring detailed HPHC disclosures in labeling and advertising, FDA should impose restrictions on the sale and distribution of ENDS products. Specifically, FDA should:

- Require all sales to be conducted in a non-self-service format, such as "behind the counter"; and

- Require implementation of a purchase registry similar to the one required for pseudoephedrine sales.

If FDA determines that, because of a product's unique technological features and/or risk profile, such marketing restrictions are not necessary for the protection of the public health, the Agency could exempt that specific ENDS product from these marketing restrictions in its PMTA approval order. Although Respira recognizes that these proposed restrictions on the sale and distribution of ENDS products are strict and potentially burdensome, given the ongoing epidemic of youth use of ENDS products and the outbreak of severe lung injuries (including several deaths), Respira believes these restrictions are essential to combating these ongoing public health crises and driving innovation toward a safer tobacco marketplace.

FDA should not allow ENDS products to be sold to consumers in self-service formats that could facilitate purchase by minors. Instead, FDA should require that all sales be conducted only after the seller has made an affirmative determination that the proposed purchaser is eligible to use the ENDS product. For example, FDA could require "behind-the-counter" placement of all ENDS products to ensure that customers do not have direct access to the product before the sale is made (to help prevent theft) and that the seller directly delivers the product to the buyer only after confirming eligibility.

In addition, FDA should require a purchase registry for all sales involving ENDS products modeled after the purchase registry for pseudoephedrine products. This would require customers to provide valid photo identification issued by the State or Federal Government confirming their age and identity. It would also require sellers to maintain records of the purchaser's information

[45] FDA may also adopt labeling and advertising restrictions pursuant to a tobacco product standard for HPHCs. *See* 21 U.S.C. § 387f(a)(4)(B)(v), (C).

(*e.g.*, name, address, age, and signature) and information about the specific sale (*e.g.*, date, time, product name, quantity). FDA should require sellers to maintain this information for a minimum time period (*e.g.*, 2 years) to facilitate FDA investigations regarding compliance. Respira believes that both of these sale and distribution restrictions would help prevent teens and young adults from gaining access to ENDS products.

Although the above-described restrictions should serve as the baseline requirement for all ENDS products, FDA should have the discretion to exempt specific ENDS products from one or more of these restrictions if it determines they are not necessary for the protection of the public health. For example, if a new ENDS product incorporates an innovative technology that significantly reduces its inherent risks and/or its appeal to youth, FDA could specify in its PMTA approval order that it is exempt from the above requirements and thus can be sold in a wider variety of formats (*e.g.*, online) and/or without the need for a registry. While Respira does not believe these exemptions will be common (at least not at first), Respira believes that the possibility of obtaining an exemption from stringent marketing restrictions could serve as a powerful incentive for innovation.

As noted above, FDA has ample authority under section 906 of the FFDCA to issue regulations restricting the sale and distribution of tobacco products if it determines such restrictions would be appropriate for the protection of the public health. *Id*. § 387e(d)(1), (2). Respira believes the troubling surge in youth usage of ENDS products in recent years provides ample evidence that the above-described restrictions would be appropriate for the protection of the public health. Respira thus requests that FDA take immediate action to initiate a rulemaking process to implement those sales and distribution restrictions. Moreover, while FDA is promulgating those regulations, Respira requests it impose the same restrictions on a case-by-case basis in all PMTA approval orders for ENDS products, as permitted under section 910 of the FFDCA. 21 U.S.C. 387j(c)(1)(B) (providing that a PMTA approval order can impose restrictions on the sale and distribution of a tobacco product to the same extent as permitted under section 906).

5. Establish a Fast Track Approval Pathway for Innovative ENDS Products

As part of a comprehensive strategy to encourage the development of innovative tobacco products, FDA should establish a fast track approval pathway for innovative ENDS products that are reasonably expected to significantly improve the risk profile of currently available tobacco products but that do not qualify as "modified-risk tobacco products." The program should be voluntary and should be implemented by FDA as resources permit. The goal of the program should be to facilitate the timely development and review of innovative products that, once approved, are expected to provide a meaningful benefit to the public health. Significantly, Respira is not requesting FDA to modify the approval requirements for tobacco products subject to the fast-track program. On the contrary, all tobacco products will remain subject to the statutory approval requirements established by Congress.

Tobacco products should be eligible for the fast track process if they: (1) are subject to approval through the PMTA process; (2) do not qualify as modified-risk tobacco products under

section 911 of the FFDCA;[46] and (3) are reasonably expected to significantly improve the risk profile of currently available tobacco products through substantial safety innovations. For example, an ENDS product may satisfy this last criterion if it incorporates a new technology that significantly reduces or eliminates HPHCs in aerosol or eliminates the risk of battery explosions. Ideally, sponsors should be eligible for inclusion in the fast track program prior to the submission or receipt of a PMTA, but FDA should consider requests for inclusion submitted with a PMTA or after PMTA submission.

The main goal of the fast track process should be to speed development and approval of innovative ENDS products that provide meaningful benefits to the public health without lowering applicable approval standards. To achieve this, the fast track program should include the following features:

- **Interactive and Timely Communication**: FDA should provide interactive and timely communication with the sponsor during product development and throughout the review process for the PMTA;

- **Senior Management Support**: Senior management should be directly involved in fast track submissions to ensure that reviews are efficient and to facilitate timely resolution of disputes;

- **Priority Review of PMTAs**: FDA should prioritize the review of innovative tobacco products that may benefit the public health to enable tobacco users more timely access to these products;

- **Efficient and Flexible Clinical Study Design**: FDA should consider proposals for efficient and flexible clinical study designs to meet applicable requirements for approval of a PMTA.

Respira believes FDA can implement a fast track program for innovative ENDS products under its existing statutory authorities without changing the otherwise applicable PMTA approval standards. Specifically, FDA could model a voluntary fast track program for tobacco products after its Safer Technologies Program for Medical Devices ("STeP").[47] There, FDA is adopting a voluntary, fast track review program for certain medical devices that do not qualify for FDA's Breakthrough Devices Program as mandated in section 515B of the FFDCA (21 U.S.C. § 360e-3) but nevertheless are reasonably expected to significantly improve the safety of currently available treatments or diagnostics. The STeP proposal is not mandated or otherwise specifically authorized by statute and does not change existing approval requirements for medical devices. Nevertheless, FDA is proposing to adopt it because it promotes the public health by giving patients more timely access to safer medical devices. Respira believes FDA can and should adopt a similar policy to

[46] For example, if a proposed ENDS product does not make explicit or implicit labeling or advertising claims (other than HPHC disclosure statements required per the request above) regarding risk reduction, it should not be considered a modified-risk tobacco product.

[47] FDA, *Draft Guidance for Industry and Food and Drug Administration Staff: Safer Technologies Program for Medical Devices* (Sept. 19, 2019) (Exhibit 9), *available at* https://www.fda.gov/media/130815/download.

speed the development and availability of innovative tobacco products that entail lower risks than existing products.

Finally, while FDA previously considered but rejected suggestions for creating an expedited approval pathway for ENDS products, *see* 81 Fed. Reg. at 28998, Respira requests FDA to re-consider its objections given the dual public health crises described above. FDA's primary objection was that it was not appropriate to provide an expedited approval pathway for all ENDS products because it was not clear at that time what types of risks they might pose. Respira, however, is not requesting that *all* ENDS products be subject to an expedited approval pathway, only those that are reasonably expected to significantly improve the risk profile of currently available tobacco products through substantial safety innovations. Significantly, Respira's proposal is targeted to ENDS products with a high potential for making a major contribution to the protection of the public health. As such, it will preserve the existing statutory scheme while driving innovation toward tobacco products with lower inherent risks.

6. Establish Expanded Mandatory Post-Market Reporting Requirements to Drive Innovation

Finally, FDA should establish mandatory post-market reporting requirements designed to drive innovation and the continual advancement of technology toward safer tobacco products. FDA has explained that because the "appropriate for the protection of public health" standard requires a comparison to the general tobacco market existing at the time of an application, "FDA believes that, over time, the premarket authorities will move the market toward less-risky tobacco products." 81 Fed. Reg. 28999. The corollary, of course, is that as newer, less-risky tobacco products are approved, previously marketed products that involve greater risks may no longer satisfy the "appropriate for the protection of the public health" standard. FDA should ensure there is a mechanism in place to periodically remove such products when the marketplace shifts toward less-risky tobacco products. Respira believes this can be accomplished using the Tobacco Control Act's postmarket reporting authorities.

Under section 910(f)(1) of the FFDCA, FDA has the authority to require, either by regulation or in a specific PMTA approval order, the submission of any records or reports deemed necessary to enable FDA to determine (or facilitate a determination of) "whether there is or may be grounds for withdrawing or temporarily suspending" PMTA approval. 21 U.S.C. § 387j(f)(1). One of the primary grounds for withdrawing or suspending PMTA approval of a tobacco product is that "the continued marketing of such tobacco product ***no longer is appropriate for the protection of the public health.***" *Id*. § 387j(d)(1)(A) (emphasis added). Because FDA expects the marketplace to evolve over time toward products that present a lower risk of user and population harm,[48] the evolution of the marketplace itself will necessarily create grounds for withdrawing approval of previously approved tobacco products that no longer can be considered appropriate for the protection of the public health.

[48] *See* 81 Fed. Reg. at 29044 ("Over time, FDA expects that its premarket review authorities will spur creative evolution and help to create a market where available products present a lower risk of user and population harm, provide a more consistent delivery under varying conditions of use, are less likely to lead to initiation of tobacco use, and/or are easier to quit.").

FDA, however, should not rely upon market forces to remove more risky ENDS products from the market. FDA has recognized that market forces alone may not be effective, particularly when the manufacturer of an innovative product has to compete against "products that are more cheaply and crudely made, yet appear to be identical to the consumer." 81 Fed. Reg. at 28983. Instead, FDA should rely on the explicit regulatory authority granted by the Tobacco Control Act to identify and remove older products whose continued marketing is no longer appropriate for the protection of the public health.

Respira thus respectfully requests that FDA issue regulations as quickly as possible implementing the postmarket reporting requirements under section 910(f)(1) of the FFDCA (21 U.S.C. § 387j(f)(1)). Those regulations should require all manufacturers of approved ENDS products to submit a post market report providing a detailed analysis whether the continued marketing of such ENDS product is still appropriate for the protection of the public health in light of the availability of the newly approved ENDS product. Such reports should be required: (1) no later than six months after the approval of a new ENDS product that represents a significant improvement in risk profile versus currently available tobacco products (*e.g.*, delivers a meaningful reduction in HPHC levels); and (2) at least every three years after approval. FDA should use these post market reports to determine whether there are grounds for withdrawal or suspension of PMTA approval in light of the evolving marketplace for tobacco products and, if so, initiate action to withdraw or suspend such PMTA approval. Because the promulgation of final post market reporting regulations likely will take several years (for administrative reasons), FDA should, in the interim, impose identical post market reporting requirements as a condition of approval in each approved PMTA order. *See* 21 U.S.C. § 387j(f)(1) (permitting FDA to impose post market reporting requirements "by order").

C. Respira's Proposal Is Consistent with the Tobacco Control Act and "Appropriate for the Protection of the Public Health"

As explained in detail in section II.B above, FDA has ample authority to implement the regulatory actions requested in this Petition. The Tobacco Control Act grants FDA broad powers to regulate ENDS products, establish product standards (including HPHC standards), impose labeling and marketing restrictions, facilitate the timely approval of innovative products, and require post-market reports to determine whether marketed products should be suspended or withdrawn because they are no longer appropriate for the protection of the public health.

Moreover, the requested regulatory actions are fully consistent with the goals of Congress in enacting the Tobacco Control Act because they are both necessary and appropriate for the protection of the public health. First, many of the proposed actions are intended to stop and reverse the epidemic of youth usage of ENDS tobacco products. Even in 2009, Congress considered "[t]he use of tobacco products by the Nation's children [to be] a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults." Tobacco Control Act, Pub. L. No. 111-21, §2(1). Congress thus enacted the Tobacco Control Act, in large part, to end the terrible toll of this "pediatric disease."

Unfortunately, ENDS products have given rise to an entirely new epidemic of pediatric initiation and use of tobacco products. The regulatory actions Respira is requesting in this Petition

are intended to help achieve the overriding goal Congress originally set in the Tobacco Control Act to reduce youth usage of tobacco products. The nicotine standard, for example, will immediately reduce the addictiveness, youth appeal and youth initiation of ENDS products. Likewise, the sales and distribution restrictions will make it more difficult for children to access ENDS products. And by clearly communicating the health risks associated with ENDS products, the HPHC warnings will correct the widespread misperception that ENDS products are safe, thereby helping to make ENDS products less appealing not just to adults, but also to children.

Respira also believes the regulatory actions requested herein will encourage the development of innovative ENDS products that drive harm reduction and protect the public health. The HPHC standard will establish a baseline that promotes the development of safer ENDS products that meet and exceed the standard. Aligning marketing restrictions, including mandatory disclosures and warnings regarding HPHC levels, to the product standard will further encourage manufacturers to develop, and users to switch to, safer, innovative ENDS products. A fast-track approval process for ENDS products that deliver meaningful reductions in HPHCs will further incentivize the development and adoption of safer technologies. And requiring manufacturers to periodically confirm through mandatory post-market reports that their ENDS products continue to be appropriate for the protection of the public health will "spur creative evolution and help to create a market where available products present a lower risk of user and population harm." 81 Fed. Reg. 28974, 29044. This is consistent with FDA's overall policies regarding the regulation of tobacco products.

The requested regulatory actions also foster transparency and consumer education. Respira believes that many consumers have the mistaken impression that ENDS products are completely safe, which may be one reason for the troubling surge in ENDS usage among youth. This mistaken belief is facilitated by the complete lack of information about the constituents, including HPHCs, contained in ENDS aerosols. Communicating detailed information about the HPHC content in specific ENDS products will encourage the development of safer ENDS technologies and provide consumers with the information they need to make informed decisions about switching to safer ENDS products. It also may deter the use of ENDS products by America's youth.

Finally, Respira believes that the regulatory proposals described above represent the type of "bold action" called for by Dr. Stephen Hahn during his recent Congressional testimony. But it is bold action that also is appropriately balanced. FDA has delayed implementing more stringent requirements for ENDS products in large part because of its concern that over-regulation could drive tobacco use toward products higher up the risk continuum, such as combustible tobacco products. Respira believes that FDA's concerns are legitimate. This is why Respira is proposing a measured approach that seeks to use the Tobacco Control Act's existing regulatory authorities to drive innovation toward safer tobacco products without tipping the balance in a way that forces tobacco users toward combustible products. In other words, Respira is advocating for FDA to adopt a bold but balanced approach toward the regulation of ENDS products.

In summary, the growing epidemic of youth usage of ENDS products and the unexplained outbreak of serious lung injury cases across the United States, including several deaths, demand swift, decisive and targeted regulatory action by FDA to protect the public health. Respira believes that the six regulatory actions requested below represent a bold but balanced strategy for

addressing these public health crises. Respira thus respectfully requests that FDA begin implementing them immediately.

D. Conclusion

For the reasons discussed above, FDA should grant Respira's petition and immediately implement the six regulatory actions requested above. These actions are necessary to reverse the troubling epidemic of youth use of ENDS products and to drive innovation toward a safer tobacco market.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30(h), 25.30(k), 25.35(b), and 25.35(c).

IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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Exhibits