KELLER AND HECKMAN LLP
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1001 G Street, N.W.
Suite 500 West
Washington, D.C. 20001
tel. 202.434.4100
fax 202.434.4646

Writer's Direct Access
Azim Chowdhury
(202) 434-4230
chowdhury@khlaw.com

VIA ELECTRONIC SUBMISSION AND HAND DELIVERY

August 24, 2020

The Honorable Alex M. Azar II, Secretary
Department of Health & Human Services
200 Independence Ave., S.W.
Washington, D.C. 20201
Alex.Azar@hhs.gov

The Honorable Stephen M. Hahn, Commissioner
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Stephen.Hahn@fda.hhs.gov

Filed at:
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
http://www.regulations.gov
Docket No. FDA-2013-S-0610

Re: Citizen Petition for Extension Of Premarket Tobacco Product Application Filing Deadline Due To The COVID-19 Pandemic

To Be Filed In Docket Nos. FDA-2019-D-0661-15418; FDA-2019-D-0661-15434; FDA-2014-N-0189; FDA-2019-D-5324; FDA-2015-D-2496; FDA-2017-D-0120; FDA-2018-D-3244

Dear Secretary Azar and Commissioner Hahn:

On behalf of the small vapor product manufacturers, retailers, and trade associations listed below ("Petitioners"),[1] as well as similarly situated businesses, the undersigned submits this citizen petition under 21 C.F.R. § 10.30 and the Family Smoking Prevention and Tobacco

[1] Cream Vapor LLC; Gentleman's Draw; HiggyCigs, LLC; Illumivaption Inc.; Jvapes, LLC; Knoxville Vapor Co./Tri Star Vape Co.; Matrix Minds LLC; Mountain Oak Vapors; Northeast Vapor Supplies, LLC; Prophet Premium Blends LLC; The Vapers Depot; Vapor Station Columbus; Vapor Source, Inc.; Chattanooga Vapor Co.; Global eVapor Consulting; Michigan Vape Shop Owners Organization; Vaping Advocates of Oklahoma; Rocky Mountain Smoke Free Alliance; Kentucky Smoke Free Association; Smoke-Free Alternatives Trade Association.

Control Act ("TCA"). Petitioners request that the Food and Drug Administration ("FDA") seek, pursuant to Fed. R. Civ. P. 60(b), a 180-day extension of the September 9, 2020 deadline for filing Premarket Tobacco Product Applications ("PMTA"), which was set by the United States District Court for the District of Maryland, due to the on-going COVID-19 pandemic. Small manufacturers continue to experience significant delays caused by the coronavirus outbreak in their efforts to complete and file timely PMTAs by the current deadline. These businesses will likely not be able to file compliant applications by the cutoff, and thus could be forced to lay-off thousands of employees and close their doors permanently if the extension is not granted.

A. Action Requested

The Petitioners request that FDA immediately seek from the federal district court a 180-day extension (until March 8, 2020) of the PMTA filing deadline (now set at September 9, 2020) for a limited set of small vapor product manufacturers based on extenuating circumstances resulting from the COVID-19 pandemic. On March 30, 2020, FDA sought a similar extension under Fed. R. Civ. P. 60(b) given the "exceptional and unforeseen" circumstances in which the spread of coronavirus was significantly delaying efforts by vapor product manufacturers to complete and file PMTAs by the court's initial May 12, 2020 cutoff.[2] That request was granted by the court on April 22, 2020.[3] As demonstrated by the attached declarations from individual small businesses and trade associations, the circumstances justifying the original extension still exist and are not expected to abate any time soon. Small manufacturers continue to experience substantial delays due to the coronavirus outbreak (*e.g.*, laboratory testing of e-liquids) that will prevent them from filing complete applications by the current deadline.

This request is limited to certain small vapor product manufacturers to ensure that any extension only applies to businesses that have in good faith been working to complete PMTAs by the September 9, 2020 cutoff and otherwise have taken steps to ensure that their products will not contribute to underage use. Specifically, each manufacturer would be required to demonstrate to FDA through documentation and other evidence that it:

- Has less than 50 employees and/or 10MM in annual revenue;
- Only manufactures open system products (*e.g.*, e-liquids) and does not produce products used in cartridge- or pod-based products;

[2] Letter from Garrett Coyle, USDOJ Trial Attorney, to Hon. Paul W. Grimm, USDC Judge (Mar. 30, 2020), at 1, *American Academy of Pediatrics, et al. v. FDA*, Case No. 8:18-cv-00883-PWG (D. Md.) ("*AAP v. FDA*") (Doc. 175); *see* Fed. R. Civ. P. 60(b) (permitting court to "relieve a party…from a[n]…order…for…any other reason that justifies relief").

[3] *AAP v. FDA*, Order (Doc. 182).

- Has taken steps to prohibit access by and sales to underage consumers for brick-and-mortar stores and/or retail websites;
- Will only market to adults and not rely on kid-friendly advertising (*e.g.*, using age-gated social media accounts);
- Is otherwise in compliance with TCA and Deeming Rule requirements (*e.g.*, facility registration, product listings, etc.); and
- Has already made progress in completing PMTAs prior to the September 9, 2020 deadline, but has been materially delayed in one or more tasks due to COVID-19.[4]

If FDA does not seek an additional extension due to COVID-19, these small businesses will likely be forced out of business and have to lay-off thousands of employees soon after the deadline expires. Moreover, adult smokers, who rely on open systems to move away from more dangerous combustible cigarettes, will no longer have access to these products. As evidence is now growing that former smokers are already moving back to cigarettes with current restrictions on vaping products (*e.g.*, flavor bans),[5] it is imperative that these small businesses be given adequate time to assemble and file complete PMTAs.[6] [7]

[4] While the extension would be based on continuing delays occasioned by the COVID-19 pandemic, Petitioners note that it would also be consistent with the federal court's remedial order in which the "FDA shall have the ability to exempt New Products [those on the market prior to August 8, 2016] from filing requirements for good cause on a case-by-case basis." *AAP v. FDA*, Mem. Op. and Order (Doc. 127) at 12. Here, the extension would only apply as a practical matter to select, small manufacturers who have made the requisite showing to the agency, on an individual company basis, that good cause exists to provide additional time.

[5] Morningstar, *Cigarette Smoking Makes a Comeback During Coronavirus Pandemic – Update* (July 28, 2020), https://tinyurl.com/y33vazgv (*see* App. at 000073).

[6] The attached declarations filed in support of this petition provide examples of these types of small businesses, where they only manufacture open system products, have minimized the chance of underage sales, do not market to youth, and have made notable progress in assembling PMTAs before the current filing deadline (*see* App. at 000001-000072).

[7] Petitioners' request for a 180-day extension is also consistent with Secretary Azar's authority under 42 U.S.C. § 247d(d) of the Public Health Service Act, which allows him to extend deadlines for the submission of data or reports "as circumstances reasonably require" due to a public health emergency. *See infra* note 20 (Secretary Azar declaring COVID-19 to be a public health emergency).

B. Statement of Grounds

1. FDA's PMTA Enforcement Policies Have Always Considered The Interests Of Manufacturers Working To File Timely Applications

Beginning with 2016's Deeming Rule, FDA has adopted PMTA enforcement policies that took into account the substantial amount of time and resources required to file complete PMTAs. As clearly evidenced by FDA's PMTA guidance, which was not issued until almost three years after the Deeming Rule was adopted, these applications are the most time-consuming, costly, and complex pathway to commercialization under the TCA.[8] Even where long-term data from human clinical and epidemiological studies are not required, manufacturers must still produce substantial amounts of information for each product to assess human health and population-level impacts, including extensive testing of constituents, toxicological and pharmacological properties, and storage/stability performance, as well as consumer perception studies, environmental assessments, and literature reviews. *Id.* at 22-50.

The Deeming Rule initially established an August 8, 2018 deadline for vapor products on the market as of August 8, 2016. If a timely PMTA was submitted, the product could be sold for up to an additional year pending FDA review. 81 Fed. Reg. 28,978. FDA said this approach balanced various stakeholder concerns, including the need for manufacturers to have adequate time to file high-quality PMTAs and to prevent the mass exit of vapor products that may help adult smokers move away from more dangerous cigarettes. *Id.* at 28,977.[9]

FDA quickly realized, however, that vapor product manufacturers would not be able to submit complete PMTAs by the original cutoff date as the agency had not yet put in "place the foundational elements of a robust and sustainable framework for regulating the non-combustible forms of nicotine delivery."[10] According to then-Commissioner Scott Gottlieb, FDA needed to "create clearer guideposts for the regulation of all products, and account for the role of all noncombustible products." *Id.* The agency concluded that this meant "extending further some of the current compliance deadlines for newly deemed products, primarily electronic cigarettes." *Id.* Critical to this approach was the recognition that a new compliance policy was also required to foster the "potential benefits to addicted cigarette smokers…of products capable of delivering nicotine without having to set tobacco on fire." *Id.* FDA then established in 2017 a PMTA filing

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[8] FDA, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, Guidance for Industry* (June 2019), https://tinyurl.com/y3s62jno.

[9] *See also AAP v. FDA*, Declaration of Mitchell Zeller at ¶ 6 (Doc. 120-1) ("Zeller Decl.").

[10] FDA Commissioner Scott Gottlieb, M.D., *Protecting American Families: Comprehensive Approach to Nicotine and Tobacco* (Speech) (June 28, 2017), https://tinyurl.com/v73kwdc.

deadline of August 8, 2022 "in order to give industry more time to comply," with products meeting the deadline able to remain on the market pending FDA review.[11]

Even after the 2017 cutoff was vacated by the Maryland federal district court, FDA continued to express concerns about not leaving manufacturers with sufficient time to file complete PMTAs. In responding to the court's request for an appropriate remedy, the agency proposed a filing deadline of May 12, 2020, in part, because the shorter period of time proposed by the plaintiffs in that case would leave manufacturers "unlikely to submit quality PMTA applications (*e.g.*, applications that are sufficiently complete and organized to enable [FDA] to efficiently conduct the required scientific review)….Instead, a longer period of time…would be appropriate to help ensure that manufacturers are better able to prepare quality submissions."[12] Indeed, FDA noted not only that manufacturers would be filing "first-ever applications for a previously novel and unregulated category of products," but also the "complexity of those applications and the scientific review process."[13] And once again, underlying the agency's desire to ensure that manufacturers have adequate time was the belief that an earlier deadline could result in a "mass market exit" of less harmful vapor products.[14]

2. FDA Cited Multiple Sources Of Delay Due To The COVID-19 Pandemic When Extending The PMTA Filing Deadline To September 9, 2020

On March 30, 2020, FDA filed a letter with the federal district court asking for a 120-day extension (until September 9, 2020) due to significant delays in the ability of manufacturers to complete work on PMTAs resulting from the coronavirus outbreak.[15] Supporting the request was

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[11] FDA, *Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule, Guidance for Industry (Revised)* (October 2017), at 4; *see also* Zeller Decl. at ¶ 7 (citing Commissioner Gottlieb's speech and emphasizing need to "encourage development of innovative tobacco products that [have] the potential to be less dangerous than cigarettes and to provide manufacturers additional time to develop higher quality applications informed by additional guidance and rules and products standards from the agency").

[12] Zeller Decl. at ¶ 16; *see also id.* at ¶ 13 (noting May 12, 2020 date "would at least make it feasible for more manufacturers to develop and submit complete and high quality applications, and for FDA to publish a proposed PMTA rule and be close to finalizing the…PMTA rules. It would also enable…manufacturers to consider and strengthen their applications based on the final PMTA for [vapor] products.").

[13] *Id.* at ¶¶ 18, 22.

[14] *Id.* at ¶¶ 12, 15 (concluding that plaintiffs' earlier cutoff "creates a genuine risk of migration from potentially less harmful [vapor] products back to combustible tobacco products within the population of addicted adult smokers who have completely switched" to vaping).

[15] *Supra* note 2.

a supplemental declaration submitted by Mitchell Zeller, Director of FDA's Center for Tobacco Products, which outlined numerous grounds for such an extension, including the following:[16]

- **Laboratory Testing Delays** – "[M]any laboratories and contract research organizations within the United States and abroad, including those with which manufacturers contract to conduct important laboratory and clinical studies, are shutting down or suspending in-person work, or reducing it significantly – some as the result of their states' or localities' closures of 'non-essential businesses,' others as a result of company policies implemented to ensure their employees' health and safety. By its nature, this type of laboratory work must be performed in person, on site." *Id.* at ¶ 7.
- **Environmental Assessment Delays** – "[T]esting labs and consultants preparing Environmental Assessment reports can no longer guarantee timely results because employees are now working at home and cannot access testing facilities or primary source materials. I also understand that restrictions on travel within the United States and internationally have hampered necessary travel between factories and offices preparing applications." *Id.* at ¶ 9.
- **Supplier Response Delays** – "Many of the suppliers are located in places such as…China, where information related to premarket review applications resides. I am also informed that industry members are experiencing disruptions in receiving finished product and packaging on samples from overseas sources. For example, factories in China have not been able to make timely deliveries of e-cigarette products." *Id.*
- **Travel Restrictions** – "Many international organizations and federal, state, and local governments have taken…measures that make travel and working on site difficult or infeasible. The CDC has issued a Label 3, Travel Health Notice, recommending that travelers avoid all nonessential travel to international destinations. Travel is currently restricted into the United States for most foreign nationals who have recently visited 27 countries…[including] most parts of China." *Id.* at ¶ 6.
- **Employee Health Concerns** – Noting a need to "prevent firms compromising their employees' health or taking actions that could risk further disease transmission to meet the current deadline….A shorter extension could put pressure on manufacturers to put their employees' health and safety at risk to make up for that lost time." *Id.* at ¶ 12.[17]

At the time, there were 140,904 confirmed COVID-19 cases in the U.S., with 2,405 deaths. The Department of Health and Human Services ("HHS"), as well as the White House,

[16] *AAP v. FDA*, Supplemental Declaration of Mitchell Zeller (Doc. 175-1) ("Suppl. Zeller Decl.").

[17] *Supra* note 2 at 1 (USDOJ stating that the "global coronavirus outbreak poses unforeseen challenges and has made the May 12 deadline a public health risk to those who cannot comply with the deadline through telework.").

had declared public health emergencies, with the World Health Organization ("WHO") also declaring the worldwide spread of COVID-19 a pandemic. Suppl. Zeller Decl. at ¶ 6.

3. The COVID-19 Conditions That Justified The Initial Extension Still Exist Today And Show No Signs Of Improving

Manufacturers continue to experience substantial delays in preparing PMTAs as COVID-19 continues to severely impact U.S. businesses and the economy, thus warranting a further extension. The attached declarations detail the numerous struggles small vapor manufacturers are still facing as the September 9, 2020 deadline fast approaches, many of which Director Zeller identified to the court earlier this year. These include the following:

- **Laboratory Testing Delays** – Many small manufacturers have not been able to secure required laboratory testing, including for pharmacokinetics, harmful and potentially harmful constituents ("HPHC"), and product stability. Due to the coronavirus outbreak, laboratories are still closed, understaffed, working through significant backlogs of work, lacking testing supplies, and/or focusing on testing related to COVID-19. Many laboratories have indicated that they will not be able to do PMTA-related testing until 2021. Some manufacturers fear that even those laboratories that are working at reduced capacity will have to shut down again as COVID-19 cases spike again. *See* Burton Decl. at ¶ 7; Owen Decl. at ¶ 7; Slis Decl. at ¶ 7; J. Wheeler Decl. at ¶ 7; Jarvis Decl. at ¶ 7; A. Wheeler Decl. at ¶ 7; Orlando Decl. at ¶ 7; Adolph Decl. at ¶ 7; Risteen Decl. at ¶¶ 5, 7; Anton Decl. at ¶¶ 11, 15; Agrafiotis Decl. at ¶ 7; Livezey Decl. at ¶ 8; Meyers Decl. at ¶¶ 5, 7; Leuer Decl. at ¶¶ 5, 7; Swafford Decl. at ¶ 7; Pellicane Decl. at ¶ 7; Wappler Decl. at ¶ 7; LeBlanc Decl. at ¶¶ 5, 7.

- **Consultant Delays** – PMTAs are complex, thus requiring the assistance and advice of multiple consultants to complete the applications. Yet COVID-19 has substantially impaired the ability of small manufacturers to work with their consultants. Travel restrictions have prevented consultants from in-person meetings. Like the laboratories, consultants are also working through backlogs that built-up during the initial shutdowns and are relying on reduced staffing levels. Progress on literature reviews and compiling PMTAs has been slowed as consultants are forced to work remotely. *See* Burton Decl. at ¶ 8; Slis Decl. at ¶ 8; J. Wheeler Decl. at ¶ 8; Jarvis Decl. at ¶ 8; A. Wheeler Decl. at ¶ 8; Orlando Decl. at ¶ 8; Adolph Decl. at ¶ 8; Risteen Decl. at ¶ 8; Anton Decl. at ¶ 10; Agrafiotis Decl. at ¶¶ 5-10; Livezey Decl. at ¶ 8; Meyers Decl. at ¶ 8; Leuer Decl. at ¶ 8; Swafford Decl. at ¶ 8; Pellicane Decl. at ¶ 8; Wappler Decl. at ¶ 8.[18]

[18] Manufacturers also have not been able to conduct pre-PMTA meetings with FDA due to staffing issues at the agency, as well as COVID-19 and travel restrictions. Anton Decl. at ¶ 13.

- **Environmental Assessment Delays** – Because many consultants are not able to travel and visit manufacturing facilities during the pandemic, some small businesses have still not been able to complete the required Environmental Assessments. *See* Burton Decl. at ¶ 8; Jarvis Decl. at ¶ 8; Orlando Decl. at ¶ 8.

- **Supplier Response Delays** – Small manufacturers are having trouble obtaining needed information from suppliers. For instance, flavor suppliers have not been able to complete their Tobacco Product Master Files ("TPMF") because of coronavirus-related shutdowns, staffing shortages, and lack of laboratory testing space. Moreover, due to travel restrictions, manufacturers have also been unable to travel to places like China where relevant information is located. *See* Burton Decl. at ¶ 9; Owen Decl. at ¶ 8; Slis Decl. at ¶ 9; J. Wheeler Decl. at ¶ 9; Jarvis Decl. at ¶ 9; A. Wheeler Decl. at ¶ 9; Orlando Decl. at ¶ 9; Adolph Decl. at ¶ 9; Agrafiotis Decl. at ¶ 9; Livezey Decl. at ¶ 8; Meyers Decl. at ¶ 9; Leuer Decl. at ¶ 9; Swafford Decl. at ¶ 9; Pellicane Decl. at ¶ 9; Wappler Decl. at ¶ 9.

- **Employee-Related Delays** – Small vapor product businesses do not have the personnel to fully dedicate to the PMTA process, as COVID-19 has resulted in reduced hours, lay-offs, and employees working remotely. Some businesses have had employees test positive who then had to quarantine; others have had employees refuse to return to work due to fears of being exposed to coronavirus or because they are immunocompromised. *See* Burton Decl. at ¶ 6; Owen Decl. at ¶ 6; Slis Decl. at ¶¶ 6, 10; J. Wheeler Decl. at ¶ 6; Jarvis Decl. at ¶ 6; A. Wheeler at ¶ 6; Orlando Decl. at ¶ 6; Adolph Decl. at ¶ 6; Risteen Decl. at ¶ 2; Higginbotham at ¶ 9; Anton Decl. at ¶ 10; Agrafiotis Decl. at ¶ 6; Livezey Decl. at ¶ 7; Meyers Decl. at ¶ 6; Leuer Decl. at ¶ 6; Swafford Decl. at ¶ 6; Pellicane Decl. at ¶ 6; Wappler Decl. at ¶ 6; LeBlanc Decl. at ¶¶ 6, 8-9.

- **Reduced Revenues for PMTAs** – Since the breakout of COVID-19, small manufacturers have seen a dramatic fall in revenues (*e.g.*, ranging between 20%-60%), as well as store closures, which have limited the financial resources that can be dedicated to the PMTA process. For example, supply chains have been disrupted, with delays in obtaining bottles and ingredients, including parts from China. Key ingredients are in short supply as propylene glycol and vegetable glycerin have been diverted for use in hand sanitizers. Manufacturers have had to spend money on safety measures for their employees (*e.g.*, PPE, sanitizers, etc.). In order to just survive day-to-day, these businesses have thus had to curtail what they spend on testing, consulting, legal advice, and scientific experts. *See* Burton Decl. at ¶ 10; Owen Decl. at ¶ 9; Slis Decl. at ¶¶ 6, 8, 10; J. Wheeler Decl. at ¶¶ 6, 10; Jarvis Decl. at ¶ 10; A. Wheeler Decl. at ¶¶ 6, 10; Orlando Decl. at ¶ 10; Adolph Decl. at ¶ 10; Risteen Decl. at ¶¶ 9, 10; Higginbotham at ¶ 7; Anton Decl. at ¶¶ 12, 14; Agrafiotis Decl. at ¶ 10; Meyers Decl. at ¶¶ 6, 10; Leuer Decl. at ¶ 10; Swafford Decl. at ¶ 10; Pellicane Decl. at ¶ 10; Wappler Decl. at ¶ 10; LeBlanc Decl. at ¶¶ 9-10; Potluri Decl. at ¶¶ 3-4.

Further, conditions on the ground are not significantly improving and may get worse. As FDA well knows, the numbers of COVID-19 cases and deaths have sky-rocketed since the initial extension was granted. There have been 5.5 million cases and 174,000 deaths in the U.S. to date, with numbers in states represented by the Petitioners just as alarming.[19] HHS's declaration of a public health emergency remains in place.[20] The U.S. Centers for Disease Control and Prevention ("CDC") continues to recommend that employers allow for teleworking and minimizing the number of workers who are onsite,[21] as well as issue travel warnings for areas where PMTA information and product samples may be housed (*e.g.*, China).[22] And experts, including former Commissioner Gottlieb, predict another increasing wave of COVID-19 infections and deaths this fall and winter.[23]

4. Thousands Of Small Businesses Will Face A Substantial Risk Of Closing And Extensive Lay-Offs Without An Extension

In the months leading up to the COVID-19 pandemic, FDA estimated it would receive "thousands" of PMTAs from vapor product manufacturers. Zeller Decl. at ¶ 18. The types of small manufacturers seeking an extension in this petition would be filing many of those applications and represent a significant number of jobs, tax revenues, and businesses lost if the requested relief is not granted.

For instance, in September 2019, over 1,400 such small businesses (mostly "mom and pop" shops) filed a letter with FDA seeking further guidance on how they could meet the May 12, 2020 deadline. They noted that this industry "was created by thousands of small business owners who exemplify the American Dream – that through dedication and hard work, everyone has the opportunity to be successful." But they also warned that if small manufacturers are unable to file timely applications, "businesses will close, thousands of jobs will be lost, many

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[19] *See, e.g.*, New York Times (Covid-19 Database), https://tinyurl.com/ybhrwqhr; Florida (593,000 cases/10,000 deaths); Michigan (104,000/6,400); Oklahoma (50,000/709); Ohio (112,000/3,900); Texas (588,000/11,000); Arizona (196,000/4,600); Tennessee (138,000/1,500); Connecticut (51,500/4,400); Colorado (54,600/1,900); Georgia (233,000/4,800); New York (433,000/32,000).

[20] *See* HHS, *Renewal Of Determination That A Public Health Emergency Exists*, https://tinyurl.com/y22a7b3d.

[21] CDC, *Interim Guidance for Businesses and Employers Responding to Coronavirus Disease 2019 (COVID-19)*, https://tinyurl.com/rbaoc55.

[22] CDC, *Travel Health Notices*, https://tinyurl.com/y8xqmjny.

[23] CNBC, *U.S. will have third act of coronavirus and it will likely be 'more pevasive,' Dr. Scott Gottlieb says* (Aug. 21, 2020), https://tinyurl.com/y3chazrp (*see* App. at 000076).

leases broken, investments lost (some even at life-changing levels) – many may lose their homes, savings, and much more."[24]

Even before coronavirus spread to the U.S., these small businesses were facing significant hurdles in completing PMTAs. As discussed above, FDA conceded in 2017 that it had not issued the foundational guidance and regulations informing businesses regarding not only what information would need to be included in the applications, but also how to generate much of the required data (*e.g.*, testing protocols). Indeed, it was not until two years later, in June 2019, did FDA issue its final PMTA guidance for vapor product manufacturers.[25] And FDA still has yet to finalize a proposed rule further governing the contents of PMTAs that was issued in September 2019, now with less than a month until the submission deadline expires.[26]

With COVID-19 only creating more delays, these companies now face a substantial risk that they will go out-of-business and have to lay-off thousands of employees. Either they will not have sufficient time to finish the necessary testing and other work or will have their PMTAs quickly rejected by FDA before getting to the scientific review stage. And this would play out at a time when the U.S. economy just recorded its largest-ever drop in GDP (32.9% in the second quarter),[27] the unemployment rate still sits in double-digits (10.2%),[28] and over 28 million Americans are currently receiving unemployment benefits.[29] A 180-day extension, at a minimum, is needed to help them from becoming another unfortunate statistic.

Indeed, it was for these very reasons that President Trump issued Executive Order 13924 as COVID-19 began to ravage the American economy.[30] The EO directs that:

> agencies shall identify regulatory standards that may inhibit economic recovery and shall consider taking appropriate action, consistent with applicable law,

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[24] *See* Letter from Amanda Wheeler, Co-Owner, Jvapes E-Liquid, to FDA (Sept. 10, 2019), at 1, 3, *AAP v. FDA* (Doc. 149-2) (*see* App. at 000080).

[25] *Supra* note 7.

[26] FDA, *Premarket Tobacco Product Applications and Recordkeeping Requirements (Proposed Rule)*, 84 Fed. Reg. 50566 (Sept. 25, 2019).

[27] National Public Radio, *3 Months of Hell: U.S. Economy Drops 32.9% In Worst GDP Report Ever* (June 30, 2020), https://tinyurl.com/y4zw6bub (*see* App. at 000083).

[28] U.S. Department of Labor, Bureau of Labor Statistics, *News Release: The Employment Situation – July 2020*, https://tinyurl.com/hu87hxo.

[29] CNBC, *US weekly jobless claims fall to 963,000, first time below 1 million since mid-March* (Aug. 13, 2020), https://tinyurl.com/yxfjop3q (*see* App. at 000091).

[30] Executive Order 13924, *Regulatory Relief to Support Economic Recovery*, 85 Fed. Reg. 31353 (May 19, 2020) ("EO"), https://tinyurl.com/y2xj5h4y.

> including …exercising appropriate temporary enforcement discretion or appropriate temporary extensions of time…for the purpose of promoting job creation and economic growth, insofar as doing so is consistent with the law and with the policy considerations identified in section 1 of this order.

In particular, the EO requests that agencies decline enforcement against businesses that have "attempted in reasonable good faith to comply with applicable statutory and regulatory standards." That is precisely what Petitioners are asking FDA to do here.

5. Granting The Requested 180-Day Extension Is Consistent With Promoting Public Health And Safety

The Petitioners are requesting an immediate 180-day extension for filing PMTAs only where small vapor product manufacturers have demonstrated they have taken necessary steps to guard against access and sales to underage consumers (under 21 years old). As the attached declarations clearly show, small businesses and the trade associations that support them are vehemently against underage use and have implemented numerous safeguards at their brick-and-mortar stores and/or on their retail websites (*e.g.*, age-verification, ID checks at front doors, etc.).[31] It would be highly unlikely, therefore, that any vapor product manufacturer that is granted an extension would contribute to underage use in the U.S.

This holds particularly true as these small businesses do not manufacture flavored, cartridge-based vapor products (like JUULs) that FDA has repeatedly acknowledged are driving underage use. In January 2020, FDA issued its current enforcement policy for vapor products.[32] Based on data from the 2019 National Youth Tobacco Survey ("NYTS"), FDA concluded that "youth overwhelmingly prefer cartridge-based ENDS products." *See* January 2020 Enforcement Policy at 15; *see also id.* at 19, 21 (noting "cartridge-based products…[are the] primary driver in youth experimentation with, and continued use of, ENDS products"), 23. This is because such products have design features that make them popular with young consumers, such as ease of use and concealability. *Id.* at 15-16, 19, 21.

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[31] *See* Burton Decl. at ¶¶ 2-4; Owen Decl. at ¶¶ 3-4; Slis Decl. at ¶¶ 3-4; J. Wheeler Decl. at ¶¶ 3-4; Jarvis Decl. at ¶¶ 3-4; A. Wheeler Decl. at ¶¶ 3-4; Orlando Decl. at ¶ 3; Adolph Decl. at ¶ 3; Risteen Decl. at ¶ 3; Higginbotham at ¶ 3; Anton Decl. at ¶¶ 4-6; Agrafiotis Decl. at ¶ 3-4; Livezey Decl. at ¶¶ 3-4; Meyers Decl. at ¶¶ 2-3; Leuer Decl. at ¶ 3; Swafford Decl. at ¶ 3; Pellicane Decl. at ¶ 3; Wappler Decl. at ¶ 3; LeBlanc Decl. at ¶ 3; Potluri Decl. at ¶ 2.

[32] FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization* (amended April 2020) ("January 2020 Enforcement Policy"), https://tinyurl.com/utxelwg.

Significantly, FDA also noted that cartridge-based products "are not the products typically produced in vape shops that mix nicotine with e-liquid flavors." *Id.* at 21. Indeed, open system vapor products sold by small businesses like Petitioners are larger in size (*e.g.*, tanks), must be manually refilled using e-liquid contained in bottles, and involve complicated settings to operate – hardly the type of product that would attract underage users. As such, the agency has prioritized enforcement against flavored, cartridge-based vapor products, while not targeting vape shops selling open system products, provided that they otherwise take steps to prevent youth access. *Id.* at 18 ("This policy should have minimal impact on small manufacturers (*e.g.*, vape shops) that primarily sell non-cartridge-based ENDS products").

This enforcement approach is also consistent with FDA's long-standing position that it must strike the "appropriate balance between restricting youth access to [cartridge-based] products, while maintaining availability of potentially less harmful options for current and former adult smokers who have transitioned or wish to transition completely away from combusted tobacco products." *Id.* at 20; *see also id.* at 21 ("Accordingly, FDA has recalibrated its balancing of public health considerations in light of the public health threats and significant new evidence [regarding cartridge-based products]. This policy reflects FDA's balancing of concerns regarding the appeal of certain flavored, cartridge-based ENDS products to youth [and] the potential public health benefit of noncombusted options by which some adult smokers might seek to transition completely away from combusted tobacco products.").

This is not surprising as extensive research shows vaping can be an effective quit aid. A recent one-year clinical trial published in the *New England Journal of Medicine* found vaping is nearly twice as effective as other cessation products (*i.e.*, nicotine replacement therapies) when both are combined with behavioral support.[33] The National Academies of Sciences ("NAS") concluded "[w]hile overall evidence from observational trials are mixed, there is moderate evidence from observational studies that more frequent use of e-cigarettes [is] associated with an increased likelihood of cessation."[34] A recent survey of almost 70,000 U.S. vapers found the vast majority had completely replaced smoking with vaping.[35] Public Health England reported almost all of the one-million-plus adult vapers in England are current or ex-smokers, many of whom are vaping to help transition away from cigarettes.[36]

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[33] Peter Hajek, *et al.*, *A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy*, N. Engl. J. Med. 2019; 380:629-637, https://tinyurl.com/ygaqwba4 (*see* App. at 000095).

[34] NAS, *The Public Health Consequences of E-Cigarettes* (Kathleen Stratton, *et al.* eds., 2018), at 18, https://tinyurl.com/ya4w37kb.

[35] Konstantinos F., M.D., MPH, *et al.*, *Patterns of flavored e-cigarette use among adult vapers in the United States: an internet survey* (2018), at 6, 20, https://tinyurl.com/yym6coxf (*see* App. at 000104).

[36] Public Health England, *Electronic Cigarettes: A report commissioned by Public Health England* (May 2014), at 17, https://tinyurl.com/y8eqetcc (*see* App. at 000133).

In fact, Director Zeller has also stated that "some addicted adult smokers use these products with a goal to end" their smoking habits and that a "mass market exit of [vapor] products would limit the availability of a potentially less harmful alternative for adult smokers seeking to transition or stay away from" cigarettes. Zeller Decl. at ¶ 15. He maintained that "[d]ramatically and precipitously reducing availability of these products could present a serious risk that adults, especially former smokers, who currently use [vapor] products and are addicted to nicotine would migrate to [cigarettes]." *Id.* He warned this was a "public health outcome that should be avoided if at all possible." *Id.* at ¶ 12; *see also id.* at ¶ 15 (noting that "these products may be less harmful at an individual level than combustible tobacco products" and "it is likely that some ENDS products may reduce harm at the individual level").[37]

Accordingly, a 180-day extension for small manufacturers of open-system vaping products fits squarely within the TCA's goals of promoting products with a relatively favorable position on the continuum of risk. The TCA "provide[s] new and flexible enforcement authority to ensure there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products." TCA § 3(4). FDA must also "promote cessation to reduce disease risk and the social costs associated with tobacco-related diseases" while "continu[ing] to permit the sale of tobacco products to adults in conjunction with measures to ensure they are not sold or accessible to underage purchasers." TCA §§ 3(7), (9). The TCA, therefore, advances the interests of adult smokers looking for harm reduction tools, a goal that will not be met if small manufacturers are forced off the market due to COVID-19 delays.

C. Environmental Impact

This action, to the extent that the National Environmental Policy Act ("NEPA") even applies (note that Petitioners are asking FDA to request a PMTA filing extension from a court-imposed deadline), would be subject to a categorical exclusion. *See* 21 C.F.R. § 25.30(h) (exempting guidance regarding the submission of applications for product approval).

D. Economic Impact

Not applicable. *See* 21 U.S.C. § 10.30(b)(3).

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[37] *See also supra* note 33 at 1 (NAS concluding that "[l]aboratory tests of e-cigarette ingredients, in vitro toxicological tests, and short-term human studies suggest that e-cigarettes are likely to be far less harmful than combustible tobacco cigarettes."); Riccardo Polosa, *et al.* (2019), *The effect of e-cigarette aerosol emissions on respiratory health: a narrative review*, Expert Review of Respiratory Medicine, https://tinyurl.com/yyl5b2f2 (finding growing evidence that e-cigarette emission aerosols are relatively safe compared to tobacco smoke) (*see* App. at 000135).

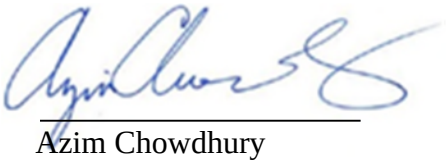
E. Certification

The undersigned certifies that, to the best of his knowledge and belief, 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.

F. Conclusion

The Petitioners and small vapor product manufacturers like them have in good faith strived to complete and file PMTAs before the September 9, 2020 deadline. They have done so because they believe that their efforts will ultimately help addicted smokers transition to a less risky product, all while protecting against sales to underage consumers. But the unprecedented COVID-19 pandemic – a 100-year event that is completely out of their control – will likely force them to permanently close absent an immediate 180-day extension, an end result that would be inconsistent with the TCA's goals and the federal government's continuing efforts to provide small businesses and their employees with economic relief during these troubled times.

Respectfully submitted,



Azim Chowdhury
KELLER AND HECKMAN LLP
1001 G Street, NW
Suite 500 West
Washington, DC 20001
Telephone: (202) 434-4100
Facsimile: (202) 434-4646
chowdhury@khlaw.com

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DECLARATION OF Jennifer Burton

I, Jennifer Burton, declare as follows:

1. As President of Vaping Advocates of Oklahoma Association (VAO), I hold meetings with my Board and Chairpersons to discuss issues within our industry and hold meetings with membership to keep them up to date on our financials, potential legislative issues, and calls to action that may be needed on a state or federal level. I work directly with our consultants to discuss strategies and plan to prepare to work with our state representatives. Additionally, I am the owner of two brick-and-mortar stores in the Tulsa/Broken Arrow, Oklahoma area and have been in business for almost eight years. I personally train all of my employees and keep them informed on any law changes with regards to our industry. I oversee all daily operations in my stores including ordering, financials, and sales.

2. I am the President of VAO, the vaping trade association for the State of Oklahoma. VAO has been in existence for eight years (formally Oklahoma Vaping Advocacy League). There are currently 35 members of VAO. Our organization represents the business owners in the state by actively working with state legislators and specialized consultants with regards to the vaping industry. VAO actively worked with several of our state representatives for several years with regards to underage use and encouraged them to implement Tobacco 21 laws in an effort to keep vaping products out of the hands of underage children. We encourage our members to refrain from carrying products that could appeal to children (cartoon characters on packaging, small, closed-pod systems, etc.). Our organization stands behind open-system devices as they are less appealing to underage users due to the complexity of the products. Our members are dedicated to age-verification for all sales either online or in-person.

3. As President of VAO and the owner of two stores, we have made it a priority to provide education to our members as well as my employees with regards to underage sales. I

have emphasized using the We Card program, which offers window decals and calendars for retailers to use in their stores to assist employees with properly identifying underage buyers. We send this information to our members, as well as an agreement for them to print and have their employees sign stating that they understand the company policy and state law on selling vaping products to consumers under the age and the repercussions for such sales. All employees know that they require a state-issued identification to verify age before each sale. We also encourage our members to make their facilities 21 years and older. For our members that have online sales, they have implemented a third-party age-verification company to ensure that the buyer is over the age of 21.

4. As a store owner, we have limited our marketing to a private page that is age restricted. We do not advertise on platforms such as YouTube or Instagram. We do not pay for advertising other than materials we occasionally have in-store. We do not sponsor events in which children are involved (sporting events or school activities). As for our social media page, our viewers are notified on each posting with the federally-required nicotine warning. We also do not, nor have we, carried any brands that imitate other child-appealing brands (Juice Box) or have cartoon characters on their labels. Our stores have been "shopped" by underage, undercover buyers and have never been cited for sales to anyone under the age.

5. My stores do not make their own liquids; however, we depend on juice makers in order to stay in business. We have several lines that we carry in store that are made in Oklahoma by VAO members. I have spoken to several of them who will not be filing because they do not have the resources (manpower or financial) to complete the PMTA as a result of the business impacts of COVID-19. The ones that are filing say that the process is overwhelming due to the fact that they too have limited resources to complete the task to file. They are doing their best to

gather the required information. My stores also carry lines by larger companies that have stated that they are in the process of completing the PMTA by September 9, 2020.

6. COVID-19 has significantly impacted our industry in more than one way. For my personal business, we reduced hours, limited access to the building, and had employees that were furloughed or laid off due to a cut back in customers and hours of operations. Many of the VAO membership were either forced to close or also let go of employees. For the members working on their PMTAs, it put them very far behind on schedule and the effort to catch up, while also running their business, has been a burden. With reduced staffing during this pandemic and the deadline quickly approaching, I foresee many will not be able to complete the PMTA before the deadline, severely crippling this industry.

7. I have spoken to several of our members that are in the process of filing PMTA and have found that the pandemic has affected their ability to do so as their third-party testing facilities for the testing required are either backlogged with testing or are running on reduced staff due to pandemic restrictions for business operations. The labs are unable to guarantee that they can have their testing done in a timely manner, therefore keeping the manufacturers from filing by September 9, 2020.

8. The same member manufacturers are having issues with the consulting companies as they are with the third-party testing facilities. Due to the pandemic, the companies providing the necessary services required for filing PMTA are limited in time and resources due to a reduced staff force. Travel restrictions have limited these companies to meet in-person to complete the facility for environmental assessments.

9. The pandemic has also slowed the ability to obtain necessary information from suppliers that are required with the filing of the PMTA.

10. COVID-19 has financially impacted everyone, especially small business owners. The members of VAO are made up of micro- and small businesses. As a small business retail shop owner, our sales have declined by 22%. I have spoken to several of our members who have seen a sales decrease of upward 45%. For the manufacturers in our membership, this has impacted their ability to have the revenue stream to financially pay for the required testing, consulting, and personnel to complete their PMTAs. Many of the manufacturers just do not have the resources financially to complete the required measures to file the PMTA by September 9, 2020.

11. Due to the adverse effects of the COVID-19 pandemic, the members, especially the manufacturers, are fearful that they may not be able to file a completed PMTA by the FDA's deadline. As the President of Vaping Advocates of Oklahoma and the owner of two retail store locations, we are asking the FDA to extending the filing of the PMTA for an additional 180 days. The extenuating circumstances are outside of anyone's control and are presenting a hardship that was brought on by the pandemic. Many companies are in the process of rebuilding their businesses and trying to keep from shutting their doors. This industry wants to comply with the federal rules and regulations; however, additional time is needed in order to do so. By extending the deadline to March 8, 2021, it would afford our members the much-needed opportunity to file their PMTA.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 17, 2020

DECLARATION OF Charlotte Owen

I, Charlotte Owen, declare as follows:

1. My responsibilities at Matrix Minds, LLC include overseeing employees, customer service, purchasing, technology support, quality control, and PMTA development.

2. I am the CEO of Matrix Minds LLC. We are a small business e-liquid manufacturer and have a retail store in Seguin, Texas. We opened our business in 2013. We currently have eight employees. Our e-liquid is for open systems only and does not come pre-packaged in any closed pod systems. Our locations have never sold closed pod systems due to their popularity with youth. We focus on older clientele that are seeking to off-ramp from combustible tobacco products.

3. There has always been a strong effort at Matrix Minds to prevent youth access. Some of the precautions we have implemented to prevent youth access include no online ordering availability, employee training that includes loss of job on the first offense, video surveillance with 60 days retention so purchasers can be identified, and ID checks for every purchaser. We are in the process of implementing Trace Verify technology so law enforcement can track purchasers more easily. No closed high-nicotine pod systems have ever been sold in our store due to their popularity among youth, and our facility does not allow minors access to the building. I personally fight for legislation that will limit youth access in our state by putting resolutions before our legislators, such as all high nicotine content vapor products must be sold in 21-and-over establishments.

4. We have taken all images off our labels (fruits, etc.) and our product names are not appealing to youth. We do not keep e-liquid products on the shelves so they are not visible to anyone that walks into the establishment. Our social media accounts are established as adult-only sites and we do not advertise at any local events or utilize advertising methods such as

billboards. If we donate to local charities such as police fundraisers, we utilize gift cards and it is done anonymously. We do not set up booths at any events or display signage at local events.

5. We have been working diligently, when hardships permit, on our PMTA. We have completed product description sheets, environmental assessments, cover letters for each SKU, a literature review and summary, 907 FD&C Act statement, quality statements, GMPs, and youth prevention documentation. We had a large selection of bottle sizes, types, and flavors, which left us with over 300,000 unique SKUs due to the definition of a product. It has been very challenging to prepare that amount of documentation for our small business. Currently, we have prepared over 4.8 million pages of documentation.

6. COVID-19 has placed extreme hardships on our business and our ability to continue to move forward with preparing PMTAs. Our lobbies in both locations were shut down for over 30 days which caused a large impact financially for us. Our flavor manufacturers and equipment distributors were also shutdown, which caused extreme sales loss. Many of our employees have been quarantined due to being exposed to family members that tested positive for COVID-19, causing employee shortages. In Texas, we are currently amid another surge of COVID-19 and, therefore, still have limited occupancy in our establishments, causing slow sales and financial hardships.

7. We have contacted numerous labs and because of the large number of products that must be tested and their limited availability, we have not been able to achieve testing. We found only one lab that was willing to take us on as a client, but their earliest availability was in January 2021.

8. Many of our industry flavor suppliers have themselves had hardships due to COVID-19 and have not been able to complete their Tobacco Product Master Files with the

FDA, which will cause us to submit incomplete data by necessity. Our small business has no recourse other than to wait on the information or to submit without that information and risk our application being rejected. Our nicotine supplier also has not submitted their master file, but has assured us it is trying to complete it in time for us to submit.

9. As stated, earlier sales have been drastically reduced during the COVID-19 pandemic. We have seen sales drop anywhere from 30 to 50 percent since the stay-at-home order was put in place in April. We are struggling and have had to take out loans to continue to operate. One of our locations will be closing due to a drastic drop in sales. That location alone has seen a drop of 60 percent in weekly sales. My company's response to COVID-19 to ensure the safety of our employees as well as customers has also caused financial hardships. We have purchased large air humidifiers, hung barriers between the staff and customers so limited contact is achieved, and increased filter changes and air equipment maintenance.

10. Due to lab unavailability, information unavailability from suppliers, financial strain, and staffing problems, I can affirmatively state that we will be unable to file a completed PMTA by the September 9, 2020, deadline. For a small company, we have made monumental accomplishments in what we have been able to achieve, but many of the problems outlined above are just out of our control due to the circumstances we now face with COVID-19. I respectfully ask for an additional 180 days to file a more complete PMTA. Our small business has been severely impacted but would like the opportunity to work with the FDA to ensure we are producing a product that is beneficial for the public.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 16, 2020

Charlotte Owen

DECLARATION OF Marc K. Slis

I, Marc K. Slis, declare as follows:

1. As a board member and Media/Public Relations officer for the Michigan Vape Shop Owners organization (MVSO), I am responsible for all communications and interaction with media and the public, along with development and evaluation of educational resources and materials such as advertising and marketing guidelines, best practices, and age verification technologies. Additionally, I serve as MVSO's point of contact with other state organizations and the VTA, our national trade organization of which the MVSO is a state chapter.

2. I am a founding board member and Media/Public Relations Officer of the MVSO. The MVSO was established in 2019 with 46 members representing independent vape shops, e-liquid, and hardware manufacturing small businesses in the state of Michigan. Our members are all small or micro-businesses dedicated to assisting Michigan smokers to safely and permanently quit smoking with open-system vaping technology.

3. The MVSO is dedicated to preserving adult access to vapor products while preventing youth access and, as such, we evaluate and recommend age verification technologies, training, and best practices for both manufacturing and retail operations. The MVSO also works with the state legislature to develop common-sense regulations, including stiffer penalties for youth sales violators, along with proper marketing and advertising/labeling restrictions.

4. The MVSO has developed a set of standards that members are required to adhere to. These standards include proper age verification technologies, advertising and marketing standards such as banning labels and imagery that appeal to youth, and agreement to refrain from use of kid-friendly platforms like Tik-Tok and Instagram. These standards are in alignment with the national standards developed by the VTA.

5. The MVSO is comprised exclusively of small and micro-businesses and, as such, our liquid and hardware manufacturing members are all struggling with various aspects of the costly, time-consuming, and complicated PMTA requirements. We have urged our members to complete the PMTA process, identifying an industry stakeholder group focused on assisting small and micro-businesses with many aspects of the process including cover letters, data entry, literature reviews, quality statements, and consumer surveys.

6. Michigan has been one of the nation's COVID-19 hot spots and has been consistently subjected to the most restrictive policies in the nation from the beginning of the outbreak. In her first COVID press conference, Michigan Governor Whitmer stated that vaping massively increased one's risk of contracting COVID, despite no evidence to support this. The governor also singled out vape shops for immediate closure in her first executive order in March. Coupled with six months of stay-at-home orders, these closures and restrictions have massively impacted our members' ability not only to pursue PMTA, but to stay in business. Revenue streams were decimated, meetings were cancelled, lab work delayed, and employees necessary for PMTA submission had to be let go. Though most of our member businesses are once again re-opened, they are in desperate financial straits and, in many cases, struggling to re-hire employees or hire new ones. They are all also experiencing disruptions in their supply chains. Vaping hardware comes from China, which was shut down completely for some time. Some e-liquid ingredients are also used in hand sanitizer and are now difficult to source. All of these factors have combined to severely limit or prohibit our members from completing the PMTA process. Across the nation, states and federal government have recognized the difficulties that the COVID-19 pandemic has created and the problems faced by individuals and businesses with the notable exception of vapers and the vaping industry. Vapers were forced back to smoking

and no relief has yet been provided for vaping manufacturers required to complete PMTA submission, which is due in the next three weeks.

7. MVSO members have reported that lab testing requirements for PMTA are now impossible to achieve. The few labs that conduct PMTA testing are experiencing the very same problems our members face in terms of manpower, supply chain and closure issues; as a result, lab testing is backlogged for up to one year. This issue and the others are beyond their control and on September 9th, they will be forced to close their doors permanently.

8. MVSO manufacturing members have also reported that COVID-19 restrictions have made travelling to meetings with consultants and the FDA difficult and, in some cases such as the FDA, impossible. Revenue streams are dwindling as their retail customers' sales have been reduced or their stores closed.

9. MVSO members have reported that they need ingredient information from their suppliers in the form of Tobacco Master Files and that this, too, has been impacted by the same conditions described above.

10. Over the last six months of stay-at-home orders, due to restrictions and forced closure of our members' businesses, revenue streams have been severely depleted and some businesses forced into permanent closure. Loss of stores, reduced staff, maintaining lease agreements, additional operating costs, all due to COVID-19 have greatly impacted our members' ability to comply with PMTA requirements and costs. During the COVID outbreak and subsequent restrictions and forced closures, it has been a difficult task for any small business to remain viable, but when faced with the costly and complicated PMTA submission, the situation has become untenable.

11. As the representative MVSO Board member, I affirmatively state that delays related to COVID-19, business and travel restrictions, and forced closures have massively and negatively impacted our members' ability to complete PMTA requirements by the September 9, 2020, deadline and request an additional 180 days additional time to submit their applications.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 17, 2020

DECLARATION OF Jourdan Wheeler

I, Jourdan Wheeler, declare as follows:

1. I am the CEO of Jvapes, LLC based in Prescott, Arizona. Jvapes operates an e-liquid manufacturing facility, five retail locations, an e-commerce platform, and a wholesale distribution business. Jvapes began operations in December 2011. We are an American E-liquid Manufacturing Standards Association (AEMSA) certified manufacturer. Currently, Jvapes has 29 employees and does approximately three million dollars in annual revenue across all locations. Our manufacturing operations are limited to open systems e-liquids exclusively.

2. As the CEO of Jvapes, I am responsible for managing the overall operations and resources of the company. I am also responsible for managing the direction and success of the company. I oversee top-level management within Jvapes and make the decisions that determine the course of our business. I am also heavily involved in Jvapes' compliance efforts to ensure our long-term viability in an ever-changing landscape of regulations pertaining to the vapor industry.

3. Jvapes has spent a significant amount of time and resources to ensure that the company is doing everything it can to prevent youth access to our products. Jvapes prohibits entry of minors into all our retail locations. We require ID verification for all purchases. Our register system requires an ID swipe for every transaction processed, and IDs are examined by retail employees to verify that the photograph on the ID matches the purchaser; then, the ID is scanned to verify that the purchaser is over 21 years old and that the ID is valid. All retail employees undergo thorough training on our age verification procedures. Our retail locations have never had a violation for sales to minors. Our e-commerce platform utilizes third-party age verification technology through Veratad. We are also implementing Trace/Verify technology on all the bottles of e-liquid we produce to assist retailers and law enforcement in efforts to prevent

minor use of vapor products. Trace/Verify utilizes QR codes placed on each vapor product sold. The QR code stores the driver's license number used to purchase the product, as well as the date and location of the transaction. This information can later be retrieved if that product is found to be in the possession of a minor in order to identify how the minor came to possess the product. Jvapes is continually looking at new and innovative ways to prevent youth access to vapor products.

4. Jvapes engages in minimal marketing to the public. We maintain Facebook pages for our business locations that are limited to audiences over 21 years of age. We do not maintain a presence on any other social media platforms. We do not market via TV, radio, print, or billboard advertising. We do not engage in advertising at local or public events. Our sole source of marketing is through our email lists of current, age-verified customers. Jvapes is committed to following industry marketing standards developed by the Vapor Technology Association, and these marketing standards can be made available upon request.

5. Given the difficulties resulting from COVID-19, Jvapes has made all possible efforts towards completing Pre-Market Tobacco Application (PMTA) requirements. We have completed cover letters, a scientific literature review and summary, product description sheets, consumer surveys, GMP and SOP documentation, quality statements, environmental assessments, youth prevention documentation, and post-market surveillance plans. We continue to work toward completion of further requirements, but we have encountered great obstacles due to the web of challenges we have encountered as a result of the COVID-19 pandemic.

6. The impact of COVID-19 on all aspects of our business cannot be overstated. We had multiple retail locations closed for a five-week period spanning March and April. During this time, our revenues decreased significantly. We also lost eight employees due to COVID-19

issues, including lack of childcare, fear of returning to work during a pandemic, or having immunocompromised family members, etc. Replacing those employees in a COVID environment has been challenging at best. Maintaining inventory has been a nearly impossible task since March. In our manufacturing facility, we have struggled to source the components necessary for production. The bottles we use for our e-liquid have been scarce due to their use for bottling hand sanitizer. Many of the base ingredients we use, including propylene glycol, vegetable glycerin, nicotine, and flavorings, have been difficult to obtain due to suppliers being affected by COVID-19-related shutdowns and employee shortages.

7. Jvapes has engaged in discussions with many laboratories that conduct product-specific PMTA testing. These laboratories have communicated to us that, at present, there is at least a one-year backlog to complete product testing. Testing is simply not able to be completed in time for the September 9, 2020, deadline. Laboratories report that they are experiencing shutdowns, as well as employee and material shortages related to the impacts of COVID-19, which is only exacerbated by the sheer number of companies attempting to secure laboratory services.

8. Due to the severity of the COVID-19 pandemic, consulting services have also been difficult to access. It has been challenging at best to meet and work with consultants given the inability to conduct in-person meetings. Our internal compliance department, who normally liaisons with our consultants, experienced pandemic-related staffing shortages. Given the loss of revenue, we were not able to financially retain the number of consultants we had planned for. Our remaining consultants have communicated to us that the inability to travel and conduct in-person meetings is severely hampering their ability to complete tasks critical to the PMTA.

9. Our suppliers report similar obstacles to retaining laboratory and consulting services, which have stalled their ability to create the Tobacco Product Master Files (TPMFs) necessary for us to progress further in our PMTA process. Suppliers have also been subject to shutdowns and internal employee shortages. Without the critical information contained in TPMFs, our PMTA documentation remains incomplete and puts us at risk of having our PMTAs rejected.

10. COVID-19 shutdowns caused Jvapes' revenue to decrease by 33%. This severe decline in revenue has significantly impacted all aspects of company budgets, including budgeting for PMTA-related expenses. As a result, we lost many of the financial resources earmarked for PMTA efforts. The loss of revenue during the pandemic has created roadblocks to completing the more financially demanding components of the PMTA requirements.

11. Declining revenues, staffing shortages, laboratory backlogs, supply chain disruptions, and difficulties accessing consultant services due to COVID-19 have created significant delays in Jvapes' efforts to complete necessary PMTA components and will impact our ability to submit a complete PMTA by September 9, 2020. As a result, Jvapes requests an additional 180 days to submit its Pre-Market Tobacco Applications.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 18, 2020

DECLARATION OF James Jarvis

I, James Jarvis, declare as follows:

1. I oversee the day-to-day retail and manufacturing operations for Jarvis Vaping Supply. These duties include product selection, manufacturing SOPs and standards, store and lab cleanliness, and store set-up. I take great pride in our product offerings, our employees, customer service, and being a responsible member of the community. We have also taken a great role in making sure we do our part to encourage proper disposal of ingredients and batteries. We developed a battery recycling program to encourage customers to bring their batteries to us for disposal once they have lost their usage by offering them a discount on new batteries with the surrender of their old ones. We collect and send them to Battery Solutions for disposal. This program was adopted by the Ohio Vapor Trade Association (OHVTA), of which I am President, and made available for all business members of OHVTA. OHVTA has implemented practices for ID verification, marketing standards, and best business practices for all members.

2. I am co-owner of our stores and liquid manufacturing company. We started Vapor Station Columbus on July 1, 2013. Our first location was at 1154 S. High St. Columbus, Ohio 43206. We currently have four locations around the Columbus Metro area. Our liquid manufacturing facility is located at 144 N. Hamilton Rd, Gahanna, Ohio 43230. We currently have 11 employees. Our business focuses on open systems e-liquid.

3. In our online business, we use an age verification program called agechecker.net. It requires potential customers to input their birthdays and submit copies of their drivers' licenses as proof of legal age. In our stores, we require ID upon entry from every customer. We also have a third-party ID verification scanner integrated into our register and every ID is scanned

before purchase. Employees are required to make sure the picture matches the person making the purchase and the scanner verifies the age by scan.

4. In our efforts to eliminate marketing to youth, we have set all our business Facebook pages to 21 years and over. We do not use television for any advertisements. For any type of print or radio we use, we always use the required FDA nicotine warnings. Our radio commercials always mention 21 years and over, ID needing to be presented upon entry, and we only advertise on stations geared predominately for adults ages 25 years and up. During our sales transactions with the customers, we ask questions to see where they are in their journey. One of the questions we ask is if they currently smoke or vape. If they answer no, we stop the conversation and let them know that we will not be able to help them as we are not here to start a new habit. We do not carry products with cartoon imagery or intellectual property infringement on the labels. Our goal is to help adults stop smoking.

5. For our PMTA process, we have dedicated countless hours to getting the product descriptions and environmental assessment documentation together. We have developed an SOP in writing, we have compiled market data documentation, and implemented GMP training for our employees. We have compiled 4,500 consumer surveys and are actively compiling the data for the FDA.

6. COVID-19 has been devastating to our business. Our stores were shut down for two months and our employees were laid off. We did pay them for the first three weeks of the shutdown but ultimately had to lay them off when we could no longer afford to do that. Once we were back open, all employees came back to work. Unfortunately, with customers out of work and not comfortable going into public, our stores have continued to suffer financially to this day. We are considering possibly closing one of our retail locations in the near future, which will

ultimately reduce our employee count. COVID-19 has also majorly disrupted our supply chain for devices, bottles, and liquids. This has also led to declines in sales due to limited availability of inventory.

7. At this time, there are no other laboratories taking on testing, as they are closed or understaffed and cannot complete testing in time for the September 9, 2020, PMTA submission date. The timeline and PMTA guidance issued before COVID-19 were impossible, and now there is no way to get what the FDA is asking for in the short period of time we were given after guidance was set forth. Our company's ability to have e-liquid testing conducted by third-party laboratories (including pharmacokinetic testing, harmful and potentially harmful constituent testing, stability testing, etc.) has been severely hampered by COVID-19. Most third-party laboratories were shut down for several months and are now slowly working through a large backlog of projects using a reduced staff. The labs cannot guarantee Jarvis Vaping Supply that they will complete the required testing so that we can finish the PMTA and file it before FDA's deadline expires.

8. The company's regulatory consultants have also been hampered by COVID-19. They have had to work with reduced personnel and a backlog of work because of being shut down for two months. This has slowed work on projects like literature reviews and preparing the actual application. Travel restrictions have also prevented our consultants from visiting our facilities to conduct activities like environmental assessments and SOP reviews.

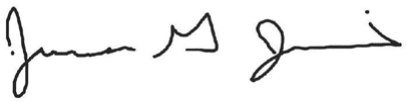
9. Additional delays have been created by suppliers who are facing the same COVID-19 work-related shutdowns. Our consultants are not able to get the information needed in a timely manner from suppliers pertaining to information on the make-up of ingredients that we use in our e-liquids.

10. COVID-19 has also significantly affected our revenues, spending, and budgets. Our sales have dropped by 65% since the start of the pandemic. This hardship has made us have to limit spending on legal, scientific, and consultant services, which are necessary to support our efforts to complete the PMTA by FDA's deadline. We do not presently have the financial resources to fully support the PMTA process.

11. Jarvis Vaping Supply may not be able to file a complete PMTA by the FDA's September 9, 2020, deadline. We are asking the FDA recognize the extenuating circumstances and extend the filing deadline 180 days until March 8, 2021, to allow small companies like mine to finish their PMTAs so that FDA has all the data and information required to adequately review our applications.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 16, 2020



DECLARATION OF Amanda Wheeler

I, Amanda Wheeler, declare as follows:

1. In my role as the President of the Rocky Mountain Smoke Free Alliance (RMSFA), I am responsible for developing and implementing policy positions for our organization, working with the state legislature to improve and promote sound legislation that supports responsible business practices as well as the health and safety of the public. RMSFA advances policies and business practices aimed at reducing youth use and access to vapor products. As part of that effort, I work with our national trade association, the Vapor Technology Association (VTA) to coordinate how national policy positions can best be implemented at a state level. Together, we develop and manage tools that act as resources for our members. These tools include marketing standards, manufacturing standards, retailer best practices, age verification technology and training, and compliance tools for local, state, and federal regulations.

2. I am the President of the Rocky Mountain Smoke Free Alliance, a 501(c)(6) non-profit trade association representing approximately 125 small businesses in the vapor industry throughout the state of Colorado. Our members include retailers, manufacturers, distributors, and suppliers. The Rocky Mountain Smoke Free Alliance (RMSFA) was founded in Denver, Colorado in 2018.

3. The Rocky Mountain Smoke Free Alliance offers resources to our membership in order to provide training and education to our retailers and their employees. Some of the guidance and tools to our members include the *WeCard* program and the *YEPP ID* program. We provide discounts on ID scanning and age verification technology. We also provide our retailers with signage for their businesses, such as window clings and countertop displays, to notify and ensure our customers are aware of age requirements and our dedication to the ID verification

tools used for sales. RMSFA has worked with the state legislature to promote and pass licensing for tobacco retailers that includes robust penalties for sales to minors, legislation to raise the age of purchase to 21, legislation to prohibit use of e-cigarettes in locations where smoking is prohibited, legislation to prevent minors from entering vape shops, and legislation preventing tobacco retailers from being located near schools, etc. RMSFA continues to be engaged with policy makers on future legislation to eliminate youth use of vapor products in Colorado. We have worked with 37 municipalities throughout the state to pass local ordinances to prevent youth use, such as licensing, taxation, zoning laws, and smoke free laws. RMSFA is diligent in making sure that our members follow and abide by all local, state, and federal laws. We do not accept membership requests from businesses who are not compliant with all laws and who do not follow sound business practices to prevent youth use. RMSFA has a protocol for terminating current members who are found to be in violation of the law or the sound business practices meant to safeguard against sales to minors.

4. RMSFA members follow and adhere to marketing restrictions developed by the VTA. These vigorous standards were developed by VTA in January of 2018 and include guidelines to ban the use of product terms that appeal to minors, ban the use of packaging that imitates products that appeal to children, ban the use of any cartoon-style imagery, ban the use of any terminology that suggests any therapeutic value or health claims, ban advertising near any schools or playgrounds, and ban any inaccurate or misleading advertising. These are just a few of the VTA marketing guidelines. A complete copy of these marketing standards can be made available for review. Our members do not advertise on social media platforms that do not have the ability to age-gate (restrict) accounts. Any social media pages for our members are limited to audiences over 21 years of age. All social media posts must abide by the marketing standards set

forth in the policies above by VTA. RMSFA is actively working with lawmakers in Colorado to adopt into state law restrictions pertaining to the marketing of vapor products.

5. RMSFA manufacturer members have varied in their ability to complete Pre-Market Tobacco Application (PMTA) requirements. RMSFA has actively encouraged members to do everything within their means to prepare for the September 9, 2020, deadline. RMSFA has provided members with crowdsourced PMTA tools to make the PMTA process as attainable and affordable as possible. At present, RMSFA has been able to partner with other industry stakeholders to make the following PMTA requirements available to our members: product description sheets, environmental assessments, cover letters, literature reviews and summaries, consumer surveys, quality statements, GMPs, SOPs, youth prevention documentation, and post-market surveillance tools.

6. Colorado was an early COVID-19 hotspot, as there were significant outbreaks in Colorado ski communities that spread throughout the state. As a result, Colorado enacted robust stay-at-home orders and closures for all businesses deemed non-essential. Vapor businesses were not considered essential and were not allowed to open in any capacity from March 26 - May 1, 2020. This was debilitating as our member businesses were not able to maintain any sort of revenue stream during that five-week period. When businesses were allowed to reopen, nearly all of them faced extreme staffing shortages due to financial instability, thus the inability to retain personnel during the shutdown. Employee fears regarding returning to work during the pandemic have also effected staffing. Upon reopening, many business owners found their consumer base depleted due to factors such as economic hardship, fears about entering public spaces due to COVID-19, or customers *who had returned to cigarette smoking* due to no availability of vapor products during business closures. These issues created employee shortages and a reduced

consumer base that persist to the current day. The entire supply chain that vapor businesses depend on to stock stores and manufacture products has been severely disrupted by COVID-19. Much of the supply chain for vaping hardware originates in China or overseas. Many of the overseas manufacturing facilities have been shut down entirely for a long period of time. Upon reopening, many of those facilities refocused production lines from vapor hardware to PPE and supplies needed for COVID response. In turn, U.S.-based distributors did not have products in stock. The distributors were also located in areas affected by shutdowns and faced employee shortages that left them unable to fill orders even for the products they were able to stock. Supplies from the United States that are essential in the production of e-liquid, such as base ingredients and bottles, have been hard to source due to their use in PPE and products such as hand sanitizer. These e-liquid component suppliers were also affected by employee shortages. Without ingredients to manufacture liquid or hardware to stock in retail locations, all of our members have dealt with an ongoing problem of severely limited revenue.

7. RMSFA members have communicated their difficulty in obtaining laboratory services for PMTA testing. Laboratories have faced a range of issues, including employee shortages, supply shortages, and a need to focus laboratory capacity and supplies on issues directly related to the United States COVID-19 response. Our members have reported that laboratories are not able to accept or are not accepting any PMTA clients at this time, and the ones that are accepting PMTA clients have waitlists extending as far as one year (note: outside of the September 9, 2020, deadline) to begin testing. In addition, the issue of the great expense involved in laboratory testing has been made worse due to severely declining revenue streams for vapor businesses due to COVID-19.

8. Prior to March, RMSFA had been conducting numerous meetings with government officials at FDA and HHS regarding PMTA and its effect on our members, and how our members could best comply with PMTA requirements. RMSFA had submitted a proposal to FDA and HHS regarding creating a streamlined PMTA process for small business. When COVID-19 cases started to surge in the United States, government agencies understandably turned their attention to the pandemic response. A side effect is that we were no longer able to meet with government officials regarding PMTA for months. We recently resumed meetings with limited ability to communicate with officials over the summer. We have not been able to travel for any substantial in-person meetings. Additionally, consultant services have been difficult to obtain due to loss of revenue and consultant unavailability.

9. RMSFA reports from our members that they have had extreme difficulty obtaining the information necessary from e-liquid ingredient suppliers who have not created Tobacco Product Master Files. As a result, members are not able to create complete PMTAs without basic information needed from ingredient suppliers. Many of these suppliers have reported that they are in the process of creating master files, but that process has been severely hampered and delayed by the problems previously described in relation to COVID-19 (employee shortages, consultant shortages, limited laboratory testing capacity, etc.). Without the foundational information needed from suppliers, our members are having great difficulty completing product-specific components of PMTA.

10. In the three and a half months our businesses have been open following the shut-downs, members have been rebuilding revenue streams but have not been able to fully recapture lost sales. Many of our members are still down in revenue by as much as fifty percent. We have had members cut payroll budgets, seek relief on leases, and close down retail locations, and we

have members who are even contemplating complete closure of their businesses due to the impact of COVID-19 on all aspects of running a business. Most small businesses in the United States are facing similar problems, but these issues are impacting the vapor industry particularly hard as we were preparing for the financially momentous endeavor of the 2020 PMTA deadline before COVID-19, which has become an especially impossible task when the difficulties associated with the pandemic are taken into account.

11. As the President of RMSFA, I can affirmatively state that delays associated with COVID-19 have impacted our members' ability to complete PMTA requirements by September 9, 2020, and request 180 days additional time to submit required PMTA documentation.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 16, 2020

DECLARATION OF Nicholas Orlando

I, Nicholas Orlando, declare as follows:

1. As President of Total Liquid and Coil Company, my responsibilities include overseeing product development, working with our manufacturers and distributors, planning marketing efforts, and managing personnel. I also coordinate the company's efforts to comply with e-vapor statutes, regulations, and ordinances locally and across the country.

2. I am the founder and President of Total Liquid and Coil Company DBA: The Vapers Depot, a small e-vapor company headquartered in Largo, Florida. Total Liquid and Coil Company was started in 2016 and contracts out the manufacturing of its premium e-liquids. The company has eight flavors of e-liquid which come in a variety of tastes and nicotine concentrations. The company operates four retail stores on the West Coast of Florida. We have approximately 15 full-time employees. Our e-liquids are used in open system products only. We do not produce e-liquids for closed or cartridge-based systems.

3. The company has taken significant steps to prohibit the sale of its products to consumers under the age of 21. At each of our retail locations, we also require each customer to produce a picture on government-issued identification. Nobody is permitted in the stores who is under 21 years old. Every purchase can only be made after a government-issued identification is produced. We specifically train our employees to implement these age-verification steps.

4. The Vapers Depot has also ensured that its branding does not include flavor names or graphics (like cartoon characters) that might readily attract underage users. For example, our brands include names like Berry Mix, Blue Raspberry, and Island Punch. Based on a recent survey conducted by our co-packer Diamond Vapor, the average age of our customer is 45-years old. The company has never been cited by a government agency for underage sales.

5. The Vapers Depot and its Co-Packer have been diligently preparing a Premarket Tobacco Product Application ("PMTA") that it had planned to file with the Food and Drug Administration ("FDA") by the September 9, 2020, deadline. Among other steps taken by the company, we have been conducting a scientific literature review to locate studies done on products similar to our e-liquids, carrying out product testing with a third-party laboratory, completing required environmental assessments, and working with suppliers to get ingredient information. This has been a substantial undertaking as we have approximately 100 variations of e-liquids when all flavors and nicotine concentrations are considered.

6. However, the company's efforts to complete the PMTA have been substantially slowed by the COVID-19 pandemic. We have taken the COVID-19 crisis seriously. Florida has been hit hard by the pandemic, where COVID-19 cases have increased in recent weeks. We are considered a non-essential business, so in response to prior government-ordered quarantines, and as well as part of our company's on-going program to minimize risk to our personnel, most employees have been working remotely. This has adversely impacted their ability to work on the application. For example, employees have been delayed in conducting onsite audits needed to complete certain parts of the PMTA as our locations were completely closed for six weeks. The Vapers Depot has had to lay off six employees who had previously been working on the PMTA. As a result, we are severely understaffed and do not have the resources to devote to the PMTA full-time.

7. We are very concerned about the impact of COVID-19 on The Vapers Depot's ability to conduct third-party testing of our e-liquids (including pharmacokinetic testing, harmful and potentially harmful constituent testing, stability testing, etc.) as required by the PMTA. Our third-party laboratory is located in Florida. With COVID-19 rates increasing in Florida, there is

also the possibility that the lab will be required to shut down again in the near future according to some local reporting.

8. The company's regulatory consultants have also been hampered by COVID-19. Like The Vapers Depot, they have had to work remotely with reduced personnel. This has slowed work on projects like literature reviews and preparing the actual application, which will be hundreds of pages long. Travel restrictions have also prevented our consultants from visiting our facilities to conduct activities like environmental assessments.

9. There have been additional delays. For instance, we have not been able to get timely responses from our suppliers for information on the make-up of ingredients that we use in our e-liquids. The suppliers are facing the same work-related slowdowns as we are.

10. COVID-19 has also significantly affected our revenues, spending, and budgets. Sales have dropped by 60% since the start of the pandemic. As The Vapers Depot is a small company, it has been cutting costs where it can to survive. For example, the company has had to limit its spending on legal, scientific, and consultant services, which are necessary to support our efforts to complete the PMTA by FDA's deadline. As a consequence, the company does not presently have the financial resources to fully support the PMTA process.

11. In light of these significant delays, The Vapers Depot may not be able to file a complete PMTA by the FDA's September 9, 2020, deadline. As a result, we ask that FDA recognize these extenuating circumstances, which have been out of my company's control, and extend the filing deadline 180 days until March 8, 2021, to allow small companies like The Vapers Depot to finish their applications so that FDA has all the data and information required to review the PMTAs.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 17, 2020

DECLARATION OF Kyle Adolph

I, Kyle Adolph, declare as follows:

1. As the CEO of Cream Vapor, I am responsible for the oversight of our entire staff. This includes overseeing accounting processes and procedures, customer services, and our sales staff. Monthly, I reconcile our sales alongside our accountant and work with our sales team to determine goals, sales projections, and marketing efforts. I also assist the warehouse with inventory control and shipping, ordering product for our warehouse, and staying apprised of local, state, and federal regulations.

2. Cream Vapor LLC began operations in August 2014. Cream Vapor is owned by three individuals and will do approximately one million dollars in sales this calendar year. We are located in Tempe, Arizona and our business is limited to sales of our proprietary e-liquid to wholesale and distribution accounts. We do not sell directly to the consumer. Our e-liquid is made for open source systems and is manufactured for use in those applications only.

3. Cream Vapor does not do direct consumer sales, so we do not currently utilize any age verification software. Our sales are centered on business to business (B2B) clients of which we vet and verify meticulously. To obtain a wholesale account, B2B clients are required to submit applications, which include their physical brick and mortar location, copy of EIN and reseller's permit, as well as all relevant contact information. Once this information is received, a member of our sales team reaches out to the business to confirm the documents are correct and that they are a legitimate business with the necessary tax/state documents to purchase and resale e-liquid. We rely on these businesses to implement and utilize industry-leading software and/or hardware to verify age at POS. In the event we learn that a store has sold to a minor, we cease business with the store immediately and decline any future sales requests.

4. Our advertising predominantly takes place inside of private groups targeted towards B2B clients. These groups are owned, moderated, and reviewed by industry stakeholders. In order to join these groups, you must have a business you represent or own. Our advertisements are targeted to the business owners inside of these groups, which eventually progress into a more direct sales cycle with the business owner. Again, due to the nature of our business, we rely on our partners to utilize and implement age verification software/ID checking protocol, and because of this, we consistently monitor and work with stores to ensure compliance with federal law.

5. In order to meet the PMTA deadline, we have aligned ourselves with industry representatives who are intimately familiar with the regulatory landscape. In conjunction with these representatives, we are working around the clock to complete the necessary documentation before the deadline.

6. COVID-19 has dramatically changed the electronic cigarette industry. First and foremost, lockdowns across the nation have forced our clients to shutter their windows, slash their budgets, layoff staff, and for many, unfortunately, to close. On a distribution level, our sales have slowed, which has resulted in an influx of demand on our sales team to work towards sales projections, leaving little time for other tasks. To be frank, companies like ourselves are very much finding themselves in an all-hands-on-deck position to keep the doors open. Furthermore, due to the unpredictable nature of COVID-19 and its impact on travel, housing, and employment, certain individuals are unavailable to assist with the PMTA process – individuals that we have come to rely on for regulatory guidance and assistance.

7. Due to state shutdowns, many labs across the country are either closed, working with a limited staff, or dealing with an insurmountable backlog. Due to the strict time window in

which to submit the required documents, it forces us to make concessions with who we work with, which could compromise our efforts to secure a PMTA due to lack of information, missing deadlines, etc.

8. Many across the country find themselves in precarious situations due to COVID-19. Whether it is a lack of income, potential home foreclosure, or a shelter in place order, COVID-19 has dramatically decreased the capability of many consultants. Travel restrictions, lockdowns, and day-to-day disruption of services have proven to be crippling for the business operations for these consultants, leaving many of them with a dwindling clientele base.

9. Some ingredient suppliers have shut down or reduced staffing, leaving companies like us waiting on crucial information on various flavoring components. Additionally, manufacturers have scaled back operations and/or shut down completely, leaving those who rely on their manufacturer without support. COVID-19 has disrupted the supply chain, leaving many manufacturers without critical flavoring components, preventing them from submitting samples to accredited labs that are 1) operational and 2) have the staff to facilitate testing in a timely manner.

10. COVID-19 has dramatically impacted sales, and our sales numbers accurately corroborate this. Due to a large portion of vape shops closing down, reducing staff, and/or going out of business completely, our sales have fallen. Additionally, the supply chain is stressed, and some manufacturers cannot meet what little demand there may be due to customs delays and/or flavoring manufacturers suffering from logistical delays. Our company relies on a strong B2B presence to remain profitable and keep our employees on payroll; but, with the dwindling sales numbers, this is an ever-increasing challenge. COVID-19 forces us to redirect available funds where necessary to ensure our staff is able to collect a paycheck, and that our operating expenses

are met. This, in addition to the burdensome financial requirements of submitting a PMTA, has proven to be extremely difficult.

11. On behalf of Cream Vapor, I can attest that delays and disruptions caused by COVID-19 have severely impacted our ability to comply with the September 9, 2020, PMTA deadline, and respectfully request that the PMTA deadline be extended an additional 180 days.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 17, 2020

Kyle Adolph

DECLARATION OF Jonathan P. Risteen

I, Jonathan P. Risteen, declare as follows:

1. As President of Gentleman's Draw, my responsibilities include overseeing the manufacturing process, working with our distributors for both wholesale and retail businesses, managing the accounting for the operation, and managing personnel. I also manage and coordinate the company's efforts to comply with state and federal vapor regulations.

2. I am the founder and President of Gentleman's Draw, located in Edgewater, Florida. Gentleman's Draw has been manufacturing e-liquid for open system vapor devices since April 2015. We have always been a small business. At one point in time, we had six employees. Unfortunately, due to COVID-19, we are down to just two employees. In October of 2018, we made the decision to shift part of the company's focus towards the retail space, and we opened our first and only retail location. When we made this change, we outsourced our manufacturing to a co-packer. When the new deadline for PMTAs was announced in the summer of 2019, we started discussions with our co-packer and we came to the agreement that if PMTAs were to be filed, we would not be receiving help from them and we would have to do them ourselves. We are currently in the process of taking the manufacturing back in-house to try to make the new September 9th deadline.

3. We take underage access to ENDS products extremely seriously at Gentleman's Draw and have taken steps since our creation in 2015 to hold ourselves to the highest of standards. We named our product line Gentleman's Draw to make sure that our brand image promoted responsibility and maturity. Our company policy for naming products is very strict and we do not allow words like "candy" on our products. We avoid any graphic design or branding that could resemble products that have been marketed towards minors in other industries. Our company policy is to follow FDA's requirements of checking IDs for anyone

who appears to be 27 years old or younger for all sales. On our retail website, we use AgeChecker.net. This third-party age verification system cross references several government databases to verify the age for all transactions. If AgeChecker.net cannot verify a consumer's age through the database system, it requires a photo of the ID for the person making the purchase. For in-person purchases at our retail store, we use TokenWorks.com's ID Scanner (https://www.idscanner.com/product/agevisor-touch/). We invested $900 in this system to help prevent any human error when checking IDs. This system will also verify the information, including name and address, that is associated with the magnetic strip or the bar code on an ID, which prevents the use of most fake IDs. We are extremely invested in the preservation of this technology, which is why we go to such lengths to prevent youth access.

4. In 2019, due to the negative media coverage of the ENDS industry, we decided to delete all content from our social media pages. Our company policy since then is that we do absolutely no marketing or advertising of our products directly to consumers. We still have ownership of our business's social media accounts, but this is just to protect the business's name on the platform from being used by other people.

5. Since the court ruling in the summer of 2019 for the new May 2020 deadline (later extended to Sept. 2020), I have been in constant contact discussing the process with our co-packer. Once we were officially informed that they would not continue manufacturing our products after the PMTA deadline or provide any help with the PMTA process, we have been working on bringing the manufacturing of our products back in-house. We have been working closely with a group of other small manufacturers in hopes of being able to have applications that are acceptable to the FDA. Unfortunately, we have not been able to secure lab space with an FDA-approved lab for the product testing portion of the application.

6. During the lockdown, our wholesale business has suffered greatly. A large percentage of our wholesale customers were shut down due to their states' responses to COVID-19. Our retail store switched to curbside pickup only, which had a negative impact on our revenue. Unfortunately, due to COVID-19 and vape shop closures, traditional combustible tobacco products were easier to access, so a large percentage of adults switched back to smoking during the lockdown. We have been the only business in our town to have a constant supply of hand sanitizer and face masks available for purchase for the community and we donate hand sanitizer to local municipalities. We have and continue to distribute thousands of masks and bottles of hand sanitizer, increasing our net positive impact on local public health.

7. It has been extremely difficult to acquire lab space. It is difficult to even receive a call back from labs at this point. I have tried to secure lab space over the past year, and it has been close to impossible due to the backlogs. The one lab I was able to speak with, their prices due to the limited space were financially impossible for us to afford. We are still in the process of trying to secure lab space and still have not been successful.

8. We are currently working with a consultant to help process our application and, due to COVID-19, we still have not been able to meet in person. Being restricted to emails, phone calls, and zoom calls has hindered our ability to communicate efficiently and has slowed down the process considerably.

9. COVID-19 has posed other problems which have had a negative impact on how much time we can focus on our PMTAs. We have been dealing with shortages of finished products for our retail location, which has turned ordering into a full-time job. We have also had major supply issues with bottles and other raw materials due to lock downs, which has impacted

our ability to focus on the overwhelming amount of paperwork needed to provide the FDA with a sufficient application.

10. COVID-19 has had a hugely negative impact on our business. We are currently down by 40% YTD from last year and have a net profit of -$4,742 YTD. After five years of operating a successful business, we are in the red for the first time due to the pandemic. The slowdown from the lock down has forced consumers to purchase products online and, since our policy is to not market directly to consumers, we are feeling the negative financial impacts of the pandemic. The lack of revenue has meant that we have had to cut back on consultants and legal representation needed to help with the preparation of our PMTAs.

11. Due to the significant impacts of COVID-19, Gentleman's Draw will most likely not be able to file a complete PMTA by the FDA's September 9, 2020, deadline. As a result, we ask that FDA recognize these extenuating circumstances, which have been out of my company's control, and extend the filing deadline until March 8, 2021, in order to allow small companies like Gentleman's Draw to finish our applications so that FDA has all the data and information required to review our PMTA.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 17, 2020

DECLARATION OF Jennifer Higginbotham

I, Jennifer Higginbotham, declare as follows:

1. I handle most of the day-to-day operations of HiggyCigs, LLC, including customer service, production, manufacturing, shipping, inventory, bookkeeping, accounting, and graphics. My husband handles IT, programming, web maintenance, server administration, marketing, and is heavily involved in advocacy and education.

2. I, along with my husband, David Higginbotham, am the co-founder and COO of HiggyCigs, LLC, a small e-liquid manufacturing company headquartered in Lilburn, Georgia. HiggyCigs, LLC was founded in 2014 in an effort to provide customers with more options to design their e-liquid to suit their specific needs. As such, we offer literally thousands of option combinations to choose from for each individual flavor. We manufacture and market our brand exclusively. However, since 2016, we have acquired two co-packing companies that we also manufacture e-liquid for. We have had employees in the past, but, currently, it is just the two of us running an online wholesale and retail store. Our products are used in refillable open systems only, and we do not sell any hardware or cartridge-based products at all.

3. HiggyCigs, LLC requires that every account upload a picture of their state-issued identification with a new account registration. If customers cannot or will not provide identification, their account is refused and they may not shop with us.

4. As a small company, our advertising abilities are very limited. We advertise exclusively through social media, specifically Facebook. Our business Facebook page is age-restricted, and when we post elsewhere, it is only in groups that are dedicated to vapers and restricted to users over 21 years of age. We have done live streams on our YouTube page, which is age-restricted, and while we have both Instagram and Twitter pages, we generally only post current events and advocacy on those platforms. Our email list is restricted only to current

customers that asked to receive our newsletter through our website. While we do carry a few products that have silly names (usually due to some back story as to why they were named that way), the overwhelming majority of our products are named after the actual flavor (e.g., Strawberry Ice Cream, Apple Crumb Cake, or Sangria).

5. HiggyCigs, LLC has been diligent in meeting all FDA deadlines put forth since 2016. We changed our bottles to CPSC-certified bottles, created and made available GCC certificates, redesigned our labels to meet FDA requirements, registered our company with CTP, assigned SKU numbers to every product option we carry, registered all SKUs and labels with CTP, and registered all ingredients and recipes with CTP by the required deadlines. The final step of assembling a PMTA is proving to be the most difficult hurdle to achieve both time- and cost-wise.

6. We are very concerned with the impact of COVID-19 on HiggyCigs, but it is actually more of a compounded concern. Last summer, when the entire vaping industry was unfairly and unjustly accused of causing the E-cigarette or Vaping Use-Associated Lung Injury (EVALI) outbreak, it was deeply damaging to our business. We had to let go of any extraneous help, our sales dropped rapidly, and it was a struggle just to keep our doors open. We used up all of our reserves. We were on the brink of shutting down when another e-liquid manufacturing company chose to close its lab and hired us to produce its products. The owner is disabled and could not run it himself, and could no longer afford his employees and office space. Our sales have been slow to come back, but we are now producing this other product along with our own to keep our doors open. Then COVID hit, and the wholesale business for both of our companies decreased greatly. Due to social distancing, many people were no longer visiting retail stores and many of them closed. We have had to rely mostly on internet traffic for sales.

7. We are a small company with very little real profit, as are the companies that we co-pack for. None of us have the extra resources it would take to have expensive testing done, especially now when we are just trying to make ends meet with reduced sales, reduced wholesale clients, and a reduced staff. I am one person, producing product for three small companies, and I am still unable to bring in any outside help.

8. When COVID-19 became a national emergency, one of the products that became hard to find was hand sanitizer. If you could find it, it was expensive. Many vaping companies began producing hand sanitizer because we already carried the main ingredients: vegetable glycerin and propylene glycol. However, very quickly there became a vegetable glycerin shortage, and as the rules of supply-and-demand follow, the price of it went up to nearly double what it was before COVID. Most of the bottle manufacturers were located in China, and with their shut downs, bottles were backordered for months. Both of these situations affected our ability to produce product efficiently.

9. As I have stated before, we have been struggling to stay open for a year now. It has only been by consolidating three companies into one production line that we have managed to weather the storm to this point. We have been hanging on in the hopes that this will pass and we can resume production at a rate that would allow us to bring in extra help. But until then, it is just the two of us trying to make ends meet and there are only so many hours in the day. Finding the time to assemble a PMTA the way that it is designed currently has proven to be an impossible task that we cannot achieve.

10. With the increased cost of materials, the decreased staff, and limited time available every day, there is simply no way that HiggyCigs can complete a PMTA by the September 9, 2020 deadline. We ask the FDA to consider these extenuating circumstances,

realize that our company also holds the future of two other companies in its ability to survive this hurdle (one of which is a disabled man's only source of income), and extend the deadline 180 days until March 8, 2021. We would also like to see a better pathway for small businesses like mine, who are just struggling to get by, that is affordable and less time consuming.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 19, 2020

DECLARATION OF Mark Anton

I, Mark Anton, declare as follows:

1. My name is Mark Anton and I am the Executive Director of the Smoke-Free Alternatives Trade Association (SFATA). SFATA is the oldest national trade association for electronic cigarettes and open system vaping products. SFATA was established in 2012 with the intent to foster and promote lawful business practices among our members. Our membership has fluctuated over the years between 300 and 1800 members. SFATA is based out of Washington, DC., and most of our members are small businesses, including what could be described as "mom and pop" shops.

2. My position at SFATA entails the development of core mission programs to assist our membership in conducting lawful businesses in a regulated environment. I am also responsible for membership campaigning and growth of membership. Most duties revolve around developing a working program with regulators to bring common sense solutions to the issues that face our industry.

3. SFATA, a 501(c)(6) non-profit organization, is a national trade association of businesses that work in, or in service of, the vapor products industry, including manufacturers, distributors and retailers. SFATA's mission is to advocate for a reasonably regulated U.S. marketplace which allows its member companies to provide smoke-free products to adult consumers, while promoting a positive public image for vapor products and educating businesses in our industry. All SFATA members must agree to adhere to the association's Statement of Principles which include, among other things, strict marketing and packaging guidelines and can be found here: http://sfata.org/content.aspx?page_id=22&club_id=89995&module_id=255471. These standards include use of product terms that do not appeal to minors, prohibit the use of packaging that

imitates products that appeal to children, and prohibits the use of any terminology that suggest a therapeutic value or health claims.

4. SFATA implemented the first national program to restrict youth access to vapor products and has been a leader in promoting good business practices regarding youth purchases. With the lack of age restrictions in the early years of the industry, SFATA developed and implemented the AGE to Vape program. Our members where asked to pledge to enforce the age restrictions of local tobacco laws on consumers who wished to purchase the products.

5. Since that time, SFATA has partnered and promoted the use of programs that train retailers and employees on proper age-verification compliance amongst our membership. We have also partnered with leading providers in the electronic age-verification market to improve the rates of compliance; including We Card training programs, We Card signage and private "secret shopping" services. This assures company compliance with the laws in any given jurisdiction related to age-restricted sales. SFATA has also provided discounts to third party age-verification software programs to its membership to encourage the use of electronic age-verification to prevent sales to minors. SFATA believes this is critical to good retailing practices for the industry to prevent youth access to age restricted products.

6. We have also hosted seminars on good retailer practices both in person and virtually, including how to maintain and develop age compliance programs, as well as battery safety programs for stores that sell individual batteries. This has resulted in a lower rate of incidences of battery mishaps over the past few years.

7. The efforts that our membership and industry players have taken to improve manufacturing and retail distribution have been extensive. But all of that will cease to exist come September 9, 2020 when Pre-Market Tobacco Applications (PMTA) come due. SFATA has

taken an active role in trying to assist manufacturers with aspects of the PMTA to meet the deadline imposed by the Maryland federal district court. This has reduced expected time frames, along with the PMTA guidance that only came out in June of 2019. We have encouraged product testing and worked with multiple groups to perform literature reviews. SFATA has been able to partner with other industry stakeholders to make the following PMTA requirements available to our members: product description sheets, environmental assessments, cover letters, literature reviews and summaries, consumer surveys, quality statements, GMP's, SOP's, marketing plans and post-market surveillance programs, and youth tracing and verifying programs to secure the sales process.

8. However, the effects of Covid-19 have been complex and far reaching. The country was asked by the President to self-quarantine for a period of 30-45 days during the height of the Pandemic. The FDA asked for an extension of the court from May 11, 2020 to September 9, 2020, which was eventually granted.

9. While the Pandemic affected primarily the Northeast and California the hardest, beginning in the summer the South and West have experienced dramatically high rates of Covid and those states were shut down. As a result, many states enacted stay-at-home orders and closure for all businesses deemed non-essential. Vapor businesses were in general considered non-essential and were either not allowed to open or had to provide other means, such as curb-side pickup, in order to provide services to their customers in states with stay-at home orders. These actions by the states have critically hampered many businesses and prevented access to needed data or the ability to perform testing during this time.

10. Moreover, when businesses were permitted to reopen, many of them faced severe staffing shortages, some due to financial instability, others due to employee fears of returning to

work during the Pandemic. Some employees also had to stay home to attend to their children with no day-care or school closings. The businesses that had the necessary testing done, or were in the process of testing, either could not get the scientific review done or had to start over as many scientists were either not available or had limited access to the materials necessary to properly prepare a document as extensive and complex as the PMTA.

11. The original shut down caused many of the labs to have a back log of work and, when they resumed testing, other areas of the country closed down. Some states have not fully opened back up at this point from the lock downs in March.

12. Industry manufacturers, due to shut-down orders in multiple states and being deemed non-essential, also saw an opportunity to make a real difference during the crisis. Some members used the resources they had and switched from manufacturing e-liquid to hand sanitizer to fill a national shortage. But this has reduced their inventories of raw materials, which has been compounded by the world-wide shortages in distribution.

13. Members have either not been able to meet with FDA for pre-PMTA meetings due to staffing issues at the agency, Covid restrictions, or travel restrictions imposed on interstate travel, such as quarantining.

14. Many of our members have sustained substantial drops in revenue due to the Pandemic restrictions. Every state varies in the effects of their restrictions but many in our membership fell under the category of non-essential businesses and were not able to open or had limited curbside delivery. Sales of vapor products during this time have dropped significantly, while the traditional channels of trade have seen a 16% drop in sales, with open system products seeing a significant drop in sales even greater than that.

15. Many of our members are trying to comply but the circumstances of the Pandemic and the lack of available lab space may have impacted our member's ability to file a PMTA by the September 9, 2020 deadline. Accordingly, on behalf of our members we request an extension of 180 days to submit our PMTAs.

Dated August 21, 2020

Mark Anton

DECLARATION OF Jimmy Dimitris Agrafiotis

I, Jimmy Dimitris Agrafiotis, declare as follows:

1. I am the CEO of Global eVapor Consulting, a company founded in 2016. We work with various open system e-liquid and hardware manufacturers. We counsel clients at every level of the tobacco, e-cigarette and vaping supply chain from manufacturers of components and additives, to manufacturers of finished products, both consumables and hardware, and their distribution and delivery to consumers. We also guide manufacturers through the PMTA process.

2. Some of our responsibilities are: International Shipping guidelines, HPHC Testing, PMTA Guidance, State and Federal Licensing, FDA Inspection Guidance, Manufacturing facility registration, and legal and scientific support to vapor product companies and their suppliers with respect to the statutory and regulatory requirements specifically imposed by the Tobacco Control Act.

3. We provide clients with tools to prevent youth access, such as age gated social media accounts, online age verification software to prevent sales to minors, and WeCard training programs for employees at physical locations.

4. My clients age gate Instagram to 21+ followers. They also use Veratad and Age Checker age verification software on their websites to prevent minor purchases. Lastly, they provide guidance, training and educational material to their wholesale distributors and retail partners with tips and tricks on how to avoid selling products to minors.

5. I am currently working with 3 medium and 4 large scale manufacturers to complete PMTA's both on hardware and open vapor e-liquid. We began the process immediately after the judge announced his decision which altered our original timeframe of completion.

6. COVID-19 has caused huge delays. A lot of the industry was shut down and companies had employees sent home due to local restrictions. A lot of the staff that was hired to help gather data on the PMTA had to be let go due to financial difficulties in these companies. China specifically had a huge impact since a lot of the employees were not allowed to travel back to Shenzhen where manufacturing occurs for 3 months due to quarantine and local restrictions from the Province.

7. Every attempt we made for lab work in the US was rejected. We ended up using a lab in Europe (Greece specifically) but even they have a huge back log and were not prepared for the work load we were bringing. Some HPHC work was completed, but time allowed was not sufficient for stability and other testing.

8. All travel for my company to shows both domestic and international were cancelled until 2021.

9. COVID-19 has also strained our ability to gather data from raw material suppliers, such as flavor houses, bulk chemical suppliers and various component suppliers.

10. All my clients have reported loss of income and a steady decrease in ordering simply because a lot of their retail partners had to shut down due to state mandates. Also, their international business has been affected due to slow shipping times and added costs.

11. We affirmatively state that due to all these delays and issues, my company's ability to assist clients in filing a PMTA by the September 9, 2020 deadline is extremely limited. We request additional time, preferably 180 days or more. This will give us the opportunity to attempt the filing of a complete mandatory minimum statutory requirement PMTA.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 19, 2020

Jimmy Agrafiotis

DECLARATION OF TERESA LIVEZEY

I, Teresa Livezey, declare as follows:

1. Bill Livezey and I own and operate two Knoxville Vapor, LLC locations along with the Tri Star Vape Co e-liquid brand. Our business opened in April 2013 and grew from a flea market location to the two brick and mortar locations we have today. Our Knoxville location opened in September 2013 and our Sevierville location in October 2014. We currently have 9 full time employees. Average salary is $41,000 per year and all of our employees have been with us for more than 3 years. Our business is strictly face-to-face retail of open system vapor products to adult consumers.

2. As owners, we are integrally involved in day-to-day operations and manage all aspects of our small retail business. Our responsibilities range from direct customer service, employee management, order management, accounting and legal matters.

3. In an effort to restrict vapor products to adult smokers, we have implemented Standard Operating Procedures along with a robust training module. All IDs are scanned using AgeVisor Touch ID scanners. Employees are required to scan IDs for any customer that appears under the age of 30. If any customer is not 21 or does not have ID, they are asked to wait outside the store. Employees are monitored constantly and disciplinary action is taken if the procedure is not followed. We utilize We Card to train all employees on a yearly basis. We also take advantage of We Card's secret shopper program where employees are presented with a green card if they pass, or a red card if they fail. Reports of these secret visits are sent directly to me from We Card on a monthly basis. Our team does an outstanding job and each of them take this task very seriously.

4. We take youth use very seriously and do everything we can to limit appeal of vapor products to them. The products on our shelves do not contain childish marketing images, cartoons or labels that we feel might attract youth. We've been fighting against this since we started our business. We advertise on a sports talk radio show where their listener base is 99% over the age of 21. We recently re-affirmed those metrics with Cumulus and are confident that we're targeting consumers between the ages of 35 – 44 years old.

5. In addition to restricting youth use, we also do our best to limit product initiation by individuals who do not currently use tobacco or nicotine products. Every new customer interested in vaping is asked a series of questions, including how much they currently smoke. If they do not use tobacco or have a nicotine addiction, we kindly explain why this product is not for them. While they can still purchase a vape if they choose to, we have a strict policy to never sell nicotine e-liquid to them (they can get e-liquid without nicotine). We are in the business of helping customers step down nicotine dependency and eventually quit and we will not be responsible to creating any new nicotine addiction.

6. We are very concerned about the approaching PMTA deadline. While we are committed to filing for our Tri Star Vape Co brand, it's currently impossible to meet all of the requirements to file a successful and complete PMTA. FDA guidelines are vague, testing laboratories are expensive and have a severe backlog and there is simply not enough time to conduct the required trials. Failure to file timely will not only prohibit sales of our Tri Star Vape Co brand, but all of the 65+ brands we currently stock will be eliminated from the market forcing our retail business to close. This will ultimately result is vapers returning to traditional tobacco.

7. It did seem as though the industry was gaining some traction on the PMTA filing process; however, COVID-19 has halted these efforts as the country has been essentially shut

down. Many vapor shops have been closed completely across the country. At our retail locations, we were limited to curb-side service and were forced to lay-off 4 of our employees while sales plummeted by more than 25%.

8. There are some essential services required to file a complete PMTA. Unfortunately, these services have been unable to operate due to COVID-19. Necessary information from suppliers has been impossible to get as they have been closed; travel and consulting services have halted; laboratory testing has halted and is now severely backlogged with no end in sight.

9. As a result of our absolute inability to file a complete PMTA for Tri Star Vape Co due to the above delays, we respectfully request a 180-day (or until March 2021) extension to the September 9, 2020 deadline.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 20, 2020

Teresa Livezey

Knoxville Vapor, LLC

Owner

DECLARATION OF April L. Meyers

I, April L. Meyers, declare as follows:

1. April L. Meyers is the Managing Partner of Northeast Vapor Supplies and is responsible for the day to day operations of the business. April works closely with the store's General Manager, John Kinne in determining which products to place on the shelves. Due to the mission and core values of the company, the dominant sales category is open system e-liquids and vapor hardware. In fact, Northeast Vapor Supplies, LLC only carries a single closed system replaceable pod product and typically offers this to consumers as a stepping stone to get them off of Juul and Juul-like devices and then onto an open system.

2. Northeast Vapor Supplies, LLC was established in 2012 as a retailer of open-system e-liquids, vapor hardware, and corresponding accessories. The company's mission is to assist the adult smoker in transitioning off of deadly combustible tobacco cigarettes by providing high quality products, outstanding service, and continuous education. Northeast Vapor Supplies, LLC operates a single retail location in Old Saybrook, CT where it employs two full-time and an additional four part-time staff. Each of the company's staff must successfully pass WeCard age verification training prior to being allowed on the sales floor and is thoroughly immersed into the company culture and mission. Northeast Vapor Supplies, LLC is committed to being a part of the solution to the combustible tobacco and youth use issues and therefore, has never carried the Juul, Puff Bar, or similar youth attractive closed-system devices or brands. Our company carefully screens all vendors for regulatory compliance and does its best to set a good example for the vapor industry.

3. As previously stated, Northeast Vapor Supplies puts all its sales staff and management through WeCard age verification training. We also participate in WeCard's self-inspection compliance programs and undergo at least three random visits per year. In addition to

this, Northeast Vapor Supplies, LLC has instituted age restricted sales categories inside of its Point of Sale system. This forces the cashier to scan the ID of a purchaser before a sale can be completed. A Socket Mobile Socketscan s740 is used to scan the IDs. Northeast Vapor Supplies, LLC also intends to participate in the TraceVerify program expected to be launched in the next couple of weeks. This means each bottle sold will be tagged with an RFID label and scanned upon receipt of inventory and again on the sale of the product. The goal of the TraceVerify program is to a) reduce or eliminate straw purchases, b) increase Northeast Vapor Supplies' age verification scanning to 100% of sales including those of our wholesale partners and c) to assist law enforcement with identifying violators of the law. For more information on TraceVerify, please visit www.traceverify.com. Northeast Vapor Supplies, LLC takes age verification quite seriously. It is our goal to be a part of the solution.

4. In order to avoid even accidentally attracting youth, we have ceased most advertising activities outside of our retail store. Although we have social media accounts, we only use them to provide information to consumers related to changes in store hours, most recently updating our customer base on COVID operations. We do one local advertisement bi-annually and are careful not to place any products in our ads, leaving them purely informational and notate that one must be at least 21 years of age to purchase any products from our establishment and that valid proof of ID is required.

5. We have been working strenuously to complete the PMTA by the September 9th deadline and have one full time and three part time staff dedicated to the task. We have gathered all the necessary data, have reached out to labs for product testing, but were unsuccessful in finding timely, cost effective space so are focused on all of the other pieces. It has been

extremely time consuming, and due to the small size of the business, my staff is torn between duties to the store and their PMTA duties.

6. Due to Executive Order, all non-essential business were shut down in the state of Connecticut for two months beginning in March of 2020. During this time, I was the only one able to continue working on our PMTA application while simultaneously keeping up with curbside orders. After about five weeks of this, one of my staff members decided to come help, which took some pressure off, but not enough. By early June we were allowed to reopen, however, COVID had impacted the availability of inventory across the entire supply chain and many of our regular patrons were slow to return. This placed further financial strain on the company. It was not until late July that sales and staff hours began to normalize. We are still experiencing supply chain issues and are still facing COVID related financial burdens. It is going to take many months to recover from the losses, if indeed, we recover.

7. Because of all the chaos and uncertainty that ensued during the Executive Order closing all non-essential businesses, we were not able to get back in touch with labs we had communicated with early in 2020. Once business began to normalize for us in July of 2020, it seemed to de-normalize for other areas of the country, specifically California - where we were looking at labs. I attempted to connect to other labs but was told the backlog was severe and was actually laughed at by one sales representative. I did not find it so funny as he. It is frustrating, to say the least.

8. As stated previously, COVID had caused the closure of all non-essential businesses in the state of Connecticut and that included one of my contractors, who was specifically hired to assist with our PMTA filing. The contractor resides across the state and

although we attempted to work collaboratively via internet meetings and email, it was not working well and so we ultimately decided to wait it out.

9. Some of the deadlines I had set for myself were not met due to my suppliers being shut down from COVID related Executive Orders in other states. This continues to go on. I am currently unable to obtain information from the supplier of my nicotine, vegetable glycerin and propylene glycol (e-liquid base components), because the state they conduct business in had closed, forcing them into a serious backlog they have not yet recovered from. For other suppliers, I should have had the data months ago but have either just received it or am still in process of receiving it.

10. COVID has significantly impacted my company's revenues and our budget has shrunk as a result. Despite obtaining an SBA loan, sales are slow to recover due to patrons preferring to shop online and/or unable to get in due to quarantine and/or safety concerns. We do not offer traditional eCommerce sales and so have lost a number of our patrons to other Ecommerce companies. All travel budgets have been cut. Marketing, software, and inventory budgets have been significantly reduced. Expansion plans have been placed on hold indefinitely. Meanwhile, a new line item budget has been created for COVID related materials. This includes (but is not limited to) personal protection equipment, plexiglass, sanitation chemicals and related cleaning supplies and labor increases necessary to maintain increased sanitary levels.

11. All of the hindrances, shut downs and their impact to the supply chain and my network of skilled labor have already impacted my internally structured timeline for an on-time PMTA submission. I am deeply concerned that COVID has negatively influenced Northeast Vapor Supplies, LLC ability to successfully complete its PMTA by September 9th, 2020 and therefore respectfully request an extension of 180 day or until March 2021.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 21, 2020

DECLARATION OF Noah Leuer

I, Noah Leuer, declare as follows:

1. I am director of compliance for Vapor Source, Inc. located in Pueblo, Colorado. We are a small company in Southern Colorado that has gone from about 45 employees to 30 employees since COVID-19. We are a small manufacturer of 73 e-liquids used for open systems only, and the nicotine milligram strengths we manufacture range from zero to eighteen at the strongest.

2. Personally I, Noah Leuer, handle the FDA FURLS and CTP updating. I also oversee two of 8 stores, as well as inventory control, warehouse management, and laboratory management. I also deal greatly with regulatory and government affairs.

3. Vapor Source has developed a system that creates a specific serial number and ID number for EVERY bottle that is sold from every single one of the stores. It is impossible to not have some sort of tracking to discover who has purchased a bottle, thus making it impossible for a minor to possess a bottle without knowing who purchased the bottle. Vapor Source also uses ID scanners in each of our stores to verify a purchaser's age. Vapor Source does not allow anyone under the age of 21 in any of our stores, no exceptions.

4. Vapor Source has completely changed our marketing to comply with FDA and societal expectations of what is NOT considered child friendly. Our marketing is completely ambiguous, without cartoons or bright colors. We also do not advertise on TV, billboard, etc.

5. As far as PMTA compliance efforts are concerned, we have completed FDA Unified Registration and Listing System and Center for Tobacco Products listings. The environmental assessments have also been completed. Vapor Source has also reached out to several laboratories to complete whatever might be necessary for the PMTA process to no avail. There are currently no labs that are offering PMTA research in a timely manner at this point.

6. Vapor Source was forced to close their doors temporarily in March and lost several employees due to COVID. Many were laid off and many were just too afraid to come back to work in a public forum.

7. All government affairs halted due to COVID and we were unable to perform some regulatory duties, company duties, and personnel duties. We were unable to get our products into a lab for testing, they were all full.

8. Our regulatory and compliance officers were laid off and stuck at home due to the lockdown. Travel was very limited, and none of the consulting agencies were accepting new clients.

9. Production was hindered, most of our staff were laid off. We were limited to minimal business. Our suppliers were going through the same thing, running on minimal staff, causing significant delays in our ability to get ingredient information necessary for PMTA filing from them.

10. COVID-19 has also significantly affected our revenues, spending, and budgets. Sales have dropped by over 55% since the start of the pandemic. We had to cut costs where we could to survive. We do not currently have the financial resources to fully support the PMTA process.

11. As a result of these significant delays, Vapor Source may not be able to file a completed PMTA by FDA's Sept. 9, 2020 deadline. We ask that FDA recognize the circumstances, and happenings that were outside of our control, and grant us an extension of 180 days, until March 8, 2021, in order for us to more accurately and completely provide FDA with all required data for the PMTA.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August 19, 2020

DECLARATION OF MOUNTAIN OAK VAPORS

I, James Swafford declare as follows:

1. I am the Operations Manager and Regulations Officer for Mountain Oak Vapors. Mountain Oak Vapors has 7 locations (4 in TN and 1 store each in Rome, GA, Oviedo, FL, and Niagara Falls, NY). Started in 2011, Mountain Oak Vapors has grown to employ 38 people between our manufacturing and retail stores. Mountain Oak Vapors prides itself in limiting our selection to open system products.

2. I oversee operations of our manufacturing facility, marketing/labeling design, and regulations compliance.

3. We utilize online Age-Verification using Veratad. We also do ID checks at our brick and mortar locations.

4. Mountain Oak Vapors has always strived to only appeal to smoking adults. From our labeling to advertisements, we do not use bright colors or imagery to attract anyone but adult customers. Mountain Oak Vapors does not use billboards or radio marketing. Our Facebook pages are our main source of marketing and those pages are age restricted to only see the page if they are of legal tobacco product purchasing age.

5. We have devoted 500 personnel hours used to collect and correlate data regarding the PMTA. Environmental Assessment and literature review are completed.

6. Due to COVID-19, company personnel availability has been limited because of quarantining due to exposure or by state/city mandated stay-at-home orders.

7. Due to COVID-19, labs have been unavailable to conduct product testing due to closings and backlogs.

8. Due to COVID-19, consultant services for the PMTA have been unavailable or hard to use effectively. The consultants are mostly unable to travel and all work has to be done through email which has slowed the processes down.

9. Due to COVID-19, communication with our suppliers has been difficult and has just started to return to normal.

10. COVID-19 has greatly impacted our company revenues. The PMTA process is very expensive and has had a significant impact on the company's budgets.

11. Mountain Oak Vapors affirmatively state that delays have impacted our company's ability to file a PMTA by the September 9, 2020 deadline and request additional time, 180 days or until March 2021.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: 8/20/2020

DECLARATION OF ILLUMIVAPTION Inc.

I, David Pellicane, declare as follows:

1. As CEO of Illumivaption Inc. I have been overseeing all aspects of our e-liquid manufacturing division since the company started doing business in Nashville, TN in 2011. The company has employed dozens of workers over the past 9 years, striving to make quality e-liquids designed to be used exclusively in open system vaporizing devices.

2. I have overseen the development of all of our products, to ensure that only the best ingredients are used in making our products.

3. We have always tried to go above and beyond to ensure that our products are only used by responsible adult consumers, and to make sure that any stores and/or websites that sell our products check ID's and/or use third-party online age verification systems.

4. We have also always made sure our branding and marketing efforts have been directed at adult consumers only, and have tried to ensure that our products do not use images that could potentially attract the attention of underage consumers.

5. Although we have always tried to go above and beyond to remain compliant with FDA guidelines, (all of our products have been registered with the FDA, and are made in an ISO clean room), we have also had our e-liquids tested by an independent lab and have been trying to compile all of the necessary data to submit our application for the PMTA, we are still struggling to complete everything before the current deadline.

6. Unfortunately, when we were planning on exerting the maximum effort to get all of our PMTA paperwork together in March, COVID-19 struck, and has derailed our initial plans. We went through a period where our business was completely shut down, and for the past five

months have been struggling just to remain open and viable as a business. Without all of our normal personnel, it has become almost impossible to complete all of the paperwork in a timely manner.

7. Because of COVID-19, it has been impossible to get our lab work finished.

8. Because of COVID-19, there have been multiple shutdowns with consulting firms, and travel has been nearly impossible.

9. Although all of our ingredients that we use to manufacture our e-liquids are considered industry standard products—widely used by all other e-liquid manufacturers—it has been almost impossible to get ingredient information from our suppliers, since many of them have gone through their own shutdowns, and have struggled with staffing issues as well.

10. COVID-19 has also taken a huge toll on our company revenue, and we have been struggling to even maintain the normal budgets we have allotted to get the PMTA application completed. Our sales have gone through a period of record lows, and we still have not seen the kind of increase in sales to make up for our shortages.

11. All of these COVID-19 issues combined have made it impossible for us to file a PMTA by the September 9, 2020 deadline and we are requesting additional time, and hope that we can be granted an extension until March of 2021.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: August, 20, 2020

David Pellicane

Signature

DECLARATION OF Dana Wappler

I, Dana Wappler, declare as follows:

1. Describe your position President, CEO of Prophet Premium Blends LLC an E-liquid company. Located at 2413 S Broadway, Sana Ana, CA 92707. Prophet Premium Blends LLC was established 2/22/2016 and has 25 employees. Prophet Premium Blends LLC is limited to Open-system e-liquid manufacturing and distribution.

2. Dana Wappler's responsibilities include managing finances and general operation of the business.

3. Prophet Premium Blends LLC has taken efforts to prevent access by and sales to underage consumers through online age-verification systems, and contracts with distributors and retailers to ensure valid ID checks.

4. Prophet Premium Blends LLC has taken efforts to limit advertising and marketing to adults only and to avoid attracting underage consumers. We use FDA compliant packaging with easy to read warnings along with visual aids for those who may not be able to read. Prophet Premium Blends LLC uses GCC compliant containers and all products are child resistant tested with flow restricted nozzles.

5. Prophet Premium Blends LLC has taken efforts to complete PMTA by the FDA deadline by joining a legal consortium for literature review, paid for Stability and HPHC testing, we have hired consultants and legal aid to complete the systems and SOPs requested for the application.

6. Prophet Premium Blends LLC has been impacted by COVID-19 on company personnel availability, including company shutdowns and slowdowns in sales. These time constraints and financial hardship have proven difficult to recover from, but we have persisted non the less.

7. Our lab did shut down and made it nearly impossible to get our results in time for the deadline.

8. COVID-19 impacted the ability of our consultant services who did not have the ability to travel. Some of whom contracted COVID-19 and were unavailable for weeks.

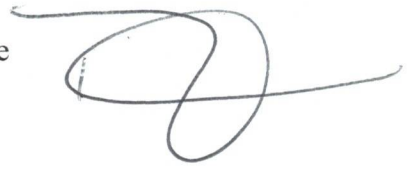
9. Due to COVID-19 it has been increasingly difficult to gather ingredient information from suppliers (CAS/TPMF) and communicate with testing facilities.

10. COVID-19 greatly impacted the staff of Prophet Premium Blends LLC. Company revenues and budgets seeing a nearly 60% drop in sales for 3 months in a row.

11. Affirmatively delays have impacted Prophet Premium Blends' ability to file a PMTA by the September 9, 2020 deadline and request an additional 180 days or until March 2021

I declare under penalty of perjury that the forgoing is true and correct.

Dated: 8/19/20

Signature 

DECLARATION OF TROY J. LEBLANC

In accordance with 28 U.S.C. § 1746, I declare under penalty of perjury under the laws of the United States of America that the following factual asserts are true to the best of my knowledge:

1. I am the President of the Kentucky Vaping Retailers, Inc., d/b/a Kentucky Smoke Free Association (KSFA). The organization is the open-system Electronic Nicotine Delivery System (ENDS) product trade association for the Commonwealth of Kentucky. KSFA was founded in March 2013 by a group of Kentucky open system ENDS product retail store owners who wished to work together to create industry standards and better educate the public and elected officials. KSFA presently has approximately 75 members located throughout Kentucky. These members are either owners of bricks-and-mortar ENDS product retail stores, distributors, or manufacturers which are devoted to ensuring the availability of open-system ENDS products to adults.

2. As KSFA's President, I oversee the day-to-day functions of the organization. Such responsibilities include communication with members across the state regarding matters of interest which pertain to the vaping industry; communicating with leaders and members of similar organizations in other states or national ENDS product trade associations; media relations, engaging in political outreach and educating federal, state and local elected officials; and overseeing the coordination with the organization's lobbyist.

3. KSFA members have been proactive since the organization's founding regarding the implementation of age-restriction policies. In fact, KSFA adopted age-restrictive policies before such policies were the law in Kentucky or nationally. These policies include requiring photo-identification from all customers upon entering the business establishment and prohibiting youth and the children of customers to enter or approach any part of the business where products

are displayed. KSFA members have also embraced the use of new technologies which allow retailers to conduct real-time verification of a customer's photo identification. Above all, KSFA members get to know their customers, not only as a good business practice, but also as a way of ensuring they do not sell to underage customers or facilitate straw purchases by adult customers intended for those who are underage.

4. KSFA has developed retail and marketing standards as a part of its membership qualifications. KSFA monitors its members to ensure that they adhere to these standards by not utilizing product packaging and marketing which might appeal to youth (*i.e.* cartoons and child appealing caricatures on packaging and marketing). Further, KSFA mandates that its members adhere to the FDA requirements with respect to package warnings.

5. From my understanding and knowledge of KSFA members, they were making efforts to move forward with completing a PMTA for their products at the time the Covid-19 pandemic began. Such efforts included assembling information concerning the members' practices, compiling information regarding the constituents of product ingredients and product recipes. It is also my understanding that KSFA members were in the process of attempting to obtain product testing by domestic labs at the time the pandemic began but were unable to move forward with testing because their businesses were shuttered by mandatory lockdowns, the labs were shuttered, or the labs were restricting their activities solely to virus testing.

6. The onset of the Covid-19 pandemic has made it virtually impossible for KSFA members to devote attention to complete work on a PMTA for their products. The legal requirements of the "essential" business mandate only allowed members to have a skeleton staff working, to the extent they were permitted to even operate. Given the customer demand for pick-up or delivery services, all available employees were devoted to such efforts. Further, several

manufacturers in Kentucky converted their operations, either wholly or partially, to making hand sanitizer for first responders during the early days of the pandemic when such product was virtually unavailable. This resulted in manufacturers having to halt work on PMTA efforts.

7. From my understanding and understanding of KSFA members, the Covid-19 pandemic has resulted in manufactures being unable to access domestic testing labs due to either the manufacturer's forced closure as non-essential businesses or the conversion of the labs to virus testing. This circumstance has forced KSFA members to either table any effort to obtain product testing or to outsource their product testing to foreign labs. It is unknown at this time, however, whether the FDA will ultimately accept the testing results from these foreign labs.

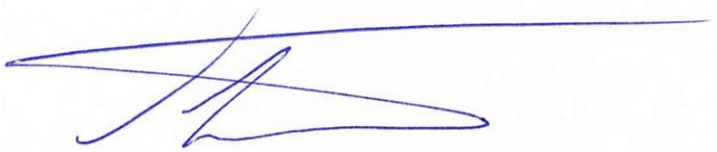
8. The onset of the Covid-19 pandemic meant that the owners of KSFA members had to become more hands-on with respect to the day-to-day operation of their businesses as they did not want to expose employees to risks which they were not willing to face themselves. One of the results of the altered business model brought about by the pandemic increased the labor intensity of customer service. This meant that more time was needed to serve customers than prior to prior to the pandemic because of the time involved in fielding remote orders and the necessity of making deliveries to customers. This left little, if any, time for KSFA members to plan, schedule, or travel to the FDA headquarters to meet with the agency officials, or to participate in a meeting with FDA officials through remote means.

9. The Covid-19 pandemic did effect KSFA members who manufacture e-liquids with respect to obtaining key ingredients which are imported from overseas. This was especially true during the first three months of the pandemic. As a retail vape shop owner and vape products distributor, I understand this was a common issue experienced by manufacturers across the country. I also understand that manufacturers in may locations were not considered "essential"

businesses, and were thus not permitted to operate for periods of time. These supply chain challenges trickled down to the distribution and retail levels of the industry as the inability of manufacturers to bottle e-liquids resulted in product shortages. This required stakeholders to devote time seeking to find substitute products which could otherwise have been used spent working on a PMTA.

10. KSFA has lost approximately 25% of its membership since the onset of the Covid-19 pandemic because of market contraction. Those surviving members who were able to operate experienced an approximately 30% to 50% reduction in revenues since March 2020 over the same period in 2019. This reduction in revenue is remarkable as members have traditionally experienced an annual increase in revenues year over year since the organization's founding in 2013.

11. The effects of the Covid-19 pandemic have set the vaping industry back by at least six months and the ripple effects are still being felt by stakeholders. In my opinion, Kentucky stakeholders are just now beginning to return to some form of normalcy in their businesses and will thus not be in a position to file a PMTA until June 2021 at the earliest. The basis for this opinion is the fact that it is rumored in Kentucky that some of the prior lockdown restrictions will be re-imposed in September through October 2020 in order to prevent a second wave of the Covid-19 virus. My fear is that KSFA's members will find themselves in a position of ramping up to prepare and complete a PMTA only to have to shelf the project again should another lockdown be imposed.



TROY J. LEBLANC, President
Kentucky Smoke Free Association

August 22, 2020

DECLARATION OF Chattanooga Vapor Co. LLC (Pramod Potluri)

1. I, Pramod Potluri, am Co-owner and President of Chattanooga Vapor Co LLC. I, along with two partners, started this company in April of 2014. We started our retail business at the local weekend Flea market and have grown to 9 full brick and mortar locations. We employee about 45 team members and have revenues in the several millions. We are 100% dedicated to serving our community and helping customer stay off of cigarettes. We do not sell any form of combustible products. Our vapor products range from limited to full open system products.

2. At CVC I am responsible for all aspects of the business, from day to day operation to marketing and advertising to growth and expansion. We take age verification very seriously. We were 18 and up from day one, well before it became law and continue to enforce the current law restricting all sales to 21 and up customers only. We check IDs when customers come in and during checkout. We do not allow underage individuals to browse the store, and we are very diligent at prevent all straw sales. All staff are trained on age verification procedures during initial training and supplemental training happens monthly. We also do not carry any products that have kid friendly packaging. Our primary focus is to help adult smokers make the switch from combustible tobacco to vapor products. We do not focus on fads or fast selling hype products that are attractive to those under 21. Our sister website uses an automatic age verification app/plugin and we do not override the system in any case regardless of the justification.

3. COVID-19 has been a huge burden on our business and staff. It is as if the pause button has been pushed on business. Our store had to go to curbside only for a several months, which took a huge amount of resources to operate properly while at the same time losing a large portion of our staff. Products were difficult to source and

communication with vendors was often limited from complete business shutdowns in many areas. Lots of commonly used household items had and continues to have a huge spike in demand and this has caused a lot of raw material used in vaping products to become difficult to source and manufacturer. Manufacturers and distributors are slammed with back orders and overwhelmed with the effort needed to process PMTA applications.

4. These are difficult times for this country and more specifically for this industry. This pause in time we have all had to face has presented an enormous burden on traveling, meeting, organizing and manufacturing. Lots of business are still not anywhere close to 100%. As a company we are very fearful of manufacturers not having enough time to complete PMTA applications by September 9, 2020.

5. We simply do not know what we will do after September 9th if manufacturers are unable to complete applications. We will essentially not have product to sell to customers. Customers will be forced to go back to cigarettes or purchase vaping products on the black market. 45 staff members will possibly be without jobs. Mortgages on homes, loans on cars, wedding plans, college tuitions and life in general will be affected drastically due to jobs being in jeopardy.

6. I humbly ask the court to address this issue and extend the deadline for a minimum of 180 days and to ask the FDA to create a more streamlined process to give this industry a fair and fighting chance to survive.

I declare under penalty of perjury that the forgoing is true and correct.

August 20th, 2020

GLOBAL NEWS SELECT

Cigarette Smoking Makes a Comeback During Coronavirus Pandemic — Update

Provided by Dow Jones
Jul 28, 2020 11:51 AM EDT

By Jennifer Maloney

Americans are smoking more during the coronavirus pandemic because they are spending less on travel and entertainment and have more opportunities to light up. They are also switching back to traditional cigarettes from vaping devices in the wake of federal restrictions on e-cigarette flavors.

Those are the observations of executives at Marlboro maker Altria Group Inc., who said Tuesday that the shifts have been significant enough to slow the yearslong decline in U.S. cigarette sales. Altria now expects U.S. cigarette unit sales to fall by 2% to 3.5% this year compared with its previous projection of a 4% to 6% decline.

Pandemic lockdowns have meant fewer social outings and more time to smoke at home, Altria CEO Billy Gifford said. Though unemployment rates are high, stimulus checks and increased unemployment benefits have helped ease the financial hardship for low- and middle-income cigarette smokers, he added. Adult cigarette smokers are making fewer trips to the store, but they are stocking up on packs when they do go.

"Fewer social engagements allow for more tobacco-use occasions," Mr. Gifford told analysts on an earnings call Tuesday. The company's Marlboro brand accounts for 43% of all cigarettes sold in the U.S.

People have been switching back to cigarettes from e-cigarettes after the federal government earlier this year barred sales of many flavored vaping products, Altria said. The Food and Drug Administration in February halted the sale of fruit and mint flavors in cartridge-based e-cigarettes in an effort to curb a surge in underage vaping. Public health officials have said that sweet and fruity flavors are popular among young people.

As those restrictions took effect, Altria noted a shift among adult vapers, particularly those older than 50, back to cigarettes. "That consumer was faced with choices," Mr. Gifford said. "It benefited the entire cigarette category."

U.S. e-cigarette unit sales in the second quarter were down 14% from a year earlier, Mr. Gifford said, adding that the vaping's growth may pause over the next two years because the FDA is requiring e-cigarette manufacturers to submit all products for agency review by September or take them off the U.S. market.

The FDA didn't immediately respond to a request for comment. Agency officials have said that their first priority is curbing underage use. They also have noted that they allowed menthol-flavored e-cigarettes to remain on the market to provide opportunities for adult cigarette smokers to switch to a less harmful option.

Cigarette smoking is associated with more than 480,000 deaths per year in the U.S., according to the Centers for Disease Control and Prevention.

Altria made a big wager on e-cigarettes in 2018 when it invested $12.8 billion for a 35% stake in Juul Labs Inc. at a time when the startup was logging strong sales of its vaporizers and cartridges. But Altria has had to take $8.6 billion in charges on the investment as Juul's business slowed. The vaping industry leader has slashed jobs and pulled most of its flavors from the U.S. market.

Altria on Tuesday reported a second-quarter profit of $1.94 billion, compared with $2 billion a year earlier. Net revenue fell almost 4% to $6.37 billion.

The company projected adjusted earnings of $4.21 a share to $4.38 a share for 2020. In April, the company suspended its earnings outlook given uncertainty

surrounding the Covid-19 pandemic. At the time, it was expecting adjusted earnings of $4.39 a share to $4.51 a share for the year.

Write to Jennifer Maloney at jennifer.maloney@wsj.com

(END) Dow Jones Newswires

July 28, 2020 11:51 ET (15:51 GMT)

HEALTH AND SCIENCE

U.S. will have third act of coronavirus and it will likely be ‘more pervasive,’ Dr. Scott Gottlieb says

PUBLISHED FRI, AUG 21 2020•8:51 AM EDT UPDATED FRI, AUG 21 2020•11:49 AM EDT

Will Feuer
@WILLFOIA

KEY POINTS

The U.S. has not yet seen a second wave of the coronavirus, but it could come in the fall and winter, former FDA Commissioner Dr. Scott Gottlieb said.

“I do think that we’re going to have a third act of this virus in the fall and the winter and it’s likely to be more pervasive spread in a broader part of the country,” he said.

Cases are already beginning to build in the West and Midwest, Gottlieb said, adding that “every community is vulnerable.”

VIDEO 03:20

Former FDA chief Scott Gottlieb on why J&J's next Covid-19 clinical trial is twice as large as others

The U.S. has not yet had a "true second wave" of the coronavirus and the country could see a resurgence of the virus in the fall and winter, former Food and Drug Administration Commissioner Dr. Scott Gottlieb told CNBC on Friday.

"I think most peoples' perception is we had one epidemic in New York, in the New York region, we came down the epidemic curve, we had another epidemic in the Sun Belt, so that really looks like and feels like a second wave," Gottlieb said on "Squawk Box." "I do think that we're going to have a third act of this virus in the fall and the winter and it's likely to be more pervasive spread in a broader part of the country."

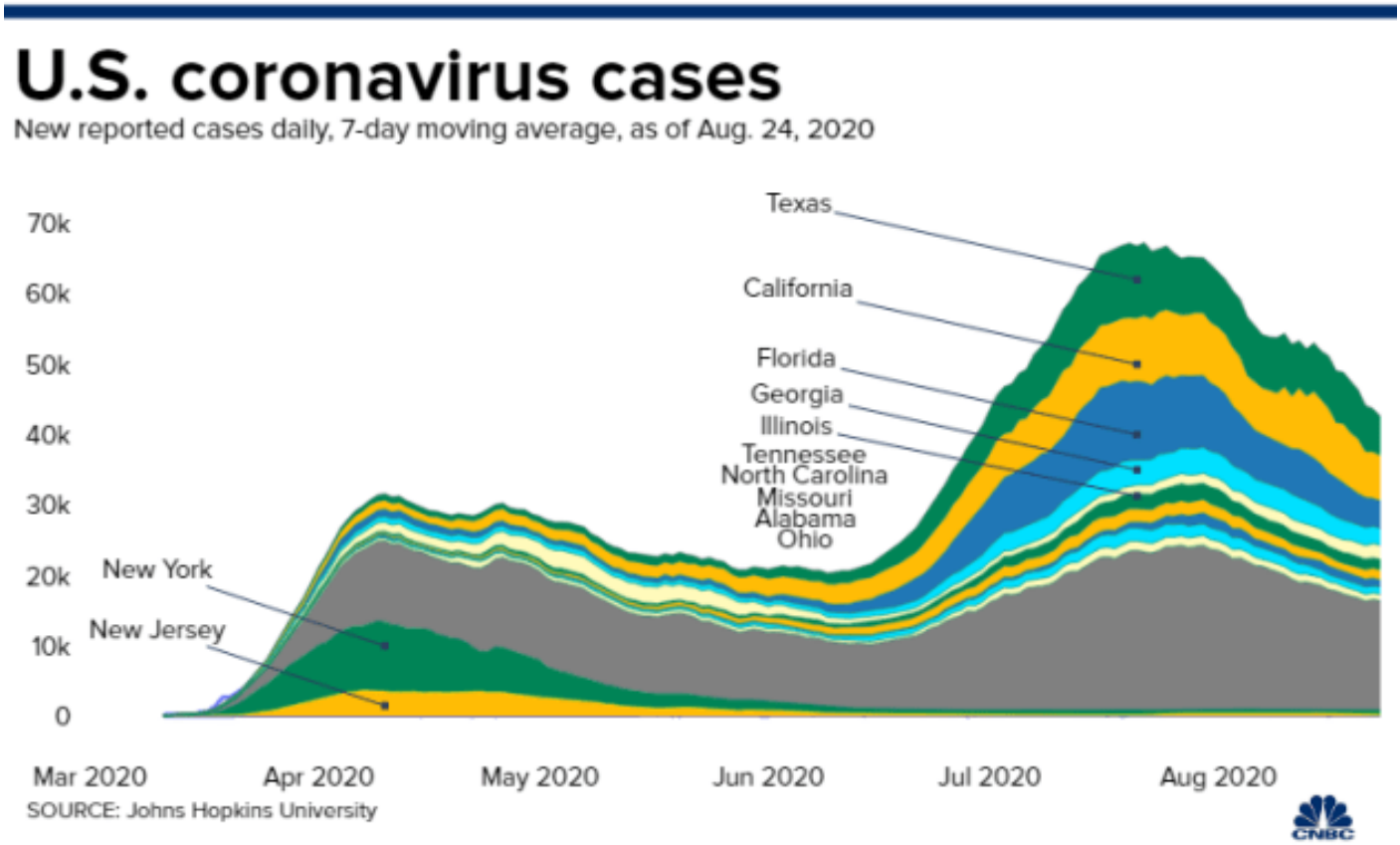
He added that the virus is likely to spread to rural parts of the U.S., some of which have been "largely unaffected to date." Cases are already beginning to build in the West and Midwest, Gottlieb said, adding that "every community is vulnerable."

He said the coronavirus does not spread like the flu, which one person might pass on to two or three others, he said, but that the virus spreads largely at "super-spreading events" such as large gatherings, especially indoor events.

"Really, an outbreak can happen anywhere," he said.

While daily new cases have fallen steadily for about a month in the U.S., the number of

U.S., on average, are still dying everyday due to Covid-19. Director of the Centers for Disease Control and Prevention Dr. Robert Redfield said Thursday he'd like to bring the number of daily new cases down below 10,000 and see daily new deaths fall to under 250.



He added that he expects both new cases and deaths to continue to fall as people and officials implement public health guidelines such as mask wearing, hand washing, social distancing and the closing of bars.

"You and I are going to see the cases continue to drop. And then hopefully this week and next week, you're going to start seeing the death rate really start to drop again." Redfield said in an interview with Dr. Howard Bauchner of the Journal of the American Medical Association. "I think we're going to start to see a decline in mortality across the country now next week as we continue to get control of these cases."

Redfield and others, including Gottlieb, have repeatedly warned that the country could be in for a particularly difficult fall and winter. Coronavirus cases could begin to rise again, especially as cold weather forces people indoors, where the virus spreads more easily. And hospitals will need to grapple with the double burden of both treating Covid-19 patients as well as the expected seasonal influenza patients.

Redfield urged Americans yet again on Thursday to get this year's flu vaccine as soon as it's available to mitigate the risk of an overwhelming flu season. Health officials are taking new steps to increase access to the vaccine. Earlier this week, the Department of Health and Human Services announced that it has authorized pharmacists in all 50 states to provide childhood vaccinations, including flu shots.

In Massachusetts, health officials said Wednesday that most students over the age of 6 months must get a flu vaccine this year in order to enroll in classes in January. That makes Massachusetts the first state to require the flu vaccination for all K-12 and college students. The state expects students to receive the vaccination by Dec. 31, unless the student provides a medical or religious exemption.

Disclosure: Scott Gottlieb is a CNBC contributor and is a member of the boards of Pfizer, genetic-testing start-up Tempus and biotech company Illumina. He also serves as co-chair of Norwegian Cruise Line Holdings' and Royal Caribbean's "Healthy Sail Panel."

September 10, 2019

Norman E. Sharpless, M.D.
Acting Commissioner
Food and Drug Administration
1903 New Hampshire Avenue
Silver Spring, MD 20993

Mitchell Zeller
Director
Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Acting Commissioner Sharpless and Mr. Zeller,

We are writing to you today to express our concern for small businesses in the open vapor product industry in regard to the current PMTA guidance. Thousands of small vape shop owners and vapor product manufacturers are on the precipice of extinction. We are facing vague, unattainable regulatory gates and the terrifying threat of regulatory termination of the most impactful tobacco harm reduction products to date. We are being forced to prepare for a future where we will not be able to afford costly and unclear premarket approval, casting small businesses out of the lifesaving industry that we once created. It is our hope that the FDA can convene with our industry representatives to develop a pathway to clear and concise industry regulation that is mutually agreeable.

Current PMTA guidance recommends extensive research into each product, which includes bottle size and nicotine variations, as well as environmental assessments. We are not large corporations that can afford to fund departments devoted to regulatory affairs, science, toxicology, and legal matters, nor do we have millions of dollars to secure these services. We are mostly “mom and pop” small businesses. Many of us started with nothing but a few thousand dollars and a desire to help smokers quit, using the same method we used ourselves. Through hard work, and a firm belief in our mission, we have been able to develop successful small businesses that have not only created job opportunities for thousands of people, but helped countless people quit smoking cigarettes, and even quit using nicotine entirely, for good. This industry was created by thousands of small business owners who exemplify the American Dream—that through dedication and hard work, everyone has the opportunity to be successful. The current PMTA structure may well turn out to be impossible to navigate or comply with, at least to any distinction of consistency and dependability for advancing products and incentivizing improvements.

Thus far, efforts to engage consultants, laboratory services, and legal counsel all seem to produce professional regulatory experts that are just as unclear on how to advance through FDA’s current regulatory structure successfully. This leaves the industry even further confused, and effectively paralyzed, as we consider the risk of potentially spending ourselves out of business – because none of these entities can provide definitive answers to a process that remains completely subjective. The estimated costs given to us by the very services we would need to utilize to achieve adequate PMTA submission, amounting to millions of dollars per SKU, are

significantly higher than the FDA's "average application cost" of $131,643 for initial e-liquid submissions. PMTA guidance, by its very nature, gives the vapor industry a loose understanding of what will and won't result in approval. These recommendations, combined with high costs for only a potential chance of approval, create an unrealistic paywall to industry compliance.

We are already beginning to see vape shops and vapor product manufacturers shut their doors—the smallest partnerships and family-owned businesses in the industry are steadily beginning to disappear. Some vapor product manufacturers are moving their American-based businesses to more vapor-friendly countries that have clear, attainable regulatory structures. Those manufacturers who do not have the ability to uproot their lives to make such a business move are instead selling their livelihood for pennies on the dollar, rather than risking a total loss when FDA exercises their enforcement discretion. Many members of the open vapor industry are making the difficult decision not to renew leases on the buildings they occupy because the pathway to remain on the market is completely subjective, undefined, and makes compliance extremely difficult, if not impossible. We will continue to see this industry slowly collapse under the heavy burden of the current regulatory framework that is unlike any other and offers no consistent baseline for the industry to follow.

It is clear that the outcome of the current regulatory structure will hand the entire vapor product industry to massive tobacco companies who have a long, sordid, and extremely profitable history of damaging the health and wellbeing of this country. The open vapor industry has and hopefully always will be able to be committed to helping combustible tobacco users transition to a nicotine delivery system that has been proven less harmful by orders of magnitude. We represent a group of businesses prepared to work with the FDA towards reasonable, realistic and sustainable regulations that are attainable for industry participants and more consistent with established and commonplace regulations for other consumable products.

Perhaps our most important concern is that combustible tobacco products, which are clearly and demonstrably harmful to public health, will be allowed to remain on the market in every smoke shop, gas station, grocery store, and convenience store in the country with little more than an age restriction and modest tax as a use deterrent. The only remaining choices Americans will have are combustible tobacco products, big tobacco company owned vapor products, or potentially hazardous, unsafe, and illegal black market products. Not only will these vague and unattainable PMTA guidelines reward tobacco companies for their current and past behavior, but they will also surely undo much of the hard work open vapor product manufacturers, distributors, and resellers have done to help millions of combustible tobacco users transition to safer nicotine delivery systems and even quit nicotine altogether.

Tobacco companies created the distrust that now exists. They also followed our lead into these less harmful alternatives while vilifying our products without factual basis. They have exponentially more resources, lobbyists, and influence, but current realities will give them the harm reduction market that we established and advanced. The current regulatory structure will take this from us and hand deliver it to those companies who created and advanced the harms of combustible cigarettes with no concern for the consequences. Furthermore, the FDA's own age-of-sale enforcement stings show that youths are not obtaining these products from our industry participants, they obtain them from the tobacco distribution pathways.[1]

[1] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-forceful-new-actions-focused-retailers-manufacturers?utm_source=Eloqua&utm_medium=email&utm_term=stratcomms&utm_content=statement&utm_campaign=CTP+News%3A+March4Announcement+-+3419&fbclid=IwAR3o1gS1Gx8R2QPExHlB_X3GUAoDp3u8rK_PGb2lD6CHTnwBGXBALeXyYVQ

So why allow tobacco companies to commandeer this industry when we are the ones who have introduced these products, created this new harm reduction strategy, and are verifiably (by the FDA's own enforcement evaluations) maintaining youth sales prevention and discouragement?

Our concerns go beyond the loss of our businesses or the added power those losses would hand tobacco companies. We are equally concerned about vapor product manufacturing being handled by irresponsible, potentially dangerous black-market entities. These black-market entities will have no incentive to ensure that their illegal products follow standardized, unadulterated manufacturing practices. Consumers will unwittingly be put at risk by potentially hazardous and unsafe vapor products.

We understand and respect the FDA's mandate to ensure reasonable consumer protections. We, the undersigned, are prepared to meet with FDA to cooperate and work together to find mutually satisfactory structures to regulate these products that will provide the requisite consumer protections, and also create a regulatory approach that is defined, clear, and attainable by those industry participants, like us, who are fully prepared to preserve and solidify the harm reduction public health benefits these products are capable of providing.

We hope the FDA will recognize and consider that this industry is different than any other. Most consumable products get introduced by big conglomerates or multinational manufacturers with correlative budgets and regulatory experts. Meanwhile, vapor products are facing regulatory approaches advanced many years after the products were already on store shelves. We acknowledge and respect the difficulties this adds for both the FDA and the industry. We are prepared to work with the FDA to find regulatory frameworks that meet our mutual goals. If we cannot find some realistic, consistent, and compliable common ground, businesses will close, thousands of jobs will be lost, many leases broken, investments lost (some even at life-changing levels) – many may lose their homes, savings, and much more.

On behalf of the undersigned 1,464 small vapor businesses, I respectfully request that you engage with us in a timely manner to navigate an attainable solution for small business owners so that we can reach our common goal: to save the lives of more than 480,000 American adult smokers a year without subjecting a new generation to nicotine addiction.

With warm regards,

Amanda Wheeler, Co-Owner
Jvapes E-Liquid
1201 Iron Springs Rd., Suite 3
Prescott, AZ 86305
(928) 533-0352
amanda@jvapes.com

THE CORONAVIRUS CRISIS

3 Months Of Hell: U.S. Economy Drops 32.9% In Worst GDP Report Ever

July 30, 2020 · 5:00 AM ET
Heard on Morning Edition

SCOTT HORSLEY

4-Minute Listen

PLAYLIST Download Transcript

A movie theater is seen closed due to the coronavirus pandemic on July 2, 2020, in Brea, Calif. The U.S. economy shrank at a record 32.9% rate in the second quarter as the pandemic cost tens of millions of jobs.

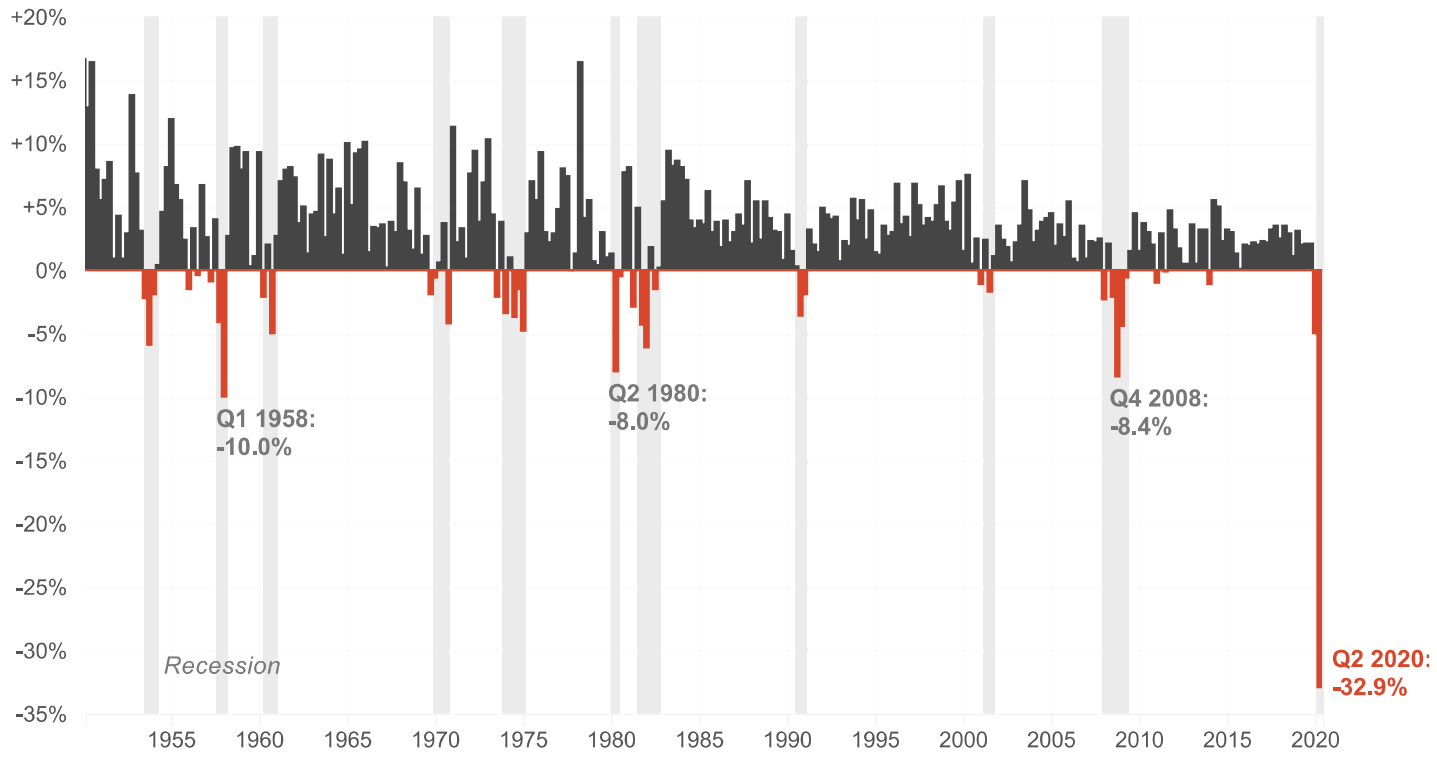
Jae C. Hong/AP

Updated at 9:32 a.m. ET

The coronavirus pandemic triggered the sharpest economic contraction in modern American history, the Commerce Department reported Thursday.

Gross domestic product — the broadest measure of economic activity — shrank at an annual rate of 32.9% in the second quarter as restaurants and retailers closed their doors in a desperate effort to slow the spread of the virus, which has killed more than 150,000 people in the U.S.

The economic shock in April, May and June was more than three times as sharp as the previous record — 10% in 1958 — and nearly four times the worst quarter during the Great Recession.



Source: Bureau of Economic Analysis

Credit: Alyson Hurt/NPR

"Horrific," said Nariman Behravesh, chief economist at IHS Markit. "We've never seen anything quite like it."

Another 1.43 million people filed for state unemployment last week, an increase of 12,000, the Labor Department reported Thursday. It was the second week in a row of increased unemployment filings and shows that the economic picture continues to remain grim.

GDP swings are typically reported at an annual rate — as if they were to continue for a full year — which can be misleading in a volatile period like this. The overall economy in the second quarter was 9.5% smaller than during the same period a year ago.

After a sharp drop in March and April, economic activity began to rebound in May and June, although that recovery remains halting and could be jeopardized by a new surge of infections.

ANALYSIS

$600 A Week: Poverty Remedy Or Job Slayer?

"As soon as the virus started to take off again in key states like Texas, California, Arizona, Florida, it's fading very rapidly," Behravesh said.

Restaurant owner Cameron Mitchell likens the pandemic to a hurricane. What appeared to be a business rebound in June turned out to be merely the eye of the storm, and he's now being buffeted by gale-force winds again.

"Our associates are more scared to work today and guests are more afraid to go out, so sales have dropped," Mitchell said.

Cameron Mitchell operates more than 50 restaurants in 13 states. He says business was rebounding in June but has dropped again with the surge in new coronavirus infections.

Cameron Mitchell Restaurants

Business at his restaurants in Florida had nearly recovered to pre-pandemic levels in June but has since fallen sharply.

Other industries have enjoyed a more durable recovery, though few are back to where they were in February.

Dentists' offices are ordinarily one of the more stable parts of the economy, but they closed for all but emergency services during much of the spring. Dental hygienist Alexis Bailey was out of work for 10 weeks before her office in Lansing, Mich., reopened at the end of May.

At first, she was reluctant to go back to work while the virus was still circulating.

"I was terrified," Bailey said. "I was not happy to be back. But I have a job to do and I like to do it and I want to help people. We talk about how essential we are, so that's what we've had to do."

Dental hygienist Alexis Bailey was initially nervous about returning to work but says she quickly grew comfortable with the new protective measures, including a face shield (not shown).

Christina Dauka, MSDH

Within an hour of returning to work, Bailey said, she began to feel comfortable, particularly with the additional protective gear and other safety precautions her office has adopted.

"I tell my patients all the time I wouldn't be here if I didn't feel safe," she said.

Nationwide, dental offices added more than a quarter-million jobs in May and another 190,000 in June. And there has been no shortage of patients.

She thought no one would want to come. "But we're booked," Bailey said. "People miss getting their teeth cleaned. They want to catch up. Every time they come in, they say, 'This has been nice to get out of the house and feel safe and talk to somebody.' "

Factory production has also begun to rebound, along with construction. But airlines and amusement parks are still struggling.

"It's very much a sort of two-tiered economy right now," Behravesh said.

The unemployment rate approached 15% in April, and in June it was still higher — at 11.1% — than during any previous postwar recession.

CORONAVIRUS LIVE UPDATES

Another Bankruptcy At The Mall: Parent Company Of Ann Taylor, Loft Is Latest To Fail

While the drop in GDP was largely driven by a decline in consumer spending, the economic fallout was cushioned somewhat by an unprecedented level of federal relief.

Wages and salaries fell sharply in April, but that was more than offset by the $1,200 relief payments that the government sent to most adults and by supplemental unemployment benefits of $600 per week.

Those government payments helped prevent an even steeper drop in consumer spending — the lifeblood of the U.S. economy — and allowed struggling families to buy groceries and pay rent.

Federal Reserve Chair Jerome Powell said Wednesday that the money "has been well spent. It has kept people in their homes. It has kept businesses in business. So that's all a good thing."

Those extra unemployment benefits are expiring this week, though. With coronavirus infections still threatening the recovery, additional federal support is likely to be necessary.

THE CORONAVIRUS CRISIS

'Tsunami' Of Evictions Feared As Extra $600 Unemployment Payments End

"Until we get the virus under control, we're going to need more help," Behravesh said. "Our view is that we're not going to get to the pre-pandemic levels of economic activity until some time in 2022."

Restaurant owner Mitchell says his business lost $700,000 in June alone. He predicts a wave of restaurant bankruptcies unless the federal government provides more relief.

"No one is looking for a handout here," he said. "We're looking to survive."

He's watching news of vaccine trials closely in hopes that eventually diners will feel comfortable eating out again in large numbers.

"I don't think it's the next couple of weeks," he said. "But I tell our team, 'Every day that goes by, it's one day closer to the end of this thing.' "

covid-19 coronavirus dentists restaurants gdp

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U.S. weekly jobless claims fall to 963,000, first time below 1 million since mid-March

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Jeff Cox@JEFF.COX.7528@JEFFCOXCNBCCOM

KEY POINTS

- First-time jobless claims totaled 963,000 last week versus the Wall Street estimate of 1.1 million.
- That was the first time below 1 million since March 14.
- Continuing claims totaled 15.5 million, down more than 600,000.

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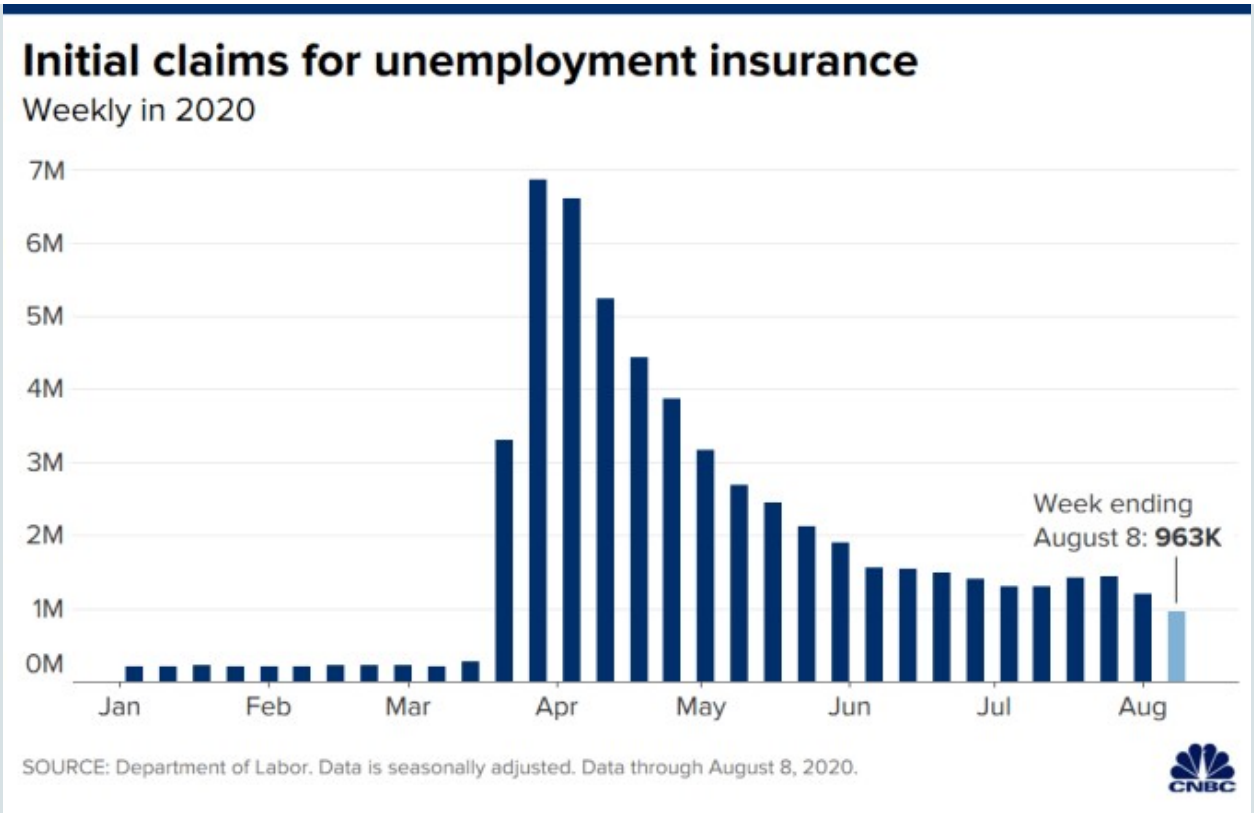
U.S. weekly jobless claims fell below 1 million, first time since mid-March

First-time claims for unemployment insurance last week fell below 1 million for the first time since March 21 in a sign that the labor market is continuing its recovery from the coronavirus pandemic.

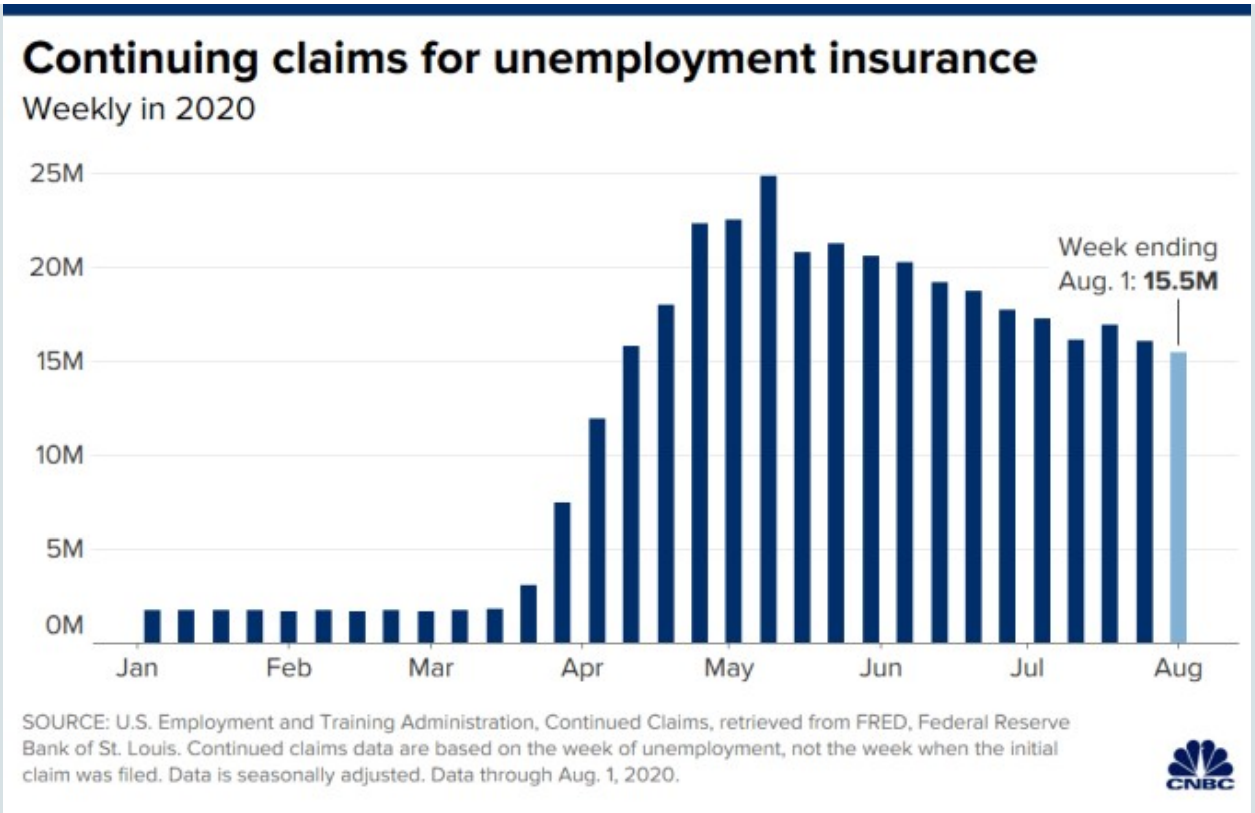
The total claims of 963,000 for the week ended Aug. 8 were well below the estimate of 1.1 million from economists surveyed by Dow Jones. That represented a decline of 228,000 from the previous week's total.

Jobless claims had totaled above 1 million for 20 consecutive weeks as the U.S. economy went into lockdown to contain Covid-19. The last time the total was below that number was March 14, with 282,000, just as the pandemic declaration first hit.



While the sub-1 million reading marks a milestone, there's still plenty of work to do for the job market to get back to normal. Those collecting benefits for at least two weeks, known as continuing claims, totaled nearly 15.5 million, a decrease of 604,000 from a week ago, but still well above pre-pandemic levels.

"The labor market continues to improve, but unemployment remains a huge problem for the U.S. economy," wrote Gus Faucher, chief economist at PNC Financial Services. "The number of people filing for unemployment insurance, both regular and PUA benefits, continues to steadily decline as layoffs abate. But job losses remain extremely elevated, far above their pre-pandemic level."



Markets cut losses following the report, and Wall Street indicated a flat open for stocks. Equities were little changed in midmorning trading.

The total marks the second week of declines since a provision expired July 31 that gave unemployment insurance recipients an extra $600 a week on top of their normal compensation. Congressional leaders are debating an extension as President Donald Trump issued an executive order that would provide an extra $400.

The decline “provides some fuel for the argument that the enhanced benefits were providing an incentive for people to stay away from returning to work if they had the option,” Jefferies said in a note. “The data of the past two weeks will not help the arguments of lawmakers fighting to extend the expired benefits.”

The total number of Americans receiving unemployment benefits fell sharply for the week ended July 25, down more than 3 million to 28.26 million, also pointing to a downward trend in joblessness. A year ago, that number was 1.7 million.

Those receiving benefits under the Pandemic Unemployment Assistance program totaled 488,622, a decline of 167,377 from a week ago. The program provides compensation to those who normally wouldn't be eligible for benefits such as independent contractors.

At the state level, the biggest drops in claims came from Florida (-23,180), New York (-21,905) and Texas (-11,233), according to numbers not adjusted for seasonality. The unadjusted total was 831,856, a decrease of 156,453. Some economists say the unadjusted number is more relevant as the current circumstances surrounding the pandemic are not subject to seasonality.

The report comes as the U.S. has recovered about half the jobs it lost during the Covid-19 closures, according to a recent nonfarm payrolls report. July saw a gain of about 1.8 million, bringing the unemployment rate down to 10.2%.

However, that remains well above the pre-pandemic level of 3.5%, which was the lowest in 50 years.

ORIGINAL ARTICLE

A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D., Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc., Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D., Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D., Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.

ABSTRACT

BACKGROUND

E-cigarettes are commonly used in attempts to stop smoking, but evidence is limited regarding their effectiveness as compared with that of nicotine products approved as smoking-cessation treatments.

METHODS

We randomly assigned adults attending U.K. National Health Service stop-smoking services to either nicotine-replacement products of their choice, including product combinations, provided for up to 3 months, or an e-cigarette starter pack (a second-generation refillable e-cigarette with one bottle of nicotine e-liquid [18 mg per milliliter]), with a recommendation to purchase further e-liquids of the flavor and strength of their choice. Treatment included weekly behavioral support for at least 4 weeks. The primary outcome was sustained abstinence for 1 year, which was validated biochemically at the final visit. Participants who were lost to follow-up or did not provide biochemical validation were considered to not be abstinent. Secondary outcomes included participant-reported treatment usage and respiratory symptoms.

RESULTS

A total of 886 participants underwent randomization. The 1-year abstinence rate was 18.0% in the e-cigarette group, as compared with 9.9% in the nicotine-replacement group (relative risk, 1.83; 95% confidence interval [CI], 1.30 to 2.58; P<0.001). Among participants with 1-year abstinence, those in the e-cigarette group were more likely than those in the nicotine-replacement group to use their assigned product at 52 weeks (80% [63 of 79 participants] vs. 9% [4 of 44 participants]). Overall, throat or mouth irritation was reported more frequently in the e-cigarette group (65.3%, vs. 51.2% in the nicotine-replacement group) and nausea more frequently in the nicotine-replacement group (37.9%, vs. 31.3% in the e-cigarette group). The e-cigarette group reported greater declines in the incidence of cough and phlegm production from baseline to 52 weeks than did the nicotine-replacement group (relative risk for cough, 0.8; 95% CI, 0.6 to 0.9; relative risk for phlegm, 0.7; 95% CI, 0.6 to 0.9). There were no significant between-group differences in the incidence of wheezing or shortness of breath.

CONCLUSIONS

E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support. (Funded by the National Institute for Health Research and Cancer Research UK; Current Controlled Trials number, ISRCTN60477608.)

From Queen Mary University of London (P.H., A.P.-W., D.P., K.M.S., N.B., H.J.M.), King's College London (F.P., P.S.), and London South Bank University (L.D.), London, the University of York, York (J.L., S.P., Q.W.), and Leicester City Council, Leicester (L.R.) — all in the United Kingdom; and Roswell Park Comprehensive Cancer Center, Buffalo, NY (M.G.). Address reprint requests to Dr. Przulj at Queen Mary University of London, Health and Lifestyle Research Unit, 2 Stayner's Rd., London E1 4AH, United Kingdom, or at d.przulj@qmul.ac.uk.

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Switching completely from cigarette smoking to e-cigarette use would be expected to reduce risks to health.[1-3] There are questions about risks and benefits of use of e-cigarettes for different purposes, but an important clinical issue is whether e-cigarette use in a quit attempt facilitates success, particularly as compared with the use of nicotine-replacement therapy.

A Cochrane review showed that e-cigarettes with nicotine were more effective for smoking cessation than nicotine-free e-cigarettes.[4] A trial that compared e-cigarettes with nicotine patches for smoking cessation used cartridge e-cigarettes with low nicotine delivery and no face-to-face contact. It showed similar low efficacy for both treatments.[5] (For further details of previous trials, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) Our trial evaluated the 1-year efficacy of refillable e-cigarettes as compared with nicotine replacement when provided to adults seeking help to quit smoking and combined with face-to-face behavioral support.

Methods

Design and Oversight

We conducted a two-group, pragmatic, multicenter, individually randomized, controlled trial. National Health Service (NHS) stop-smoking services are available free across the United Kingdom.[6] This trial was conducted in three service sites from May 2015 through February 2018. The Health and Lifestyle Research Unit that delivers the service for two London boroughs (Tower Hamlets and City of London), along with the Leicester and East Sussex services, recruited participants and delivered the interventions. Participating services included trial information in their advertising. Participants were also recruited through social media. Adult smokers were invited to participate if they were not pregnant or breast-feeding, had no strong preference to use or not to use nicotine replacement or e-cigarettes, and were currently not using either type of product.

The trial was approved by the National Research Ethics Service (reference number, 14/LO/2235). Collective unblinded data were seen only for the purposes of the meetings of the data monitoring and ethics committee. Data analyses were conducted with blinding to treatment assignments. All the authors contributed to the trial design, participated in the interpretation of the data, vouch for their completeness and accuracy, and made the decision to submit the manuscript for publication. All the authors vouch for the fidelity of the trial to the protocol, available at NEJM.org.

Procedures

Smokers were provided with trial information, prescreened for eligibility, and, if eligible, invited to a baseline session. There, eligibility was confirmed, written informed consent and baseline data were obtained, and participants set up their quit date (normally the following week).[7]

Randomization took place on the quit date to limit differential dropout. Randomization sequences (1:1 ratio in permuted blocks of 20, stratified according to trial site) were generated with the use of a pseudorandom number generator in Stata software and were embedded into an application that only revealed the next treatment assignment once a participant had been entered into the database.

Product use started immediately after randomization. All the participants received the same multisession behavioral support as per U.K. stop-smoking service practice.[7,8] This support involved weekly one-on-one sessions with local clinicians, who also monitored expired carbon monoxide levels for at least 4 weeks after the quit date.

Participants were contacted by telephone at 26 and 52 weeks. Interviewers asked about product use and thus were aware of the treatment assignments. Participants who reported abstinence or a reduction in smoking of at least 50% at 52 weeks were invited back to provide a carbon monoxide reading. Participants were compensated £20 ($26 U.S.) for their travel and time at the 52-week validation visit.

Nicotine-Replacement Group

Participants were informed about the range of nicotine-replacement products (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs) and selected their preferred product. Use of combinations was encouraged, typically the patch and a faster-acting oral product. Participants were also free to switch

products. The way that nicotine replacement was provided differed slightly among trial sites (see the Supplementary Appendix). Supplies were provided for up to 3 months, as per standard practice. The cost to the NHS of a 3-month supply of a single nicotine-replacement product is currently approximately £120 ($159 U.S.).

E-Cigarette Group

A starter pack, called One Kit (Aspire, U.K. Ecig Store), was provided to facilitate initial use and teach participants how to use refillable e-cigarette products, along with one 30-ml bottle of Tobacco Royale flavor e-liquid purchased from U.K. Ecig Store, containing nicotine at a concentration of 18 mg per milliliter. The kit had a 2.1-ohm atomizer and 650-mAh battery. During the trial, the company discontinued this kit, so One Kit 2016 (Innokin, U.K. Ecig Store), with a 1.5-ohm atomizer and 1000-mAh battery, was used for 42 participants. Participants were asked to purchase their future e-liquid online or from local vape shops and to buy a different e-cigarette device if the one supplied did not meet their needs. They were encouraged to experiment with e-liquids of different strengths and flavors. Those who were unable to obtain their own supply were provided with one further 10-ml bottle, but this was not offered proactively. Participants received oral and written information on how to operate the e-cigarette.

The original One Kit, including five atomizers, U.K. adapter, spare battery, and e-liquid, was purchased wholesale for £19.40 ($26 U.S.). The cost of One Kit 2016, including the same extras, was £30.25 ($40 U.S.).

Participants in the e-cigarette group and those in the nicotine-replacement group were asked to sign a commitment to not use the nonassigned treatment for at least 4 weeks after their quit date. This was to minimize contamination between the trial groups.

MEASURES

At trial visits, the following data were recorded: smoking status, expired carbon monoxide level (at baseline, 4 weeks, and 52 weeks), use and ratings of trial products, ratings of withdrawal symptoms (weeks 1 through 6), adverse reactions (presence or absence of nausea, sleep disturbance, and throat or mouth irritation), and respiratory symptoms (presence or absence of shortness of breath, wheezing, cough, and phlegm). The Supplementary Appendix provides further details of trial measures.

The primary outcome was 1-year sustained abstinence, calculated in accordance with the Russell Standard[9] as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date, validated biochemically by an expired carbon monoxide level of less than 8 ppm at 1-year follow-up and not contradicted by any previous self-report or validation result. Carbon monoxide validation is the standard measure in trials assessing nicotine-containing products (see the Supplementary Appendix). Participants who died (one in each group) were excluded. Participants who were lost to follow-up or did not provide biochemical validation were classified as not being abstinent in the primary analysis.

Secondary abstinence outcomes included sustained abstinence from 26 to 52 weeks, at 4 weeks, and at 26 weeks and the percentage of participants without sustained abstinence from 26 to 52 weeks who reduced their cigarette consumption by at least 50%. We also assessed 7-day abstinence at 4, 26, and 52 weeks. In addition, we compared the trial groups with respect to relapse rate and time to relapse and with respect to the measures listed above.

STATISTICAL ANALYSIS

We calculated that a sample of 886 participants would provide the trial with 95% power (at a two-sided alpha level of 0.05) if the true percentages of 1-year abstinence were 23.8% in the e-cigarette group and 14.0% in the nicotine-replacement group (relative risk, 1.7). Since trial setup, the abstinence rate in stop-smoking service clinics declined to 10%, but the sample of 886 participants would provide 85% power if the percentages were 17.0% and 10.0% in the respective groups.

The primary and secondary abstinence outcomes were analyzed by regression of smoking status at each time point onto trial group. Primary analyses were adjusted for trial center to account for the stratification factor. In sensitivity analyses, each model was further adjusted for baseline covariates selected with the use of stepwise regression. Binary regressions were conducted by means of the generalized linear model

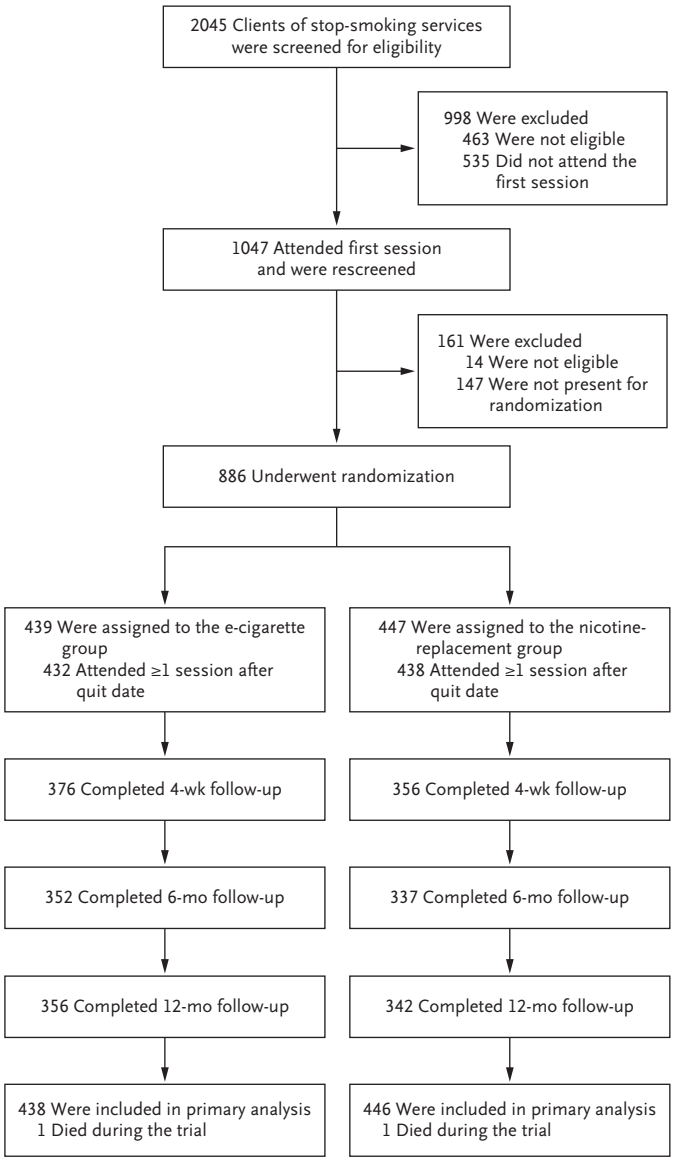

Figure 1. Screening, Randomization, and Follow-up.

Reasons for ineligibility in 463 of the 2045 persons screened are detailed in Table S11 in the Supplementary Appendix. Of the 438 participants in the e-cigarette group who were included in the primary analysis, 3 stopped treatment and declined follow-up and 13 stopped treatment and permitted follow-up. Of the 446 participants in the nicotine-replacement group who were included in the primary analysis, 5 stopped treatment and declined follow-up and 36 stopped treatment and permitted follow-up.

with binomial distribution and logarithmic link to estimate the relative risk for e-cigarettes as compared with nicotine-replacement therapy.

To assess the effect of missing data on the primary outcome, we conducted four prespecified sensitivity analyses, which excluded participants who did not attend at least one behavioral-support session, excluded participants who used the nonassigned product for at least 5 consecutive days, excluded participants who did not complete the 52-week follow-up, and imputed missing information with the use of multiple imputation by chained equations.[10] Missing data were imputed for 136 participants in each group, and 50 data sets were imputed.

We also estimated mean differences and 95% confidence intervals between trial groups in product ratings and in change scores between baseline and follow-up time points in withdrawal symptoms, as well as between-group differences in the percentage of participants who had adverse reactions or respiratory symptoms, using binomial regression with adjustment for trial center (see the statistical analysis plan, available with the protocol at NEJM.org). Analyses were conducted with the use of Stata software, version 15 (StataCorp).

RESULTS

PARTICIPANTS

A total of 2045 clients of stop-smoking services were screened, and 886 underwent randomization (439 to the e-cigarette group and 447 to the nicotine-replacement group). Of the randomly assigned participants, 78.8% completed the 52-week follow-up (Fig. 1). The sample was composed largely of middle-aged smokers, with 40.7% entitled to free prescriptions (a marker of social disadvantage or poor health) (Table 1, and Table S1 in the Supplementary Appendix).

EFFECTS OF TREATMENT ON ABSTINENCE

The rate of sustained 1-year abstinence was 18.0% in the e-cigarette group and 9.9% in the nicotine-replacement group (relative risk, 1.83; 95% confidence interval [CI], 1.30 to 2.58; P<0.001) (Table 2). The absolute difference in the 1-year abstinence rate between the two groups was 8.1 percentage points, resulting in a number needed to treat for one additional person to have sustained abstinence of 12 (95% CI, 8 to 27). The result did not change substantially in the four sensitivity analyses (relative risk, 1.75 to 1.85; P≤0.001 for all comparisons) (Table S2 in the Supplementary Appendix). Abstinence rates were higher in the e-cigarette group than in the nico-

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Total (N=884)
Median age (IQR) — yr	41 (33–53)	41 (33–51)	41 (33–52)
Female sex — no. (%)	211 (48.2)	213 (47.8)	424 (48.0)
Employed — no. (%)	299 (68.3)	316 (70.9)	615 (69.6)
Entitled to free prescriptions — no. (%)	181 (41.3)	179 (40.1)	360 (40.7)
Median no. of cigarettes per day (IQR)	15 (10–20)	15 (10–20)	15 (10–20)
Median expired carbon monoxide level (IQR) — ppm	20 (13–27)	21 (13–28)	20 (13–28)
Score on the Fagerström Test for Cigarette Dependence†	4.5±2.5	4.6±2.4	4.6±2.4
Past use of nicotine replacement — no. (%)	328 (74.9)	334 (74.9)	662 (74.9)
Past use of e-cigarettes — no. (%)	186 (42.5)	181 (40.6)	367 (41.5)

* Plus–minus values are means ±SD. There were no significant differences between the trial groups. IQR denotes interquartile range. Data on additional characteristics are provided in Table S1 in the Supplementary Appendix.
† Scores range from 1 to 10, with higher scores indicating greater dependence.

Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI)†	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46)‡
Secondary outcomes				
Abstinence between wk 26 and wk 52 — no. (%)	93 (21.2)	53 (11.9)	1.79 (1.32–2.44)	1.82 (1.34–2.47)§
Abstinence at 4 wk after target quit date — no. (%)	192 (43.8)	134 (30.0)	1.45 (1.22–1.74)	1.43 (1.20–1.71)¶
Abstinence at 26 wk after target quit date — no. (%)	155 (35.4)	112 (25.1)	1.40 (1.14–1.72)	1.36 (1.15–1.67)‡
Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)	44/345 (12.8)	29/393 (7.4)	1.75 (1.12–2.72)	1.73 (1.11–2.69)‖

* Abstinence at 52 weeks was defined as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date, validated biochemically by an expired carbon monoxide level of less than 8 ppm at 52 weeks. Abstinence between week 26 and week 52 was defined as a self-report of smoking no more than five cigarettes between week 26 and week 52, plus an expired carbon monoxide level of less than 8 ppm at 52 weeks. Abstinence at 4 weeks was defined as a self-report of no smoking from 2 weeks after the target quit date, plus an expired carbon monoxide level of less than 8 ppm at 4 weeks. Abstinence at 26 weeks was defined as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date to 26 weeks; there was no validation by expired carbon monoxide level.
† The analysis was adjusted for trial center only.
‡ The analysis was adjusted for trial center, marital status, age at smoking initiation, and score on the Fagerström Test for Cigarette Dependence.
§ The analysis was adjusted for trial center, age, score on the Fagerström Test for Cigarette Dependence, and age at smoking initiation.
¶ The analysis was adjusted for trial center, education level, partner who smokes (yes or no), and score on the Fagerström Test for Cigarette Dependence.
‖ The analysis was adjusted for trial center, sex, age, and partner who smokes (yes or no).

tine-replacement group at all time points (Table 2, and Table S3 in the Supplementary Appendix).

We conducted a post hoc analysis, in which participants with 1-year abstinence who used nonassigned products (see the Supplementary Appendix) were removed from the sample (3% [2 of 79] in the e-cigarette group were using nicotine replacement and 20% [9 of 44] in the nicotine-replacement group were using e-cigarettes). This resulted in a 1-year abstinence rate of 17.7% in the e-cigarette group, as compared with 8.0% in the nicotine-replacement group (relative risk, 2.21; 95% CI, 1.52 to 3.22).

Among participants in whom full abstinence

Table 3. Attendance and Treatment Adherence.

Variable	E-Cigarettes (N = 438)	Nicotine Replacement (N = 446)
Median no. of contacts completed (IQR)*	5 (4–5)	5 (4–5)
Maximum no. of contacts completed — no. of participants (%)		
1	8 (1.8)	10 (2.2)
2	25 (5.7)	40 (9.0)
3	38 (8.7)	45 (10.1)
4	86 (19.6)	106 (23.8)
5	281 (64.2)	245 (54.9)
Use of assigned products during the initial 4 wk†		
Median no. of days on which product was used (IQR)	28 (25–28)	24 (19–27)
Daily use during the entire 4 wk — no. (%)	232 (53.0)	46 (10.3)
Median no. of days on which product was used in past wk (IQR)‡	7 (7–7)	6.5 (3.5–7)
Use of assigned products at 26 wk — no. (%)	180 (41.1)	33 (7.4)
Use of assigned products at 52 wk — no. (%)	173 (39.5)	19 (4.3)

* The maximum number of contacts was five: at the target quit date, 1 week, 4 weeks, 26 weeks, and 52 months.
† For use of assigned products, missing information was imputed from the information from the next weekly behavioral-support consultation, if available (e.g., for missing information at consultation 3, information was taken from consultation 4).
‡ The results were similar for weeks 1 through 4.

was not achieved, more had a carbon monoxide–validated reduction of smoking by at least 50% in the e-cigarette group than in the nicotine-replacement group (Table 2). Time to relapse and relapse rates at 52 weeks among participants with sustained abstinence at 4 weeks did not differ substantially between the two trial groups (hazard ratio for time to relapse, 1.14; 95% CI, 0.96 to 1.34; relative risk of relapse at 52 weeks, 1.27; 95% CI, 0.93 to 1.73).

TREATMENT ADHERENCE AND RATINGS AND EFFECTS ON WITHDRAWAL SYMPTOMS

Overall adherence was similar in the two groups, but e-cigarettes were used more frequently and for longer than nicotine replacement (Table 3). In the nicotine-replacement group, 88.1% of participants used nicotine-replacement combinations. In the e-cigarette group, practically all participants used refillable e-cigarettes (Table S4 in the Supplementary Appendix).

Among participants with 1-year abstinence, 80% (63 of 79) were using e-cigarettes at 52 weeks in the e-cigarette group and 9% (4 of 44) were using nicotine replacement in the nicotine-replacement group. Further details of product use (including the use of nonassigned products) are provided in the Supplementary Appendix, including Tables S4 and S5.

Both e-cigarettes and nicotine-replacement products were perceived to be less satisfying than cigarettes. However, e-cigarettes provided greater satisfaction and were rated as more helpful to refrain from smoking than nicotine-replacement products (Table S6 in the Supplementary Appendix).

Among participants with abstinence at 1 week after their quit date as well as participants with abstinence at 4 weeks, those in the e-cigarette group had less severe urges to smoke than did those in the nicotine-replacement group (Table 4). They also reported a smaller increase from baseline in irritability, restlessness, and inability to concentrate than those in the nicotine-replacement group during the first week of abstinence. Between-group differences in hunger and depression were in the same direction but less substantial. By week 4, participants in either group who were abstinent reported little withdrawal discomfort (Table S7 in the Supplementary Appendix).

Table 4. Urges to Smoke in Participants with Abstinence at 1 Week or 4 Weeks after Quit Date.*

Variable	1 Wk after Quit Date		Mean Difference (95% CI)	4 Wk after Quit Date		Mean Difference (95% CI)
	E-Cigarettes (N=158)	Nicotine Replacement (N=131)		E-Cigarettes (N=186)	Nicotine Replacement (N=132)	
Score for frequency of urge	2.5±1.1	2.8±0.9	–0.4 (–0.6 to –0.1)	1.9±0.9	2.2±0.8	–0.3 (–0.5 to –0.1)
Score for strength of urge	2.7±1.1	3.2±1.0	–0.5 (–0.7 to –0.2)	2.1±1.1	2.4±1.0	–0.3 (–0.6 to –0.1)
Composite urge score	2.6±1.0	3.0±0.9	–0.4 (–0.6 to –0.2)	2.0±1.0	2.3±0.9	–0.3 (–0.5 to –0.1)

* Plus–minus values are means ±SD. Scores for frequency of urge ranged from 1 (not at all) to 6 (all the time). Scores for strength of urge ranged from 1 (no urges) to 6 (extremely strong). The composite score (range, 1 to 6, with higher scores indicating more severe urges) is an average of the frequency and strength scores.

Table 5. Respiratory Symptoms at Baseline and at 52 Weeks.*

Symptom	E-Cigarettes (N=315)		Nicotine Replacement (N=279)		Relative Risk (95% CI)†
	Baseline	52 Weeks	Baseline	52 Weeks	
	number (percent)				
Shortness of breath	120 (38.1)	66 (21.0)	92 (33.0)	64 (22.9)	0.9 (0.7–1.1)
Wheezing	102 (32.4)	74 (23.5)	86 (30.8)	59 (21.1)	1.1 (0.8–1.4)
Cough	173 (54.9)	97 (30.8)	144 (51.6)	111 (39.8)	0.8 (0.6–0.9)
Phlegm	137 (43.5)	79 (25.1)	121 (43.4)	103 (36.9)	0.7 (0.6–0.9)

* Symptoms were assessed by asking whether participants had the symptom (yes or no).
† Relative risk was calculated by means of logistic regression. Symptoms at 52 weeks were regressed onto trial group, with adjustment for baseline symptoms and trial center.

SAFETY EVALUATION

Two participants died during the trial. One died from ischemic heart disease in the e-cigarette group and one from traumatic spine injury in the nicotine-replacement group.

There were 27 serious adverse events in the e-cigarette group and 22 in the nicotine-replacement group (Table S8 in the Supplementary Appendix). No serious adverse event in either group was classified by the trial clinician as being related to product use, but we noted 1 respiratory event in the nicotine-replacement group and 5 in the e-cigarette group (2 in participants who were smoking and not vaping, 2 in participants who were smoking and vaping, and 1 in a participant whose status with respect to smoking and vaping was not known) (see the Supplementary Appendix).

Of the prespecified adverse reactions of interest, nausea was reported more frequently in the nicotine-replacement group (37.9%, vs. 31.3% in the e-cigarette group) and throat or mouth irritation more frequently in the e-cigarette group (65.3%, vs. 51.2% in the nicotine-replacement group). There was little difference between the two groups in the percentage of participants reporting severe nausea (6.6% in the e-cigarette group and 6.5% in the nicotine-replacement group) or severe throat or mouth irritation (5.9% and 3.9%, respectively) (Tables S9 and S10 in the Supplementary Appendix).

Regarding the prespecified respiratory symptoms of interest, the incidence of cough and phlegm production declined in both trial groups from baseline to 52 weeks. However, among participants who reported cough or phlegm at baseline, significantly more were symptom-free at the 52-week follow-up in the e-cigarette group than in the nicotine-replacement group (Table 5). To determine whether this was due to the higher abstinence rate in the e-cigarette group, we ran an exploratory analysis that controlled for

abstinence status at 52 weeks. This did not change the results (relative risk for cough, 0.8; 95% CI, 0.6 to 0.9; relative risk for phlegm, 0.7; 95% CI, 0.6 to 0.9).

DISCUSSION

E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy in this randomized trial. This is particularly noteworthy given that nicotine replacement was used under expert guidance, with access to the full range of nicotine-replacement products and with 88.1% of participants using combination treatments.[11]

Our trial showed a stronger effect of e-cigarettes than previous trials.[5,12,13] This could be due to the inclusion of smokers seeking help in quitting, the provision of face-to-face support, and the use of refillable e-cigarettes with free choice of e-liquids. Previous trials provided limited or no face-to-face support and used first-generation cartridge products. Refillable devices are generally more efficient at nicotine delivery.[14]

The trial provides some indications of why e-cigarettes had better results than nicotine-replacement treatments. As in previous studies,[5,15] e-cigarettes were more effective in alleviating tobacco withdrawal symptoms and received better ratings than nicotine-replacement therapy. They may also have allowed better tailoring of nicotine dose to individual needs.

The rate of continuing e-cigarette use was fairly high. This can be seen as problematic if e-cigarette use for a year signals ongoing long-term use, which may pose as-yet-unknown health risks. On the positive side, ongoing e-cigarette use may ameliorate withdrawal symptoms, such as constipation,[16] mouth ulcers,[17] and weight gain,[18] and continue to provide some of the positive subjective effects previously derived from smoking.[19] Provided that ongoing e-cigarette use has similar effects to long-term nicotine-replacement use, for heavy smokers with a high risk of relapse, long-term e-cigarette use may also assist with preventing relapse.[20] Among participants in our trial in whom full abstinence was not achieved, those in the e-cigarette group were more likely to reduce their smoke intake than those in the nicotine-replacement group, but it is unclear whether this affects future abstinence.

E-cigarettes caused more throat or mouth irritation, and nicotine replacement caused more nausea; these effects were mostly mild. There were mixed signals regarding the effects of e-cigarettes on the respiratory system. More participants in the e-cigarette group than in the nicotine-replacement group reported respiratory serious adverse events, although the difference was not significant and some of the affected participants were not vaping. Meanwhile, we detected positive effects of e-cigarette use on some respiratory outcomes. Similar positive effects were reported previously. A switch to e-cigarettes was accompanied by a reduction in respiratory infections in an online survey,[21] and two case studies described nonsmokers with chronic throat and nose infections that resolved after they started to vape. Antibacterial effects of propylene glycol and glycerin were suggested as possible explanations.[22,23] (For more on e-cigarettes and the respiratory system, see the Supplementary Appendix.)

The trial had several limitations. Product assignments could not be blinded. Positive expectations have limited effects on long-term abstinence, but if nicotine replacement was seen as an inferior option, participants in the nicotine-replacement group could have put less effort into their quit attempt than those in the e-cigarette group. We tried to limit expectation effects by recruiting only participants with no strong product preference. Abstinence rates in the nicotine-replacement group were also at least as high as in usual practice[24] (see the Supplementary Appendix). Nevertheless, lack of blinding could affect the results. Carbon monoxide validation detects smoking only over the past 24 hours, so there may have been some false negative results. Several participants in the nicotine-replacement group used e-cigarettes during the trial, but this would dilute rather than amplify any effects of e-cigarettes. The 1-year follow-up rate of 79% was similar to the rates of 78%,[19] 79%,[5] and 75%[20] observed in other studies involving the same general population and setting. Achieving higher follow-up rates among smokers engaged in face-to-face treatment is difficult, because they tend to feel embarrassed if they do not quit, and some avoid further contact. Multiple imputation showed consistent results; nevertheless, incomplete follow-up represents another limitation of the trial.

The findings are likely to be valid for depen-

dent smokers who seek help but may not be generalizable to smokers who are less dependent or who try e-cigarettes for reasons other than quitting smoking. In addition, they may not be generalizable to less effective first-generation e-cigarettes. Moreover, not all service clients want e-cigarettes. In a previous study, 69% accepted the offer of an e-cigarette starter pack.[25] (For comparison, 57% of service clients opt for nicotine replacement and 25% for varenicline.[26])

Further trials are needed to determine whether our results generalize outside the U.K. services. In addition, e-cigarette studies are needed that compare different levels of support. This is important for focusing public health messages on either encouraging smokers to switch to e-cigarette use within support services or recommending use with less intensive or no support.

In our trial, refillable e-cigarettes had greater efficacy than nicotine-replacement therapy, even though nicotine replacement was provided in combinations and under expert guidance.

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Patterns of flavored e-cigarette use among adults vapers in the United States: an internet survey.

Authors. Konstantinos Farsalinos, MD, MPH,[1,2,3] Christopher Russell, PhD,[4] George Lagoumintzis, PhD,[2] Konstantinos Poulas[2]

[1] Onassis Cardiac Surgery Center, Greece

[2] Department of Pharmacy, University of Patras, Greece

[3] National School of Public Health, Greece

[4] Centre for Substance Use Research, Scotland, UK

Corresponding author

Konstantinos Farsalinos, MD, MPH

Email: kfarsalinos@gmail.com

Tel: +306977454837

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Introduction

Electronic cigarettes (e-cigarettes) have been marketed in recent years as alternative to smoking products and have rapidly grown in popularity in several countries including the United States (US) [1-3]. Characteristically, they are the most popular smoking cessation aid in the US [4,5]. E-cigarettes consist mainly of a battery and an atomizer where liquid is stored and gets evaporated by energy supplied to an electrical resistance. The liquid contains mainly propylene glycol and glycerol, with the option to include nicotine. A major characteristic of the e-cigarette market is the availability of a variety of flavorings in e-liquids. Besides tobacco-like flavors, the consumer can choose flavors consisting of fruits, sweets, drinks and beverages and many more. This is thought to be a major feature accounting for the appeal of e-cigarettes to adult smokers as an alternative to continuing to smoke cigarettes. An estimated 7700 unique e-liquid flavors were identified in 2014 [6] and it is very likely that the number has further increased in recent years. Evidence from cross-sectional surveys of dedicated e-cigarette users suggests that smokers tend to initiate e-cigarette use with tobacco-flavored e-cigarettes but transition to exclusive or predominant use of non-tobacco flavored products—particularly fruit, sweet, and dessert flavors—with increased frequency and duration of e-cigarette use [3,7,8]. Dedicated e-cigarette users who are also former smokers report that switching between flavors within the same day is common and that regular use of multiple e-liquid flavors was associated with significantly higher odds of having quit smoking, with fruit and sweet flavors being the most popular choices among established long-term vapers [8].

The availability of so many different flavorings has been criticized by authorities stating that there is a potential to attract youngsters. This could potentially habituate youth to the effects of nicotine, and in turn, youth who would otherwise not have smoked in the absence of flavored e-

cigarettes will “graduate” to use of more harmful tobacco products, such as cigarettes, that deliver nicotine more efficiently [9]. Studies have shown that the majority of youth and young adults who have ever tried an e-cigarette started their use with fruit or sweet flavors rather than a tobacco flavor, while rates of use of flavored tobacco products are higher among youth and young adults than among older adults [7,10,11]. To address the public health impact of flavorings in e-cigarette liquids and make appropriate regulatory decisions, the US FDA issued an advance notice of proposed rulemaking (ANPRM) on March 21, 2018, to obtain information related to the role that flavors play in the population’s use of tobacco products. This ANPRM is seeking data, research results, comments, and other information about, among other things, the extent to which certain flavors may attract youth to initiate use of a tobacco product and the extent to which certain flavors may help adult cigarette smokers quit or reduce cigarette use and switch to potentially less harmful products. FDA is seeking this information to inform regulatory actions that FDA might take with respect to flavored tobacco products under the Federal Food, Drug, and Cosmetic Act, as amended by the Tobacco Control Act.

The purpose of this study was to obtain information on patterns of flavored e-cigarette use in a large sample of dedicated adult e-cigarette users residing in the US. The study sample is important since any overly restrictive regulatory decisions (e.g. ban on popular flavors) could have unintended consequences among established adult vapers who may have reduced or quit smoking with the help of e-cigarettes. A recent overview on e-cigarettes reported that their public health impact can be largely identified using the formula [12]:

$$\textit{Public health impact}_{EC} = (\textit{hazard}_{SM\text{-}EC} \times \textit{smoking cessation}) - (\textit{hazard}_{EC} \times \textit{use among non-smokers}) - (\textit{hazard}_{SM} \times \textit{smoking initiation})$$

where EC: electronic cigarette; SM: smoking; SM-EC: difference in hazard between smoking and electronic cigarette use; $hazard_{SM}$: refers to smoking initiation due to e-cigarettes (gateway to smoking effect). The formula identifies the risk reduction in smokers who quit with the help of e-cigarettes as one of the determinants of their public health impact. Therefore, the regulatory framework should consider the balance between protecting population subgroups from unintended (from a public health perspective) use and causing harm to people who use e-cigarettes as smoking substitutes.

Methodology

Study sample and online platform

The study sample consisted of individuals aged 18 and older living in the US who have ever used an e-cigarette (even a single puff). Participants were invited to complete an online questionnaire that was available through Dacima Survey software (Dacima, Montreal, Quebec, Canada). Of note, this tool is FDA 21 CFR Part 11 compliant (http://www.dacimasoftware.com/products/dacima-survey). Before entering the main survey questionnaire, participants had to read an informed consent form and check that they agreed to participate. The informed consent presented the purpose of the survey, the names and contact details of the study investigators, information about who is eligible to take part and how survey data will be used, assurances of participant anonymity and confidentiality. Subsequently, participants were asked if they are permanent residents of the US, their age and if they have ever used an e-cigarette (even once or twice). Participants satisfying the inclusion criteria (adults, permanent residents of the US and having used an e-cigarette) were directed to the main

questionnaire. No financial or other incentive was offered in exchange for participation. The study was approved by the ethics committee of the University of Patras in Greece.

The questionnaire was open for participation from April 3rd to May 2nd, 2018. The survey link was promoted by major US e-cigarette advocacy, consumer and business groups and associations in order to attract US residents who are using e-cigarettes. No personal identifying details were collected, besides the usual demographic information collected in any type of cross-sectional survey (see Results section). The IP address was recorded with the purpose of removing double entries.

Questionnaire design

The questionnaire assessed in detail the past and current smoking status of participants. Participants were defined as current smokers if they were smoking in the past 30 days. Former smokers were defined as people who had ever smoked (even 1 or 2 puffs) but had not smoked in the past 30 days. Never smokers were those who responded that they had never smoked a tobacco cigarette.

All participants were by definition ever e-cigarette users. The patterns of use and reasons for e-cigarette use initiation were recorded. Specifically, the age of e-cigarette use initiation, regular e-cigarette use and daily e-cigarette was recorded. Additionally, participants were asked to report whether they use e-cigarettes at the time of the survey every day, some days or not at all. A specific question among former smokers examined whether they were using e-cigarettes at the time of quitting smoking. This question was considered important to more accurately identify former smokers who had quit smoking with the help of e-cigarettes. Questions about e-cigarette

flavors use were asked in 3 sections addressing 3 different periods: A. At the time of e-cigarette use initiation; B. At the time of survey participation; C. At the time of quitting smoking. The latter was recorded only for former smokers who responded that they were using e-cigarettes at the time of quitting.

Results

Descriptive analysis for all participants

After removing double entries through the IP address, the study sample consisted of 69,233 adult e-cigarette users living in the US. The reported residence state of participants is presented in **Table 1**. Only 0.7% (n = 506) did not report their residence state (missing data). Participant demographics are presented in **Table 2**.

Table 1. Residence state of all participants (n = 69,233).

States	%
Alabama	2.4%
Alaska	0.2%
Arizona	2.4%
Arkansas	1.2%
California	6.4%
Colorado	1.7%
Connecticut	1.0%
Delaware	0.3%
District of Columbia	0.1%
Florida	5.6%
Georgia	3.8%
Hawaii	0.4%
Idaho	0.7%
Illinois	4.0%
Indiana	2.9%
Iowa	1.4%
Kansas	0.9%

Kentucky	2.6%
Louisiana	1.2%
Maine	0.4%
Maryland	1.9%
Massachusetts	1.7%
Michigan	3.1%
Minnesota	1.3%
Mississippi	1.0%
Missouri	2.2%
Montana	0.3%
Nebraska	0.7%
Nevada	1.0%
New Hampshire	0.6%
New Jersey	2.0%
New Mexico	0.5%
New York	4.5%
North Carolina	3.0%
North Dakota	0.2%
Ohio	5.5%
Oklahoma	1.8%
Oregon	1.1%
Pennsylvania	4.5%
Rhode Island	0.3%
South Carolina	1.6%
South Dakota	0.3%
Tennessee	4.5%
Texas	6.7%
Utah	1.1%
Vermont	0.2%
Virginia	2.9%
Washington	2.1%
West Virginia	1.1%
Wisconsin	1.8%
Wyoming	0.3%
Missing (no response)	0.7%

Table 2. Participant demographics (n = 69,233)

	Mean / %
Age	34.6
Gender	
Male	72.4%
Female	26.5%
Marital status	
Married	40.6%
Never married	44.9%
Divorced	11.2%
Separated	2.2%
Widowed	0.9%
Employment status	
Not currently working for pay	16.9%
Full-time working, at least 35h/week	70.8%
Part-time working, 15-34h/week	9.9%
Part-time working, < 15h/week	2.1%
Education	
Less than high school	0.9%
Some high school, no diploma	4.0%
GED	7.6%
High school graduate—diploma	25.3%
Some college but no degree	32.9%
Associate degree—occupational/vocational	9.4%
Associate degree—academic program	5.5%
Bachelor's degree (ex: BA, AB, BS)	10.0%
Master's degree (ex: MA, MS, MEng,Med, MSW)	2.1%
Professional school degree (ex: MD,DDS, DVM, JD)	0.5%
Doctorate degree (ex: PhD, EdD)	0.3%
Currently enrolled in a degree program	
Yes	9.6%
No	85.8%
Household income per 12 months	
Less than $10,000	6.7%
$10,000 to $14,999	6.2%
$15,000 to $24,999	10.9%
$25,000 to $34,999	13.1%
$35,000 to $49,999	15.7%
$50,000 to $74,999	18.3%
$75,000 to $99,999	10.4%
$100,000 to $149,999	8.6%
$150,000 to $199,999	2.5%
$200,000 or more	2.0%

The smoking history of participants is presented in **Table 3**. Almost 95% of participants reported that they were ever smokers. The majority had quit smoking, while 61% of current smokers were occasional smokers (smoking on some days). Only 5.2% of the study sample reported being never smokers. The smoking status of the participants is presented in **Figure 1**. Former smokers who were using e-cigarettes at the time of smoking cessation are presented as a separate bar in **Figure 1**. Almost 92% of former smokers reported that they were using e-cigarettes at the time of quitting.

Table 3. Smoking history and current smoking status of the participants (n = 69,233).

	%	95% CI	N
Ever smoked a cigarette (even 1 or 2 puffs)			
Yes	94.8%	94.6-94.9%	65600
No (1)	5.2%	5.0-5.4%	3633
Established smokers (smoked > 100 cigarettes)	81.6%	81.3-81.9%	56469
Current (past 30-day) smokers	13.4%	13.1-13.7%	9300
Now smoking (2)			
Every day	1.9%	1.8-2.0%	1335
Some days	8.2%	8.0-8.4%	5685
Not at all	3.3%	3.2-3.4%	2280
Former smokers (3)	81.3%	81.0-81.6%	56300
Quit time for former smokers			
Within past 12 months	13.1%	12.8-13.4%	9056
More than 12 months ago	68.2%	67.9-68.5%	47244

(1) Classified as never smokers.
(2) Responders were current (past 30-day) smokers.
(3) Former smokers were defined as ever smokers (even 1 or 2 puffs) who are not current (past 30-day) smokers.

Figure 1. Smoking status of the study participants (n = 69,233).

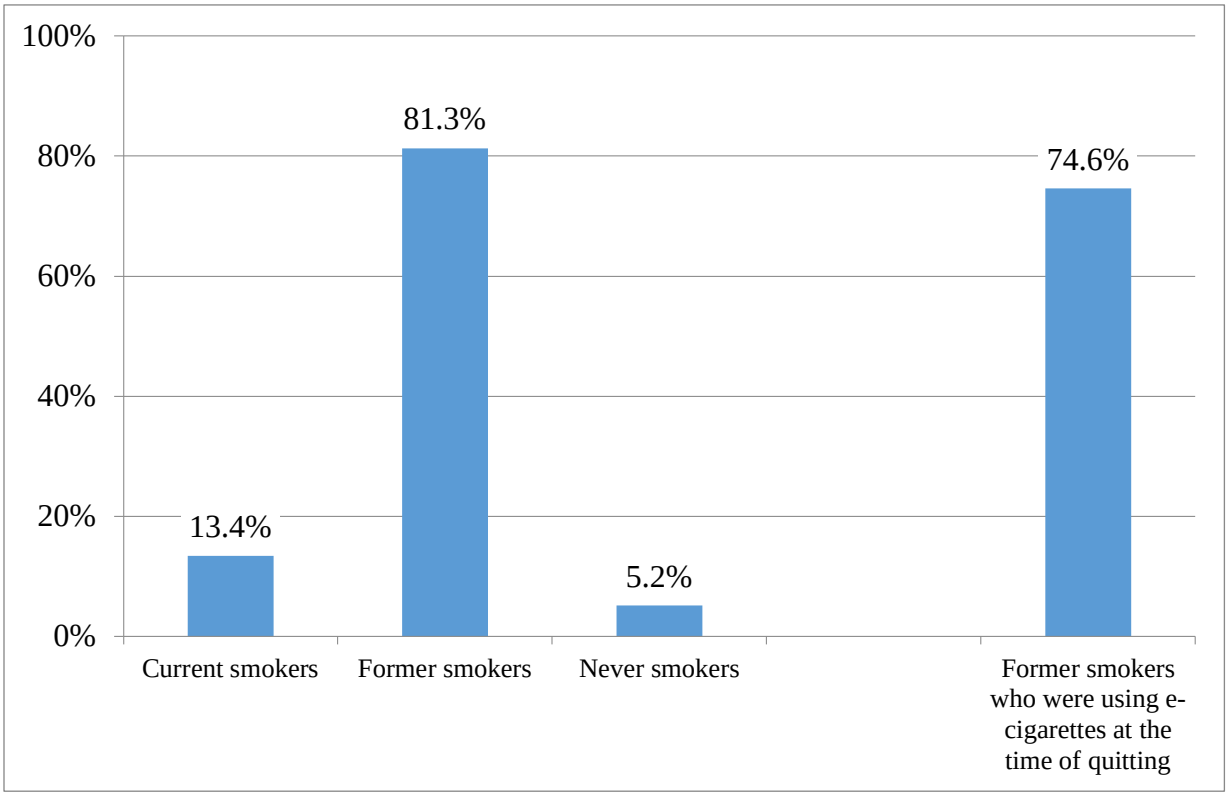


Table 4 presents the e-cigarette use characteristics and reasons for e-cigarette use initiation. The average age of e-cigarette use initiation was approximately 30 years. The vast majority of participants (almost 99%) were using e-cigarettes in the past 30 days, with most using them every day. The main reasons for initiating e-cigarette use were to quit smoking, because e-cigarettes might be less harmful than smoking for themselves or for people around them. Of note, a substantial proportion of participants responded that flavors were also a reason to initiate e-cigarette use. It should be mentioned that the question was not formatted in a way to examine the importance of each reason and responders could choose all options that were applicable to them.

Table 4. E-cigarette use characteristics and reasons for e-cigarette use initiation (n = 69,233).

	Mean or %	SD or 95% CI	N
Age of first time e-cigarette use	30.3	11.2	69233
Ever used e-cigarettes fairly regularly	99.1%	99.0-99.2%	68589
Age of regular e-cigarette use	31.2	11.1	68589
E-cigarette use in past 30-days (even 1 or 2 puffs)	98.9%	98.8-99.0%	68473
Now use e-cigarettes			
Every day	93.5%	93.3-93.7%	64754
Some days	5.2%	5.0-5.4%	3575
Not at all	0.2%	0.2-0.2%	144
Age of everyday e-cigarette use	31.5	13.7	64754
Reasons for initiating e-cigarette use			
To help me quit smoking	89.2%	89.0-89.4%	61784
To help me cut down smoking but not quit completely	21.6%	21.3-21.9%	14969
To use in places where smoking is prohibited	23.6%	23.3-23.9%	16321
Because e-cigarettes might be less harmful to me than smoking	86.9%	86.6-87.2%	60129
Because e-cigarettes might be less harmful to people around me than smoking	83.6%	83.3-83.9%	57888
E-cigarettes have flavors I like	78.4%	78.1-78.7%	54254
Vapor from e-cigarettes smells better than cigarette smoke	85.7%	85.4-86.0%	59336
To save money compared to smoking	73.0%	72.7-73.3%	50552
People in media or public figures use e cigarettes	7.8%	7.6-8.0%	5416
I was told using e-cigarettes feels like smoking	15.8%	15.5-16.1%	10935
Using e-cigarettes is more acceptable to non smokers	33.9%	33.5-34.3%	23504
People important to me were using e-cigarettes	21.6%	21.3-21.9%	14960
To use while socializing	18.5%	18.2-18.8%	12817
The advertising for e-cigarettes was appealing to me	7.5%	7.3-7.7%	5201
I was curious to try an e-cigarette	45.8%	45.4-46.2%	31695
I read information about the health benefits of switching from smoking to e-cigarette use	60.2%	59.8-60.6%	41705
People told me using e-cigarettes helped them quit smoking	77.7%	77.4-78.0%	53819
A health professional advised me to switch from smoking	23.5%	23.2-23.8%	16267
I liked than e-cigarettes came with a variety of flavors	83.6%	83.3-83.9%	57879
Someone who uses e-cigarettes recommended I buy one	52.1%	51.7-52.5%	36082
I liked the look of e-cigarettes	28.1%	27.8-28.4%	19445
I read good reviews online about e-cigarette products	47.1%	46.7-47.5%	32596

E-cigarettes looked easy to use	42.0%	41.6-42.4%	29087

Table 5 presents the e-cigarette equipment and flavors used by the participants at e-cigarette use initiation. Most participants initiated e-cigarette use with advanced devices (variable voltage/wattage) or eGO-style batteries. A small minority used first generation (cigarette-like, "ciga-like") devices. The most popular nicotine concentration at initiation was 1-6 mg/mL followed by 18-24 mg/mL. For most participants, it was easy to find the flavors of preference at e-cigarette use initiation, which is expected considering the unrestricted large variability available until now. Participants were asked to report all different flavors that they were using regularly, but they were also subsequently asked to report the single most regularly used flavor. The most popular flavors were fruit and dessert/pastry/bakery, while only approximately 20% reported using tobacco flavors. Similarly, fruit and dessert/pastry/bakery were the most popular single flavors used most often at e-cigarette use initiation.

Table 5. E-cigarette equipment and flavors use at e-cigarette use initiation (n = 69,233).

	%	**95% CI**	**N**
First device used			
Disposable	8.1%	7.8-8.3%	5635
Rechargeable ciga-like with prefilled cartridges	17.5%	17.2-17.8%	12135
eGo-style	32.5%	32.2-32.8%	22477
Pod mod	1.2%	1.1-1.3%	811
Mechanical device	3.7%	3.6-3.8%	2544
Variable voltage/wattage (advanced personal vaporizer)	35.6%	35.2-36.0%	24657
Something else	1.4%	1.3-1.5%	974
Initial nicotine concentration			
0 mg/mL	4.1%	4.0-4.2%	2827
1-6 mg/mL	38.1%	37.7-38.5%	26411
7-12 mg/mL	17.5%	17.2-17.8%	12117

13-17 mg/mL	4.5%	4.3-4.7%	3083
18-24 mg/mL	26.1%	25.8-26.4%	18088
25-49 mg/mL	3.3%	3.2-3.4%	2294
50 mg/mL or more	0.6%	0.5-0.7%	402
How difficult was it to find the flavor you like at e-cigarette use initiation?			
Very difficult	3.1%	3.0-3.2%	2133
Difficult	9.9%	9.7-10.1%	6836
Neither easy nor difficult	21.8%	21.5-22.1%	15078
Easy	27.1%	26.8-27.4%	18742
Very easy	38.2%	37.8-38.6%	26444
Flavors choices (used regularly) at e-cigarette use initiation			
Tobacco	20.8%	20.5-21.1%	14373
Menthol	21.9%	21.6-22.2%	15133
Mint/wintergreen	13.8%	13.5-14.1%	9581
Fruit	82.8%	82.5-83.1%	57320
Dessert/pastry/bakery	68.6%	68.3-68.9%	47509
Candy/chocolate/sweet	52.2%	51.8-52.6%	36160
Spice	12.5%	12.2-12.7%	8659
Coffee	26.4%	26.1-26.7%	18306
Alcohol/cocktail	7.5%	7.3-7.7%	5211
Non alcoholic/non coffee drink	18.7%	18.4-19.0%	12980
Unflavored	1.0%	0.9-1.1%	715
Other	17.3%	17.0-17.6%	12006
Single flavor most often used at e-cigarette use initiation			
Tobacco	7.7%	7.5-7.9%	5301
Menthol	6.3%	6.1-6.5%	4382
Mint/wintergreen	1.9%	1.8-2.0%	1306
Fruit	48.5%	48.1-48.9%	33574
Dessert/pastry/bakery	25.8%	25.5-26.1%	17872
Candy/chocolate/sweet	4.1%	39.5-42.5%	2823
Spice	1.0%	0.9-1.1%	726
Coffee	2.3%	2.2-2.4%	1570
Alcohol/cocktail	0.3%	0.3-0.3%	220
Non alcoholic/non coffee drink	1.1%	1.0-1.2%	779
Unflavored	0.1%	0.1-0.1%	89
Other	0.9%	0.8-1.0%	591

Table 6 presents the e-cigarette equipment and flavors used by the participants at the time of survey participation. The patterns were for the most part similar to the data at e-cigarette use initiation. Even more participants were using advanced devices (variable voltage/wattage) at the

time of survey participation. Use of disposable or rechargeable first generation devices was rare. By far the most popular nicotine concentration at initiation was 1-6 mg/mL, which is compatible with the well-documented gradual transition to lower nicotine concentration over time. The most popular flavors were again fruit and dessert/pastry/bakery. Use of tobacco flavors was less prevalent compared to e-cigarette use initiation, which has also been documented in other surveys. In fact, only 2% of participants reported that the single most often used flavor at the time of survey participation was a tobacco flavor. Many participants reported using multiple flavors within the same day.

Table 6. E-cigarette equipment and flavors use at the time of survey participation (n = 69,233).

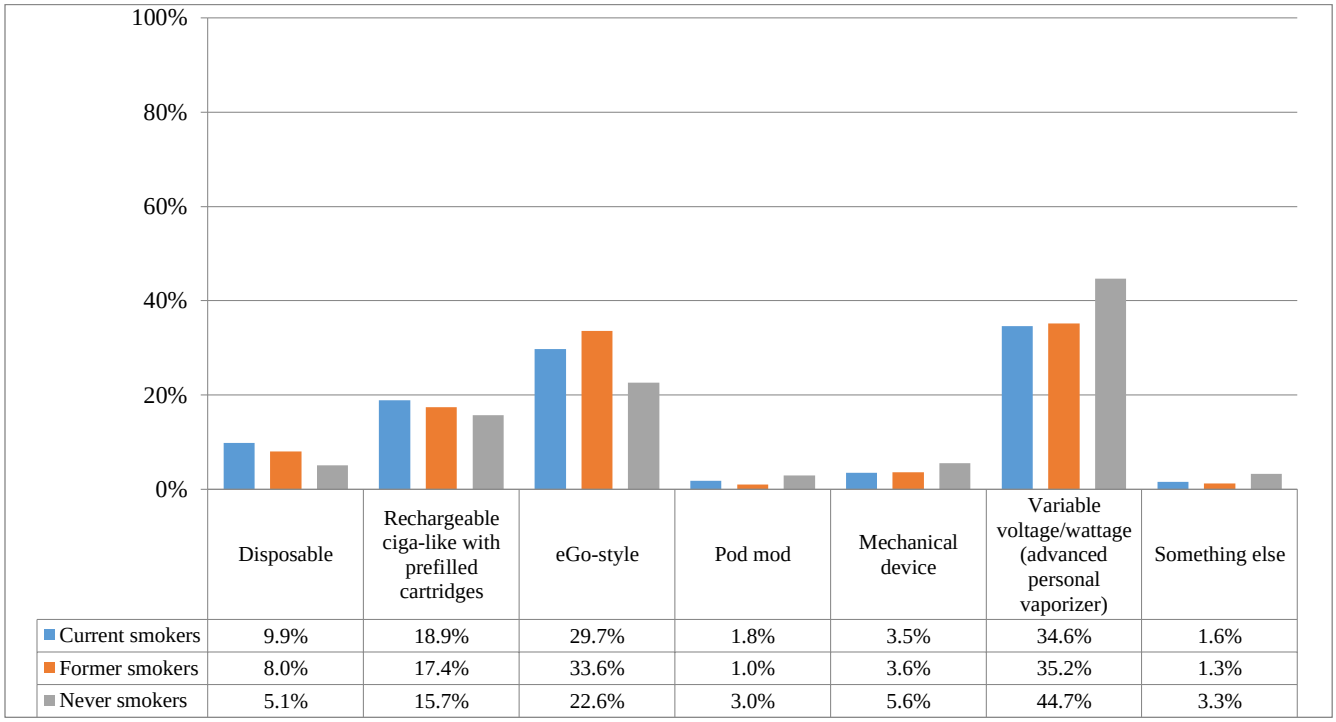
	%	95% CI	N
Device used now			
Disposable	0.2%	0.2-0.2%	155
Rechargeable ciga-like with prefilled cartridges	3.1%	3.0-3.2%	2179
eGo-style	3.5%	3.4-3.6%	2409
Pod mod	3.0%	2.9-3.1%	2059
Mechanical device	10.7%	10.5-10.9%	7388
Variable voltage/wattage (advanced personal vaporizer)	76.7%	76.4-77.0%	53128
Something else	1.5%	1.4-1.6%	1011
Nicotine concentration now			
0 mg/mL	6.2%	6.0-6.4%	4258
1-6 mg/mL	82.4%	82.1-82.7%	57057
7-12 mg/mL	4.7%	4.5-4.9%	3238
13-17 mg/mL	0.8%	0.7-0.9%	561
18-24 mg/mL	1.7%	1.6-1.8%	1172
25-49 mg/mL	1.3%	1.2-1.4%	928
50 mg/mL or more	1.1%	1.0-1.2%	762
Flavors choices (used regularly) now			
Tobacco	7.8%	7.6-8.0%	5395
Menthol	13.3%	13.0-13.6%	9217
Mint/wintergreen	9.6%	9.4-9.8%	6616
Fruit	83.0%	82.7-83.3%	57447
Dessert/pastry/bakery	70.5%	70.2-70.8%	48823

Candy/chocolate/sweet	46.3%	45.9-46.7%	32064
Spice	9.2%	9.0-9.4%	6394
Coffee	19.3%	19.0-19.6%	13385
Alcohol/cocktail	6.9%	6.7-7.1%	4746
Non alcoholic/non coffee drink	13.5%	13.2-13.8%	9368
Unflavored	0.9%	0.8-1.0%	630
Other	11.5%	11.2-11.7%	7945
Single flavor used most often now			
Tobacco	2.1%	2.0-2.2%	1481
Menthol	2.5%	2.4-2.6%	1734
Mint/wintergreen	1.2%	1.1-1.3%	862
Fruit	49.0%	48.6-49.4%	33893
Dessert/pastry/bakery	35.3%	34.9-35.7%	24436
Candy/chocolate/sweet	4.4%	4.2-4.6%	3062
Spice	0.6%	0.5-0.7%	389
Coffee	1.3%	1.2-1.4%	903
Alcohol/cocktail	0.3%	0.3-0.3%	206
Non alcoholic/non coffee drink	0.8%	0.7-0.9%	552
Unflavored	0.2%	0.2-0.2%	131
Other	1.0%	0.9-1.1%	680
Frequency of using different flavors			
Use multiple flavors in the same day	42.0%	41.6-42.4%	29112
Change flavors every 2-3 days	21.1%	20.8-21.4%	14574
Change flavors every 4-5 days	6.7%	6.5-6.9%	4642
Change flavors every week	9.4%	9.2-9.6%	6474
Change flavors every 2 weeks	8.2%	8.0-8.4%	5701
Change flavors every month	11.3%	11.1-11.5%	7826

Comparison between current, former and never smokers

Device choice and flavors preference was analyzed according to the smoking status of the participants at the time of survey participation. Cross-tabulations and chi-square tests were used in the comparison. **Figure 2** shows the device choice at e-cigarette use initiation. Small but statistically significant differences were found between groups.

Figure 2. Choice of device at e-cigarette use initiation among current smokers, former smokers and never smokers (n = 69,233).

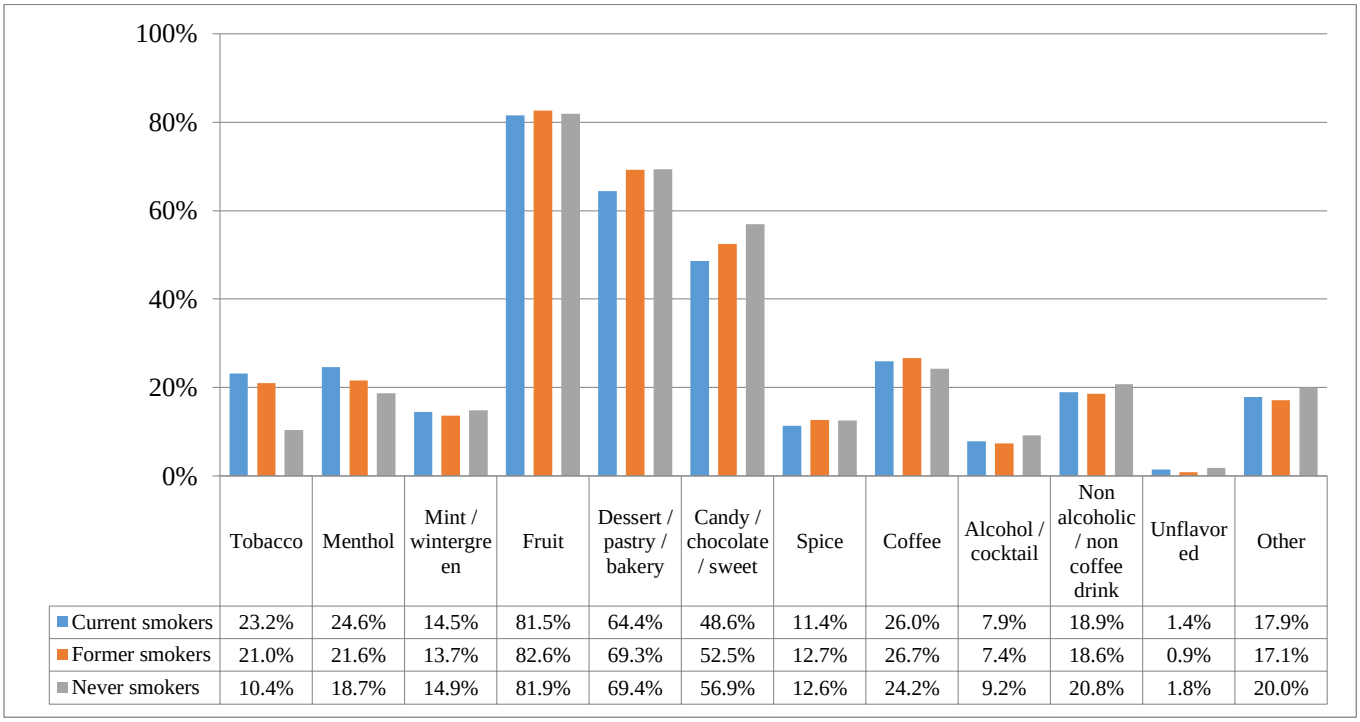


	Disposable	Rechargeable ciga-like with prefilled cartridges	eGo-style	Pod mod	Mechanical device	Variable voltage/wattage (advanced personal vaporizer)	Something else
Current smokers	9.9%	18.9%	29.7%	1.8%	3.5%	34.6%	1.6%
Former smokers	8.0%	17.4%	33.6%	1.0%	3.6%	35.2%	1.3%
Never smokers	5.1%	15.7%	22.6%	3.0%	5.6%	44.7%	3.3%

Advanced devices (variable voltage/wattage) were the most popular option for all groups, followed by eGo-style devices. Never smokers were more likely than former and current smokers to initiate e-cigarette use with advanced devices, while former smokers were more likely than current and never smokers to initiate with eGo-style devices.

Figure 3 presents the choice of flavors at e-cigarette use initiation according to the smoking status at the time of survey participation. For all groups, fruit flavors were the most popular, followed by dessert/pastry/bakery and candy/chocolate/sweet flavors. Never smokers were statistically more likely to choose these flavors at e-cigarette use initiation, but the differences were small.

Figure 3. Choice of flavors at e-cigarette use initiation among current smokers, former smokers and never smokers (n = 69,233).

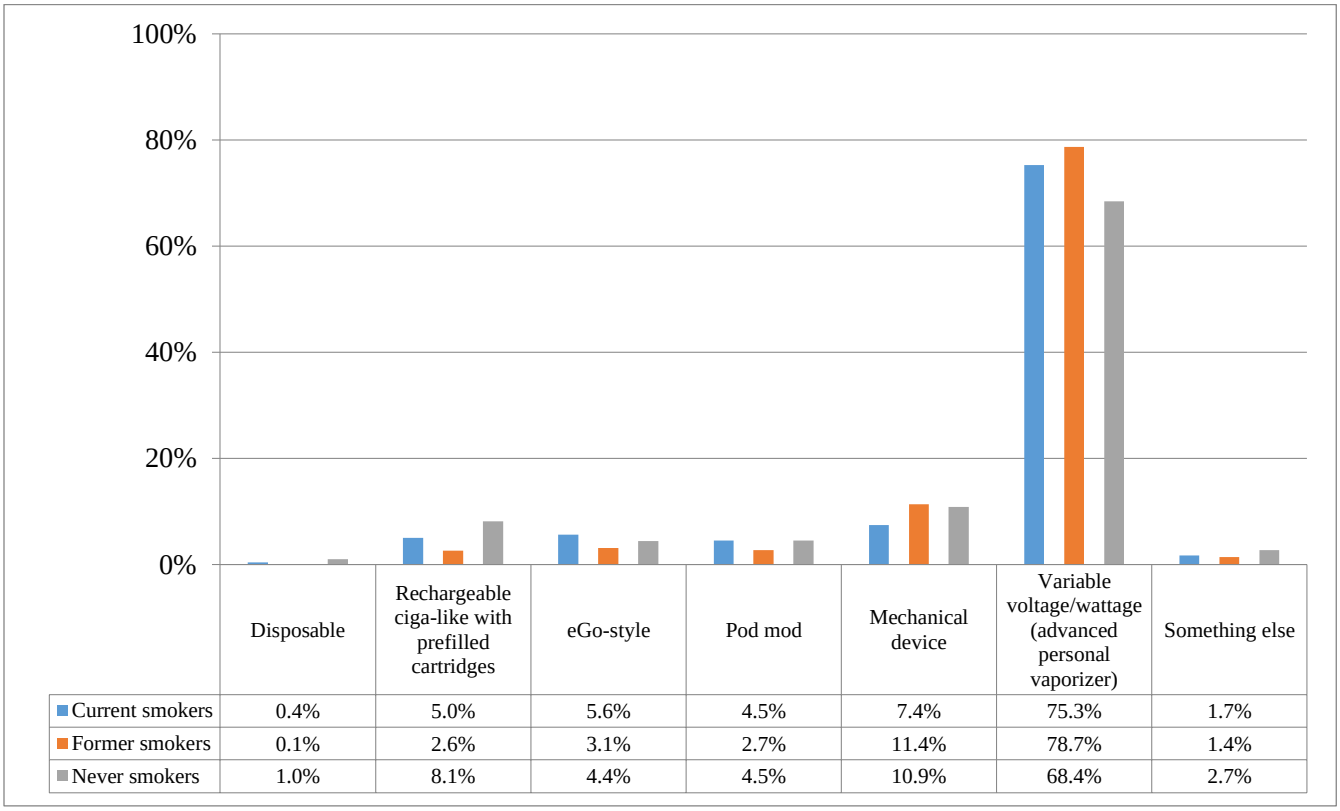


	Tobacco	Menthol	Mint / wintergreen	Fruit	Dessert / pastry / bakery	Candy / chocolate / sweet	Spice	Coffee	Alcohol / cocktail	Non alcoholic / non coffee drink	Unflavored	Other
Current smokers	23.2%	24.6%	14.5%	81.5%	64.4%	48.6%	11.4%	26.0%	7.9%	18.9%	1.4%	17.9%
Former smokers	21.0%	21.6%	13.7%	82.6%	69.3%	52.5%	12.7%	26.7%	7.4%	18.6%	0.9%	17.1%
Never smokers	10.4%	18.7%	14.9%	81.9%	69.4%	56.9%	12.6%	24.2%	9.2%	20.8%	1.8%	20.0%

Tobacco flavors were more prevalent among current compared to former and never smokers, and were least prevalent among never smokers.

Figure 4 shows the device choice at the time of survey participation according to the smoking status. Small but statistically significant differences were found between groups. Advanced devices were by far the more popular overall, but were statistically less prevalent among never compared to former and current smokers. Disposables or rechargeable ciga-like devices were rarely used at the time of survey participation.

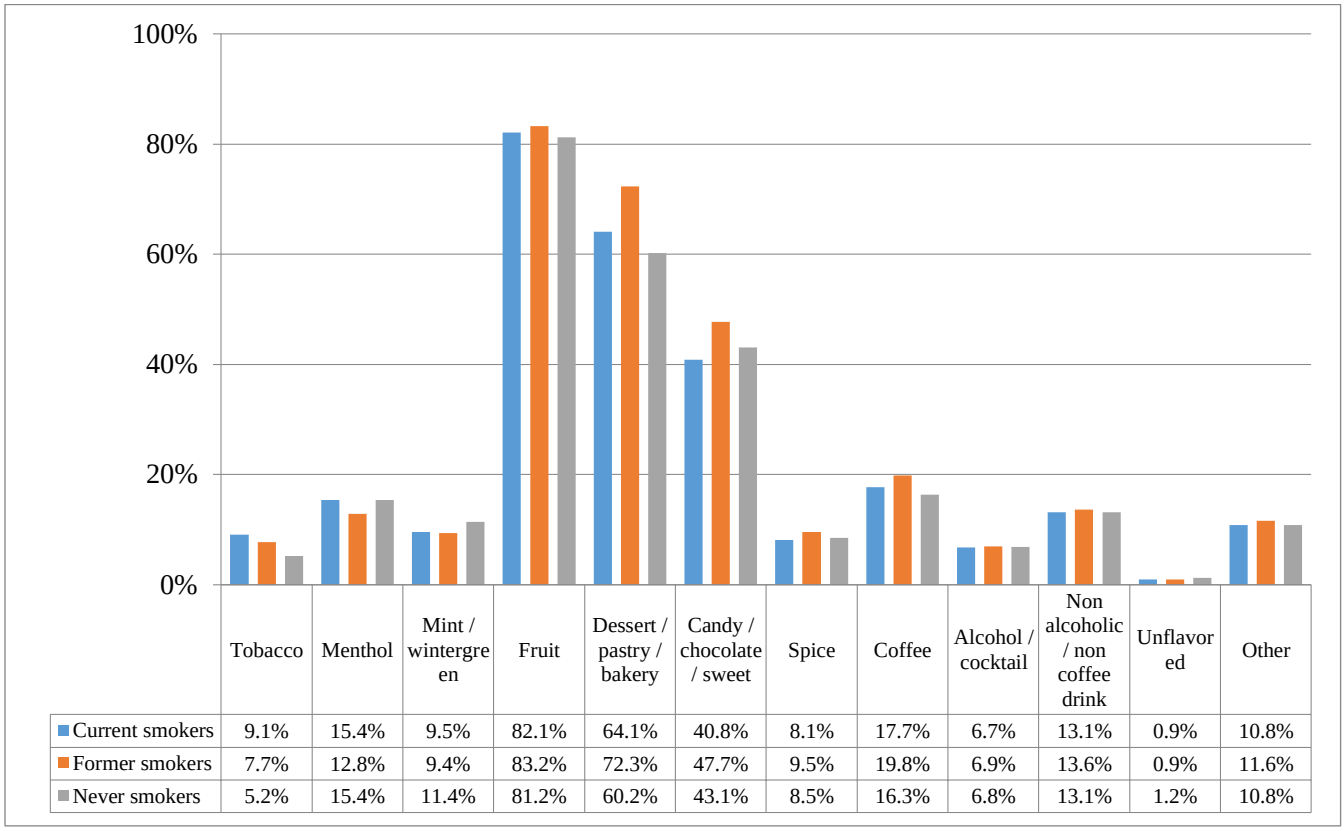
Figure 4. Choice of device at the time of survey participation among current smokers, former smokers and never smokers (n = 69,233).



	Disposable	Rechargeable ciga-like with prefilled cartridges	eGo-style	Pod mod	Mechanical device	Variable voltage/wattage (advanced personal vaporizer)	Something else
Current smokers	0.4%	5.0%	5.6%	4.5%	7.4%	75.3%	1.7%
Former smokers	0.1%	2.6%	3.1%	2.7%	11.4%	78.7%	1.4%
Never smokers	1.0%	8.1%	4.4%	4.5%	10.9%	68.4%	2.7%

Figure 5 presents the choice of flavors at the time of survey participation according to the smoking status at the time of survey participation. Again, fruit flavors were the most popular, followed by dessert/pastry/bakery and candy/chocolate/sweet flavors. Tobacco flavors prevalence was substantially lower compared to the period of e-cigarette use initiation for all groups. Dessert/pastry/bakery and candy/chocolate/sweet flavors were more prevalent among former compared to current and never smokers.

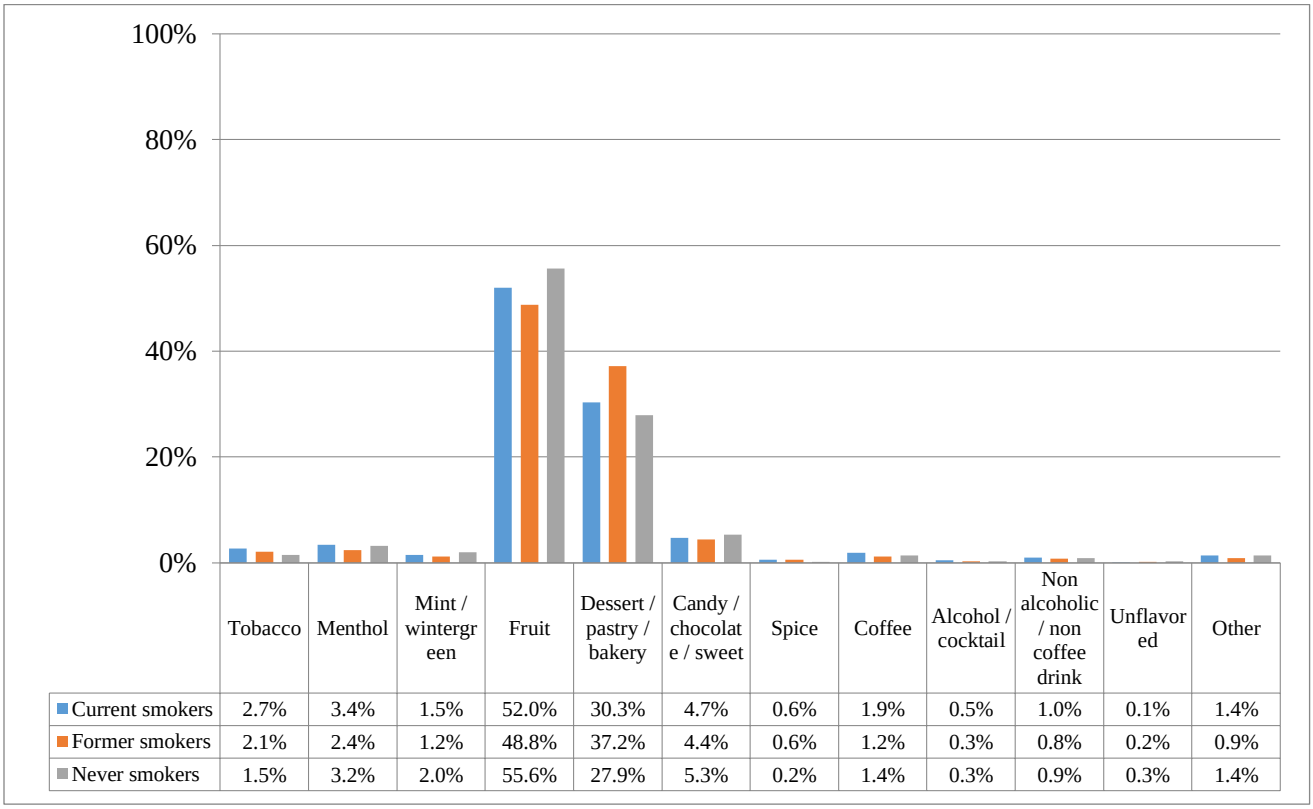
Figure 5. Choice of flavors at the time of survey participation among current smokers, former smokers and never smokers (n = 69,233).



	Tobacco	Menthol	Mint / wintergreen	Fruit	Dessert / pastry / bakery	Candy / chocolate / sweet	Spice	Coffee	Alcohol / cocktail	Non alcoholic / non coffee drink	Unflavored	Other
Current smokers	9.1%	15.4%	9.5%	82.1%	64.1%	40.8%	8.1%	17.7%	6.7%	13.1%	0.9%	10.8%
Former smokers	7.7%	12.8%	9.4%	83.2%	72.3%	47.7%	9.5%	19.8%	6.9%	13.6%	0.9%	11.6%
Never smokers	5.2%	15.4%	11.4%	81.2%	60.2%	43.1%	8.5%	16.3%	6.8%	13.1%	1.2%	10.8%

Figure 6 presents the choice of the one most often used flavor at the time of survey participation according to the smoking status at the time of survey participation. Fruit flavors were the most popular, followed by dessert/pastry/bakery. Minimal use of tobacco flavors was observed in all groups.

Figure 6. Choice of the one flavor most often used at the time of survey participation among current smokers, former smokers and never smokers (n = 69233).



	Tobacco	Menthol	Mint / wintergreen	Fruit	Dessert / pastry / bakery	Candy / chocolate / sweet	Spice	Coffee	Alcohol / cocktail	Non alcoholic / non coffee drink	Unflavored	Other
Current smokers	2.7%	3.4%	1.5%	52.0%	30.3%	4.7%	0.6%	1.9%	0.5%	1.0%	0.1%	1.4%
Former smokers	2.1%	2.4%	1.2%	48.8%	37.2%	4.4%	0.6%	1.2%	0.3%	0.8%	0.2%	0.9%
Never smokers	1.5%	3.2%	2.0%	55.6%	27.9%	5.3%	0.2%	1.4%	0.3%	0.9%	0.3%	1.4%

Former smokers who were using e-cigarettes at the time of quitting

A sub-analysis of the survey focused on former smokers who were using e-cigarettes at the time of smoking cessation. They represented 74.6% of the study sample (n = 51,641, **Figure 1**).

Table 7 presents the e-cigarette use patterns, equipment and flavors used by this subgroup of study participants at the time of quitting smoking. From all former smokers, 8.3% reported that they were not using e-cigarettes at the time of quitting; they were excluded from the present

analysis. The vast majority of the former smokers analyzed reported that they would definitely or probably still be smoking today if they had never started using e-cigarettes. The majority were using advanced e-cigarette devices. The most popular nicotine concentration at the time of quitting was 1-6 mg/mL, followed by 18-24 mg/mL. The vast majority considered finding the flavor of preference as an extremely or very important factor in their attempt to quit smoking. The most popular flavor choices at the time of quitting smoking were fruit flavors, followed by dessert/pastry/bakery. Only 15% of participants were using tobacco flavors. Fruit and dessert/pastry/bakery were also the most prevalent choices that were particularly helpful for quitting smoking and to avoid relapse to smoking.

Table 7. E-cigarette use patterns, equipment and flavors use by former smokers at the time of quitting smoking (n = 51,641).

	%	95% CI	N
At the time of quitting smoking, were you using e-cigarettes: (1)			
Every day	85.1%	84.8-85.4%	47933
Some days	6.6%	6.4-6.8%	3708
Not at all (2)	8.3%	8.1-8.5%	4659
If you had never started using e-cigarettes, would you still be smoking today?			
Definitely yes	72.2%	71.8-72.6%	37265
Probably yes	23.9%	23.5-24.3%	12359
Probably no	1.7%	1.6-1.8%	881
Definitely no	2.2%	2.1-2.3%	1136
Device used at time of quitting smoking			
Disposable	1.9%	1.8-2.0%	1005
Rechargeable ciga-like with prefilled cartridges	9.8%	9.5-10.1%	5044
eGo-style	26.8%	26.4-27.2%	13827
Pod mod	1.2%	1.1-1.3%	625
Mechanical device	5.2%	5.0-5.4%	2666
Variable voltage/wattage (advanced personal vaporizer)	54.4%	54.0-54.8%	28081
Something else	0.8%	0.7-0.9%	393
Nicotine concentration at time of quitting smoking			

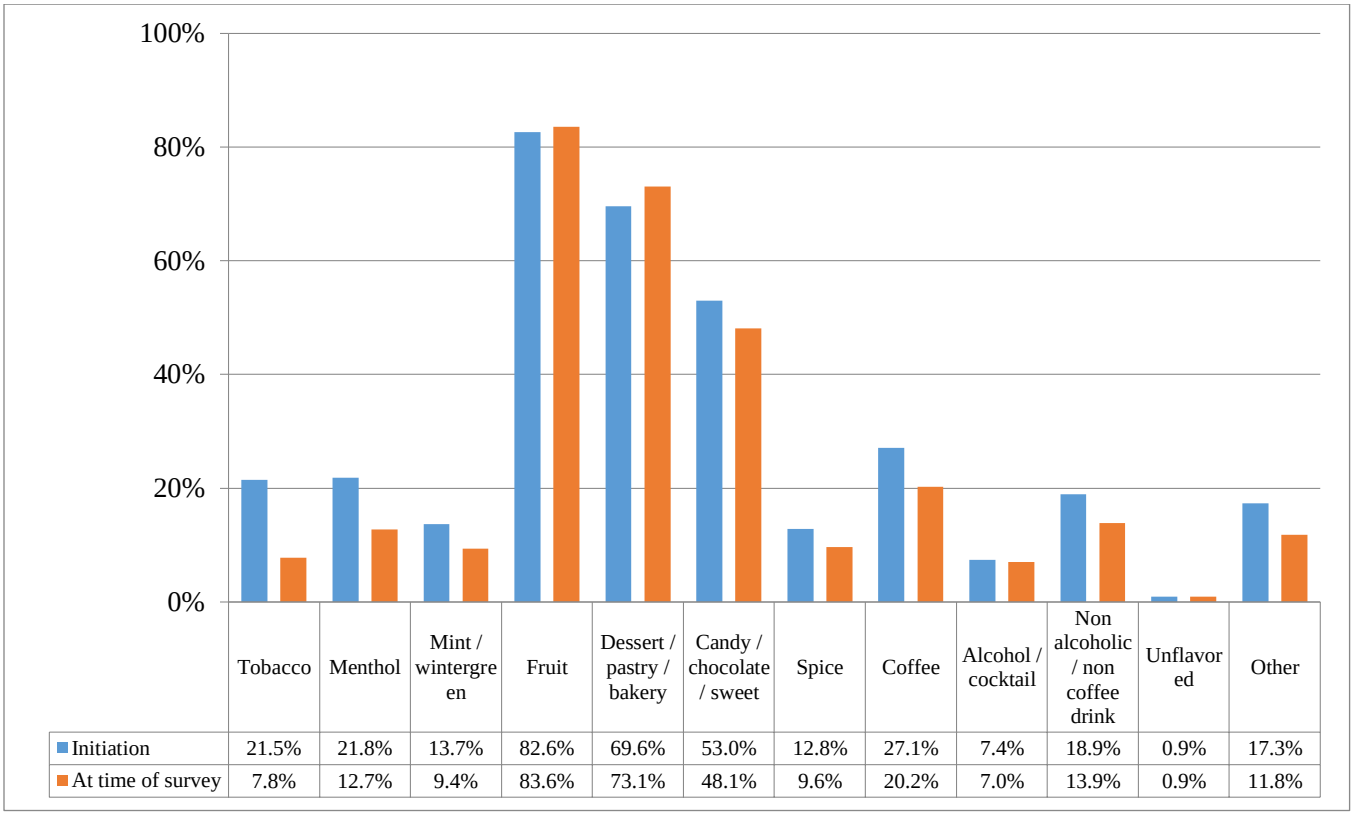
0 mg/mL	1.5%	1.4-1.6%	798
1-6 mg/mL	46.9%	46.5-47.3%	24220
7-12 mg/mL	19.3%	19.0-19.6%	9973
13-17 mg/mL	4.2%	4.0-4.4%	2161
18-24 mg/mL	23.1%	22.7-23.5%	11927
25-49 mg/mL	2.7%	2.6-2.8%	1418
50 mg/mL or more	0.7%	0.6-0.8%	365
How important was finding an e-cigarette/e-liquid flavor you liked in your attempt to quit smoking?			
Extremely important	69.7%	69.3-70.1%	35979
Very important	17.6%	17.3-17.9%	9070
Important	8.7%	8.5-8.9%	4508
Slightly important	3.1%	3.0-3.2%	1579
Not important	1.0%	0.9-1.1%	505
Flavors choices (used regularly) at time of quitting smoking			
Tobacco	15.0%	14.7-15.3%	7763
Menthol	18.2%	17.9-18.5%	9394
Mint/wintergreen	11.5%	11.2-11.8%	5934
Fruit	83.3%	83.0-83.6%	43012
Dessert/pastry/bakery	68.0%	67.6-68.4%	35106
Candy/chocolate/sweet	44.5%	44.1-44.9%	22986
Spice	9.6%	9.3-9.9%	4951
Coffee	19.9%	19.6-20.2%	10298
Alcohol/cocktail	5.9%	5.7-6.1%	3050
Non alcoholic/non coffee drink	13.1%	12.8-13.4%	6766
Unflavored	0.7%	0.6-0.8%	349
Other	9.2%	9.0-9.4%	4761
Single flavor used most often at time of quitting smoking			
Tobacco	5.1%	4.9-5.3%	2617
Menthol	4.7%	4.5-4.9%	2430
Mint/wintergreen	1.6%	1.5-1.7%	841
Fruit	49.3%	48.9-49.7%	25483
Dessert/pastry/bakery	30.3%	29.9-30.7%	15657
Candy/chocolate/sweet	4.1%	3.9-4.3%	2105
Spice	1.1%	1.0-1.2%	593
Coffee	1.8%	1.7-1.9%	953
Alcohol/cocktail	0.3%	0.3-0.3%	142
Non alcoholic/non coffee drink	0.9%	0.8-1.0%	476
Unflavored	0.1%	0.1-0.1%	40
Other	0.6%	0.5-0.7%	304
Flavors choices that were particularly helpful for quitting smoking			
Tobacco	9.3%	9.0-9.6%	4813
Menthol	11.7%	11.4-12.0%	6020
Mint/wintergreen	7.4%	7.2-7.6%	3820
Fruit	60.8%	60.4-61.2%	31393
Dessert/pastry/bakery	48.9%	48.5-49.3%	25277

Candy/chocolate/sweet	29.7%	29.3-30.1%	15327
Spice	7.1%	6.9-7.3%	3649
Coffee	13.9%	13.6-14.2%	7201
Alcohol/cocktail	4.7%	4.5-4.9%	2438
Non alcoholic/non coffee drink	9.6%	9.3-9.9%	4943
Unflavored	0.5%	0.4-0.6%	264
Other	8.0%	7.8-8.3%	4130
Flavors choices that were particularly helpful to avoid relapse to smoking			
Tobacco	7.3%	7.1-7.5%	3792
Menthol	11.5%	11.2-11.8%	5925
Mint/wintergreen	8.8%	8.6-9.0%	4525
Fruit	72.1%	71.7-72.5%	37244
Dessert/pastry/bakery	61.9%	61.5-62.3%	31958
Candy/chocolate/sweet	40.6%	40.2--41.0%	20981
Spice	9.2%	9.0-9.4%	4735
Coffee	19.1%	18.8-19.4%	9857
Alcohol/cocktail	6.6%	6.4-6.8%	3425
Non alcoholic/non coffee drink	12.9%	12.6-13.2%	6641
Unflavored	0.7%	0.6-0.8%	363
Other	9.3%	9.0-9.6%	4816

(1) Data on participants who were using e-cigarettes every day or on some days when quitting smoking are presented in the rest of the table.
(2) These participants were excluded from the rest of the analysis in the present table.

Figure 7 presents the transitions in flavors choice from e-cigarette use initiation to the time of survey participation by former smokers who were using e-cigarettes at the time of quitting smoking. Small increase in prevalence of fruit and dessert/pastry/bakery use was observed over time, as well as a substantial decrease in the use of tobacco flavors. As shown in the table above, fruit, dessert/pastry/bakery and candy/chocolate/sweet were the most prevalent flavors used by this subgroup of participants.

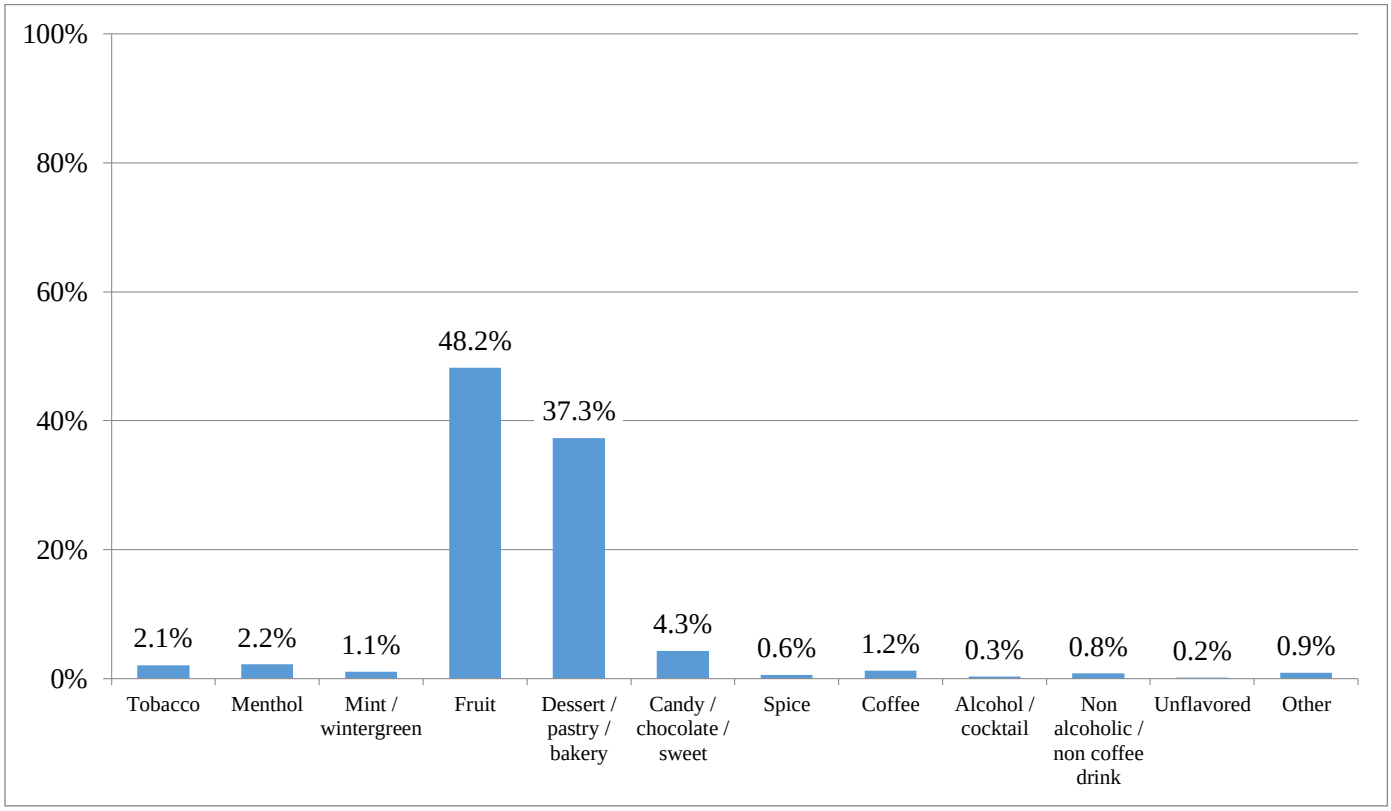
Figure 7. Transitions in flavors choice from e-cigarette use initiation to the time of survey participation by former smokers who were using e-cigarettes at the time of quitting smoking (n = 51,641).



	Tobacco	Menthol	Mint / wintergreen	Fruit	Dessert / pastry / bakery	Candy / chocolate / sweet	Spice	Coffee	Alcohol / cocktail	Non alcoholic / non coffee drink	Unflavored	Other
Initiation	21.5%	21.8%	13.7%	82.6%	69.6%	53.0%	12.8%	27.1%	7.4%	18.9%	0.9%	17.3%
At time of survey	7.8%	12.7%	9.4%	83.6%	73.1%	48.1%	9.6%	20.2%	7.0%	13.9%	0.9%	11.8%

Figure 8 shows the one flavor most often used at the time of survey participation by former smokers who were using e-cigarettes at the time of quitting smoking. Again, fruit flavors were the most popular, followed by dessert/pastry/bakery. Use of tobacco flavors was rare.

Figure 8. Choice of the one flavor most often used at the time of survey participation by former smokers who were using e-cigarettes at the time of quitting smoking (n = 51,641).



Discussion

This is by far the largest survey ever performed on e-cigarette use in terms of sample size, with almost 70,000 participants. The main findings of the study are that non-tobacco flavors, especially fruit and dessert/pastry/bakery flavors, are the most prevalent choices of the adult established, dedicated US e-cigarette users who participated to this study. They are particularly popular not only during long-term e-cigarette use but also at the period of e-cigarette use initiation. Additionally, these flavors are very popular among former smokers who were using e-

cigarettes at the time of smoking cessation. Fruit and dessert/pastry/bakery flavors were also considered particularly important in their effort to quit smoking and to prevent relapse to smoking. Tobacco flavors are generally used by a minority of the study participants, and their use prevalence decreased substantially over time. The patterns of e-cigarette flavors use observed herein are in agreement with a recent cross-sectional study examining the responses of more than 20,000 participants from the US [13]. Since the regulation on e-cigarette flavors should consider the balance between protecting from unintended use (e.g. by adolescents or never smokers) and avoiding adverse effects and potential harm (e.g. by preventing smokers from switching to e-cigarettes in a harm reduction approach to quitting smoking), we hope the FDA will find the data presented in this study useful in preparing the appropriate regulatory framework. The data raise the possibility that an overly-restrictive regulation, such as banning the sales of specific flavor groups (especially fruit and dessert/pastry/bakery flavors), might prevent smokers from switching to e-cigarette use or may increase the relapse rate among former smokers who have managed to quit with the help of e-cigarettes.

A major limitation of the study is the cross-sectional design and the recruitment of a convenience sample of dedicated e-cigarette users. The sample is not representative of the general US adult population and the study was not designed or intended to estimate the prevalence or frequency of e-cigarette flavors use. The flavor preferences and patterns of e-cigarette use reported by the present sample of dedicated e-cigarette users may more closely represent those of the 21.3% of current e-cigarette users in the USA who use e-cigarettes daily and not the majority who are infrequent users or experimenters [14]. Still, this survey presents the patterns of use of a very large sample of adult US e-cigarette users, most of which self-reported that they were successful in quitting smoking with the help of e-cigarettes. While flavors seem to play an important role in

their smoking cessation attempt, it should be mentioned that other characteristics, such as the more prevalent use of advanced e-cigarette devices compared to ciga-likes, may also contribute to a successful quit attempt.

In conclusion, this cross-sectional study of a very large sample of adult US e-cigarette users, most of which were former smokers, identified the importance of non-tobacco flavors in e-cigarette use initiation and sustained use, and their contribution to smoking cessation and relapse prevention. This information should be considered by regulators in order to avoid unintentional adverse effects of over-restrictive regulation on e-cigarette flavors.

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Public Health England

Electronic cigarettes

A report commissioned by Public Health England

Authors: Professor John Britton and Dr Ilze Bogdanovica
UK Centre for Tobacco and Alcohol Studies
Division of Epidemiology and Public Health, University of Nottingham

UKCTAS
UK Centre for Tobacco & Alcohol Studies

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5. Potential benefits of electronic cigarettes

The potential benefits of electronic cigarettes lie in their role as a reduced-hazard competitor for cigarettes.

5.1 Who uses electronic cigarettes and why?

The great majority of the more than one million users of electronic cigarettes in the UK are current or former smokers.[46] Most users use them to either replace cigarettes in places where smoking is prohibited or discouraged, to cut down on smoking, to reduce harm from smoking, or to quit smoking.[20] As the nicotine delivery kinetics of electronic cigarettes improves with technological developments, these products may prove to be more effective than conventional NRT as a tobacco substitute as their physical and behavioural characteristics replace many of the co-stimulatory factors that contribute to nicotine addiction.[7] Availability in convenience stores, competitive pricing, non-medical image and social acceptability also probably contribute significantly to use. Prevalence of use is similar between genders and socio-economic groups, though higher in younger than in older smokers.[20, 46]

According to the Smoking Toolkit Study, use of electronic cigarettes is much more common among heaver smokers and ex-smokers (figure 5), and more recent ex-smokers report current use of electronic cigarettes than conventional NRT (figure 5).

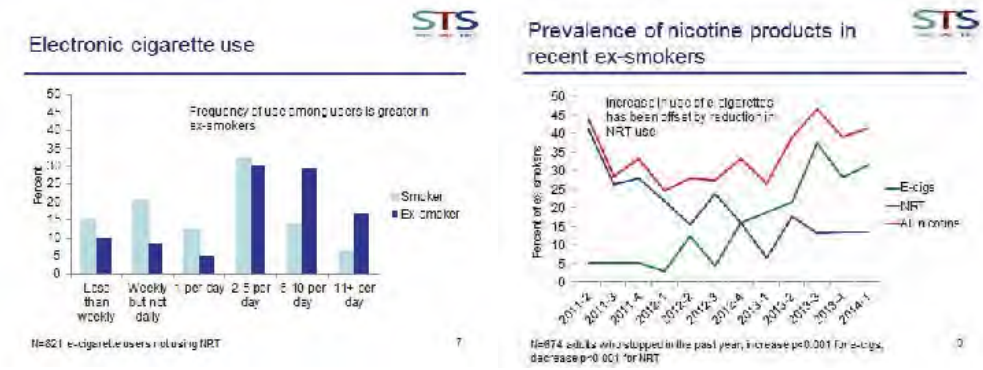

Figure 5: Use of electronic cigarettes by current and ex-smokers (left panel) and of nicotine products in recent ex-smokers (right panel; data from Smoking Toolkit Study[44])

The increase in electronic cigarette use over recent years appears to reflect in part, smokers using electronic cigarettes instead of NRT; and in part, users who would not otherwise have used NRT. This is particularly true of smokers attempting to quit, among whom electronic cigarettes are now the first choice. In this group, increasing

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REVIEW

The effect of e-cigarette aerosol emissions on respiratory health: a narrative review

Riccardo Polosa[a,b], Renée O'Leary[c], Donald Tashkin[d], Rosalia Emma[e,f] and Massimo Caruso[e,f]

[a]Centro per la Prevenzione e Cura del Tabagismo (CPCT), Azienda Ospedaliero-Universitaria "Policlinico-V. Emanuele", Università of Catania, Catania, Italy; [b]Center of Excellence for the acceleration of HArm Reduction (CoEHAR), University of Catania, Catania, Italy; [c]Canadian Institute for Substance Use Research, Victoria, Canada; [d]David Geffen School of Medicine at the University of California, Los Angeles (UCLA), Los Angeles, CA, USA; [e]Dipartimento di Medicina Clinica e Sperimentale (MEDCLIN), University of Catania, Catania, Italy; [f]Dipartimento di Scienze biomediche e biotecnologiche (BIOMETEC), University of Catania, Catania, Italy

ABSTRACT

Introduction: Due to the uptake in the use of e-cigarettes (ECs), evidence on their health effects is needed to inform health care and policy. Some regulators and health professionals have raised concerns that the respirable aerosols generated by ECs contain several constituents of potential toxicological and biological relevance to respiratory health.

Areas covered: We critically assess published research on the respiratory system investigating the effects of ECs in preclinical models, clinical studies of people who switched to ECs from tobacco cigarettes, and population surveys. We assess the studies for the quality of their methodology and accuracy of their interpretation. To adequately assess the impact of EC use on human health, addressing common mistakes and developing robust and realistic methodological recommendations is an urgent priority. The findings of this review indicate that ECs under normal conditions of use demonstrate far fewer respiratory risks than combustible tobacco cigarettes. EC users and smokers considering ECs have the right to be informed about the relative risks of EC use, and to be made aware that findings of studies published by the media are not always reliable.

Expert opinion: Growing evidence supports the relative safety of EC emission aerosols for the respiratory tract compared to tobacco smoke.

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1. Introduction

The use of electronic cigarettes (ECs) has significantly increased over the past decade. These consumer products have been rapidly gaining ground on conventional cigarettes due to their efficiency in reducing tobacco consumption, their competitive price, the consumer perception of EC as a less harmful alternative to smoking, and because EC provide 'smoking experience without smoking' [1–3]. Earlier designs have evolved over the past decade, and now the devices are available in multiple formats and models. Basically, ECs are battery powered electronic devices that operate by heating an element (most commonly, a metal coil) that vaporizes a solution (e-liquid) mainly consisting of glycerol, propylene glycol (PG), distilled water, and flavorings, and which may or may not contain nicotine. The user inhales the aerosol generated by vaporizing the e-liquid in a process commonly referred to as 'vaping.' ECs do not contain tobacco, do not create smoke, and do not rely on combustion to operate.

The composition of EC aerosol is by far less complex than that of cigarette smoke [4–10], which – by contrast – is known to contain thousands of harmful and potentially harmful constituents [11]. Some of main toxins identified in cigarette smoke are also present in EC aerosol emissions, but at much lower levels than in cigarettes smoke, and often at exposure levels no greater than present in the general environment.

EC use is regarded as having lower levels of risks than smoking as reported by the Royal College of Physicians [12], Public Health England [13] and others [14,15]. The RCP estimates that ECs are at least 95% less harmful than conventional cigarettes, although there is concern that long-term exposure to EC aerosol emissions could carry some health risks. Because the particle size in EC aerosols is well within the respiratory range [16,17], aerosol particles will penetrate into the lungs [18] making the airways the primary target of any potentially harmful effects.

Unfortunately, very little is known about the health effects of long-term vaping and this is of particular concern for those never smokers who have just started using ECs. Therefore, studies of the toxicological and biological effects of EC aerosol emissions, using in vitro human airway cell systems, animal models, and clinical studies, are needed to investigate the potential health risks of using these devices. Whether or not chronic exposure to EC will result in lung disease can only be evaluated by large scale, long-term studies of daily EC users who have never smoked in their life, a study that would be challenging to carry out at present, as most EC users have had prior or current cigarette smoke exposure. It goes without saying that nicotine consumption must be actively discouraged among youths, and – besides smoking – this includes vaping as well.

In this review article, we critically appraise published studies that have investigated the potential toxic effects of ECs using preclinical models, such as cell culture, animal models,

CONTACT Riccardo Polosa polosa@unict.it Department of Clinical and Experimental Medicine, Università di Catania, Catania, Italy
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and clinical studies (with the exclusion of case reports). Preclinical studies may not fully predict the response of the human body to the exposure, therefore animal studies are still required for regulatory toxicological testing. Significant technological advances with in vitro models are slowly being acknowledged as acceptable alternatives. With these methodological issues in mind, we present an overview of the emerging literature on respiratory health findings. The narrative review begins with a description of EC aerosols followed by discussions of the literature grouped by research type: cell testing, animal studies, and research on respiratory health.

2. Constituents of concern in EC aerosols

Upon activation, ECs generate respirable aerosols [16–18] containing several constituents of potential toxicological and biological relevance to respiratory health, but at much lower levels than in cigarette smoke [6–9]. One of the most comprehensive assessment of EC chemical emissions has shown that of the 150 constituents examined in the EC aerosol (including all tobacco smoke harmful and potentially harmful constituents, and additional toxic species reportedly present in EC emissions) 104 were not detected and 21 were present due to laboratory background [9]. Of the 25 remaining detected aerosol constituents, 9 were present at levels too low to be quantified. Only 16 were generated in whole or in part by the EC from: i) major e-liquid constituents (nicotine, PG, and VG); ii) recognized impurities in Pharmacopoeia-quality nicotine; and iii) 8 thermal decomposition products of PG or VG. By contrast, approximately 100 constituents were detected in mainstream cigarette smoke. The emissions of toxicants were from 82 to >99% lower on a per-puff basis from the EC compared with those from tobacco cigarettes. Although the aerosol from the EC is compositionally less complex than cigarette smoke and contains significantly lower levels of toxicants, a thorough characterization of EC chemical emissions will require non-targeted analytical assessments of a wide range of commercial products.

Among the commonly detected aerosol constituents, glycerol, PG and their thermal degradation products (i.e. carbonyl compounds), chemical flavorings, nicotine, and metals have attracted most attention. The US Food and Drug Administration (FDA) and the US Environmental Protection Agency (EPA) categorize vegetable glycerine (VG) and PG as Generally Recognized as Safe [19]. Although PG can be also found in cigarette smoke, high levels are normally present in EC aerosol emissions. Hence, it is necessary to have a better understanding of PG's safety by inhalation. All animal and human studies that analyzed the effect of the inhalation of PG have indicated that PG does not appear to pose a significant hazard via the inhalation route [20]. In fact, in several of these animal studies the concentrations of PG used were higher than the concentration used in EC and did not give rise to any toxic effects. However, human studies using PG concentrations similar to that in ECs are required to confirm the safety of inhalation of PG from vaping products.

Despite their good safety profile, exposure to glycerol and PG aerosols has been shown to elicit some irritant effects [21–23]. The possibility that chronic airway irritation may have long term consequences cannot be dismissed, and more research in this area is required. Additionally, PG, has been implicated as a potential cause of oral allergic contact dermatitis [24], and some users may report signs and symptoms compatible with contact dermatitis around the mouth or in the oral mucosa [25].

Thermal degradation of glycerol and PG during EC vaporization may generate toxic carbonyls including formaldehyde, acetaldehyde, and acrolein. Nevertheless, studies evaluating low-power cigalike and closed-system modular EC devices found formaldehyde, acetaldehyde, and acrolein at much lower levels than in cigarette smoke [8,9,26]. Aerosol generated from more-advanced high-power devices may produce levels of aldehydes approaching or even exceeding those of cigarette smoke [27]. However, it is now known that high aldehyde levels can be generated only when the EC is overheated, a condition generally seen in certain experimental protocols, and as a result these findings bear little relevance to normal use [28]. EC users find the taste delivered from overheated EC, known as 'dry puff,' to be so unpleasant that they cannot inhale the aerosol [29], thus avoiding potential exposure to high levels of aldehydes. Under normal vaping conditions, the aldehyde emission levels are far lower than in cigarette smoke and lower than the levels found in the environment [30,31]. Daily exposure from vaping (assuming a daily consumption of 5 g EC liquid) was 5 to 31-fold lower for formaldehyde, 191 to 528-fold lower for acetaldehyde and 25 to 193-fold lower for acrolein compared to daily smoking (assuming a daily consumption of 20 tobacco cigarettes). This represents a 79.0–96.8% reduction in formaldehyde, 99.5–99.8% reduction in acetaldehyde and 96.0–99.5% reduction in acrolein exposure from EC use (5 g/day liquid consumption) compared to smoking 20 tobacco cigarettes. Aldehydes such as formaldehyde are ubiquitous in the environment. According to the World Health Organization, indoor air of homes can have up to 250 $\mu g/m^3$ formaldehyde, but the average levels are under 50 $\mu g/m^3$. Therefore, considering a daily ventilation volume of 20 m^3, the daily formaldehyde exposure from breathing indoor air is approximately 1000 µg. This level is far higher than the total daily exposure from consuming 5 g of e-liquids. Moreover, newer devices are being fitted with better wicking designs (e.g. bottom coil vs top coil) and some have been fitted with automatic temperature control features to prevent overheating and excessive formation of carbonyls. Nonetheless, the possibility that temperature control features in some current devices may not perform accurately cannot be discounted [32].

Food flavorings are normally present in e-liquids. These chemicals have largely unknown effects when heated and inhaled. Chronic exposure to high levels of diacetyl, a butter flavoring processed in microwave popcorn factories, has been associated with cases of bronchiolitis obliterans ('popcorn lung') [33,34]. Although some e-liquids contain high concentrations of diacetyl [35,36], there have been no reports that this has caused bronchiolitis obliterans in EC users. Cigarette smoke also contains diacetyl, but at much higher levels (up to 750 times higher) than are found in EC aerosol [37]. Yet, cigarette smoke has not been linked conclusively with bronchiolitis obliterans as stated by the US Occupational Safety and Health Administration [38]. Nonetheless, it is reasonable to

assume that flavoring chemicals (or their thermal degradation products) in EC aerosol could have potential risks. Besides possible toxic effects upon the lung from chronic exposures, such as bronchiolitis obliterans, other respiratory effects to be studied should include respiratory irritation and potential allergic responses [39,40].

Most if not all of the lung damage observed in smokers is not caused by nicotine, but from the process of burning tobacco cigarette and the inhalation of thousands of toxic chemicals generated during combustion. The development of smoking-related diseases is currently attributed to oxidative stress, airway inflammation, and the direct toxic effects of thousands of chemicals and carcinogens present in tobacco smoke [41]. Nicotine is not classified as a carcinogen by the International Agency for Research on Cancer [42] and is relatively safe for human consumption at low concentrations [43]. The 2014 US Surgeon General's report examined the harm caused by nicotine and concluded that although nicotine may adversely affect fetal and adolescent brain development, it does not contribute to smoking-related diseases [44]. In terms of nicotine delivery, earlier ECs designs are generally less efficient than conventional cigarettes at delivering nicotine to the body [45–47], but the most recent and innovative EC devices have been reported to deliver nicotine at levels equivalent to those obtained from cigarettes [48].

Most likely class of compounds that may be found in some EC aerosols but not usually found in cigarette smoke (depending on materials used for the heating element in the vaping device – will be metals that may leach from metals and alloys sometimes used in ECs. Cigarette smoke also contains metals present in the tobacco leaves. When evaluating the hazardous potential of metals in EC aerosol, it must be noted that daily exposure levels from EC use are many order of magnitude lower compared to acceptable exposure from inhalational medications and by orders of magnitude lower than the regulatory limits for daily occupational exposure. Health risk assessment analyses show that levels of metals exposure from EC use were of minimal apparent health concern [49].

The key points about EC aerosols are that 1) EC aerosols contain constituents of concern, including formaldehyde, acetaldehyde, and acrolein, although, in almost every case, at substantially lower levels than cigarette smoke; 2) in the testing where higher levels were measured, the devices had been overheated, a condition very unlikely to occur in normal use; 3) the pyrolysis of flavouring components needs to be studied, as well as additional research on the base e-liquid components; and 4) prior research has already demonstrated that nicotine, which may or may not be a component in e-liquid, is not a carcinogen. With these facts in mind, we review the studies on EC research in cells cultures, animal models, and human subjects.

3. Effects of EC aerosols on airway cell cultures

The potential for EC toxicity has been investigated by exposing cell cultures to e-liquids or to aerosol generated by ECs. In general, these studies could help to gain insight into the biologic and toxicological effects of EC aerosols. These effects have been studied using a wide range of cell types, including neutrophils [50], macrophages [51], embryonic stem cells [52–54], murine fibroblasts [55], carcinoma cell lines [56,57], human endothelial cells [58], and lung fibroblasts [52,59,60]. The airway epithelium is primarily and extensively exposed to the aerosol emissions of ECs, so our focus will be on studies using human airway epithelial cells [61–64].

As there are many cell types available to researchers, it is important to be aware of their different sensitivity and responses across the test matrix. Differences in cellular metabolism, apoptotic rates and genetic characteristics can contribute to the observed variability in results between cell lines. For example, one study examined the response of several cell types to EC exposures to identify an appropriate test system [65]. Both A549 cells and the CL-1548 cell line showed reduced sensitivity (in term of cell viability) to e-liquid aerosol compared to primary NHBE cells, with increased sensitivity of CL-1548 compared with A549 cells. In another study [63], researchers investigated lung cell line, BEAS2B; the responses observed were similar to those in other cell lines. Strangely, in this study there was variability in the quantity of e-liquid consumed between identical EC exposure experiments.

The use of 3D tissue systems, whether 'home grown' or commercially available cultures, is becoming more routinely used for inhalation toxicology studies, due to improved tissue reliability and stability and the cost of production. A number of studies [64–66] have used 3D differentiated immortalized primary normal HBEC for EC assessment. Differentiated normal HBEC were exposed at the air–liquid interface (ALI) to EC aerosols (with or without nicotine), PG, VG, and reference 3R4F cigarette smoke, in a CULTEX® RFS compact module. Cigarette smoke led to eight times lower cell viability and five times higher oxidative stress than EC [64]. A shortcoming of this study is that it lacked a standard puffing regime and a standard protocol for aerosol generation.

In another study, Aufderheide et al. [66] repeatedly exposed differentiated immortalized primary HBEC (CL-1548) to cigarette smoke and EC aerosol to evaluate phenotypic changes associated with respiratory disease (e.g. COPD). Cultures exposed to mainstream cigarette smoke and e-cigarette vapor showed a clear reduction in mucus-secreting cells and their secretion activity as well as in cilia beating, with the effect less pronounced for the cells treated with the e-liquid aerosol. These observations suggest that EC aerosols may have a reduced risk for respiratory disease compared to cigarette smoke.

Shen et al. [67] conducted RNA sequencing analysis on differentiated normal HBEC exposed to 1R5F tobacco reference cigarettes and EC aerosols (with or without nicotine) at the ALI. Cigarette smoke elicited differential gene expression and cell cytotoxicity, but EC aerosol provoked less response. Neilson et al [68] reported on the use of the commercial 3D tissue culture EpiAirway™ (MatTek) to assess the irritancy of EC aerosols generated with the Vitrocell® VC1 system, and cigarette smoke exposure reduced cell viability to 12% while cells remained viable with EC exposure. The limitation of this study is the short exposure to EC aerosol that may minimize overall

toxicity. Other researchers used the 3D commercial tissue culture MucilAir™ (Epithelix) to evaluate EC toxicity. Matched nicotine doses of EC aerosol and cigarette smoke were tested with short repeated exposures [69] or a single acute exposure [70] to assess changes in gene-expression profiles using RNA sequencing. In both exposure studies, the more substantial changes in gene expression were observed with cigarette smoke than with EC aerosol. Even when the EC nicotine dose was doubled, the gene expression profiles remained significantly lower than those with cigarette smoke exposures. These studies were characterized by a short exposure to EC aerosol which minimized overall harmfulness.

The lack of high level of gene expression after EC aerosol exposure in the aforementioned studies contrasts with recent work in which nasal scrape biopsies, nasal lavage, urine, and serum from nonsmokers, cigarette smokers, and EC users were assessed for changes in immune gene expression profiles [71]. The authors found that vaping ECs resulted in decreased expression of immune-related genes similar to that from smoking cigarettes. However, little consideration was given to the fact that previous exposure to tobacco smoking in the vapers group (vapers are ex-smokers) would have induce irreversible epigenetic/gene expression changes [72]. Given that all EC users in the study were former smokers, it is impossible to decouple the effects of EC aerosol emission from those of previous tobacco smoke exposure. Also, the observed association between e-cigarette use and changes in gene expression does not imply causation given its cross-sectional design. Obviously, a longitudinal study of regular vapers who have never smoked in their life would have been more appropriate to establish potential causation of the e-cigarette exposure effect on gene expression and related clinical implications.

The same methodological shortcoming occurs in another cross-sectional design study which investigated markers of innate lung responses in sputum samples from smokers, EC users and non-smokers [73]. The authors concluded that EC use and smoking alters the profile of innate defence proteins, but failed to consider the obvious confounder of previous andcurrent exposure to tobacco smoke among EC users who are ex-smokersor dual users). Proteomic analysis of sputum supernatants in former smokers has shown high levels of azurocidin 1, neutrophil elastase and CXCL8 [74]. Moreover, mucin concentrations are known to be elevated both in current and former COPD smokers with MUC5B and MUC5AC levels being approximately 3-fold (for current COPD smokers) and 10-fold (for former COPD smokers) higher than in controls who had never smoked [75]. It is important to consider the within subject instability of sputum endotypes due to the large variability observed with difference of the order of 1000 in the levels of analysed markers). The log-scales in the y-axis are typically used to make up for this variability.

Ghosh et al. [76] performed a proteomic investigation of bronchial brush biopsies and bronchoalveolar lavage obtained with a bronchoscopy of healthy non-smokers, cigarette smokers, and EC users, and found that ~300 proteins were differentially expressed in smokers and vapers airways. This paper is also subject to the same methodological flaws noted earlier, as vapers in the study were mostly dual users and the exclusive EC users were ex-smokers.

The least sophisticated studies expose two-dimensional (2D) submerged cellular systems to e-liquids, not aerosols. They employ continuous or immortalized cell lines or primary cells isolated from either human or animal tissues. These studies enable researchers to screen a large number of e-liquids using basic endpoints such as cell viability. Cytotoxic effects are measured using commonly used assays. One measurement is neutral red uptake where viable cells can take up neutral red via active transport whereas non-viable cells cannot so that the amount of released dye can be measured to determine the total number of viable cells. Thus estimating cytotoxicity. Another measurement is lactate dehydrogenase release (LDH) where a cytosolic enzyme is released into cell culture media to show plasma membrane damage and MTT (Abbreviation for the dye compound 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromidefor; a marker of cell proliferation).

In one study [52], effects of 35 e-liquids were screened using human embryonic stem cells (hESC), mouse neural stem cells (mNSC), and human pulmonary fibroblasts (hPF). The MTT assay was used to determine NOAELs (no-observed-adverse-effect-level) and half maximal inhibitory concentration values, IC50s. It was found that hESC and mNSC were more sensitive to e-liquids than hPF. In other findings, the researchers attributed cytotoxicity to some flavors, but not to nicotine or PG/VG [52]. In an extension of this study, highly flavored e-liquids were examined and the researchers identified cinnamaldehyde, an ingredient in cinnamon-flavored e-liquids, as of particular toxicological concern [59]. In a later paper by the same group, cytotoxicity was also observed by aerosolized forms of these liquids, but in this case it was ascribed to VG/PG thermal degradation products (i.e. carbonyl compounds) rather than to flavourings [53].

Lerner et al. [60] also reported oxidative stress and cell morphological changes in human lung fibroblasts (hLF) in response to e-liquids, particularly cinnamon flavored e-liquids. that stimulated IL-8 secretion and caused loss of cell viability. They suggested that e-liquids have oxidative properties, and that sweet or fruit flavors made the e-liquids even stronger oxidizers. In the same study, exposure of human airway epithelial cells (H292) to EC aerosol at the ALI led to an increase in inflammatory cytokines. The authors explored the contribution of flavorings from e-liquids to lung barrier function and inflammation in human bronchial epithelial cells. In these studies, acetoin, diacetyl, pentanedione, maltol, ortho-vanillin, coumarin, and cinnamaldehyde, all flavors found in e-liquids, did not affect cell viability [77]. The conflicting results are due to lack of a standardized approach to in vitro toxicology assessments of vaping products (e.g. e-liquid vs EC aerosols, fibroblasts vs epithelial cells, etc).

Alveolar macrophages (AMs) are a unique lung cell population that eliminate airborne irritants and infectious agents, while also orchestrating resolution of lung inflammation, and impairments in AM function could therefore enhance susceptibility to airway infections and respiratory diseases [78]. Scott et al. [79] have shown that human AMs exposed to EC aerosol condensate increased cytotoxicity, ROS production, inflamma-

tory cytokines and inhibited their phagocytic activity, as would be expected given that EC aerosol contains oxidant and other pro-inflammatory constituents. Since EC are used almost exclusively by current or former smokers, the key question is how this adverse effect compares with that of exposure to cigarette smoke. Unfortunately, this study does not address that question.

High-content screening platforms provide useful tools for the initial hazard characterisation of e-liquids to help determine what toxic end points might need further investigation. Use of real-time cell analyzer (RTCA) technology (such as the xCELLigence platform) enables the screening of cytotoxic effects of e-liquid flavors on immortalized HBEC. Two studies have used these methods. First, Sherwood and Boitano [80] demonstrated that the different flavors tested varied in their cytotoxicity profiles, with vanillin and 2,5-dimethylpyrazine causing abnormalities in transepithelial resistance and ion conductance. This effect may have negative consequences for airway surface liquid homeostasis in individuals who use ECs regularly. Second, Iskandar et al. [81] discussed the utility of high-content screening of e-liquids using multiple basic endpoints, including cell viability, oxidative stress and cellular function on a Cellomics platform.

Omics tools have also been applied to investigate the global impact of e-liquids has in cellular systems. One study utilized untargeted metabolomics on primary normal human bronchial epithelial cells (HBEC) treated with e-liquids and cigarette smoke condensates demonstrated shifts in the HBEC metabolome following treatment. E-liquid exposure provoked a smaller response than cigarette smoke [82].

In addition to studies on toxicity, e-liquids have also been investigated for immune defense responses. Wu et al. [83] demonstrated that cultures of human airway epithelial cells infected with human rhinovirus increased viral load and production of anti-viral proteins with e-liquid treatment. Although cell viability was not altered, the data suggest that e-liquids could impair immune host defense.

These studies have shown a response to e-liquid exposure regardless of the cell systems and that some cell systems are more responsive than others. These studies have been criticized as not being representative of exposures under normal conditions of use, for example testing high doses and using continuous exposure protocols, in some cases as long as 48 hours. Also, some of these studies did not compare the effects of EC with conventional tobacco products. Tobacco products in most assays elicit significantly higher responses than ECs, as observed by Misra et al. [84]. A549 human lung epithelial carcinoma cells were exposed to e-liquids and aerosol extracts of e-liquids with or without nicotine and menthol flavoring, or to 3R4F total particulate matter (TPM). No cytotoxic, genotoxic, or inflammatory effects were observed for any of the EC treatments under investigation, whereas comparable exposures to cigarette smoke extracts resulted in markedly cytotoxic and genotoxic responses [84]. One obvious limitation of this study is the use of A549 cells that are known to be more resistant to cytotoxic stimuli. Moreover, the use of submerged cell monolayers does not reflect the real exposure of airway cells to EC aerosol.

In real life, exposures from ECs come from aerosols, not e-liquids. Therefore, exposing the cells and tissues to aerosol is a more appropriate way to investigate the biological responses to ECs. Extracts of aerosols can be generated by either collecting EC aerosol particulate matter onto a Cambridge filter pad [85] or generating aqueous extracts (AqEs) of aerosols by bubbling them through cell culture media [86] or by directly exposing cell cultures to EC aerosol emissions [54]. These exposures enable the delivery of more appropriate and realistic doses of EC.

Taylor et al. [86] investigated oxidative stress responses in H292 cells exposed to AqEs from ECs and 3R4F reference cigarettes. As expected, the authors found that 3R4F induced significant oxidative stress, whereas no responses were observed with the AqEs from ECs. In this study, the quality control of AqE generation and nicotine quantification was integral to the understanding of the cellular responses and should be the best practice method for generating AqEs, but underestimation of the overall risk could have resulted from the use of a tumour lung cell line (H292) in submerged culture and from the fact that only soluble components of the EC aerosol are present in AqEs,

Yu et al. [56] used several cell types, including human head and neck squamous cell carcinoma cell lines HN30 and UMSCC10B, to assess the potential of EC to cause DNA damage and cell death compared to cigarette smoke. The authors generated AqEs by drawing EC aerosol (with or without nicotine) or cigarette smoke through media. EC-exposed cells were reported to show significantly reduced cell viability, clonogenic survival and DNA strand breaks, regardless of EC nicotine content. However, in this study the authors neglected to report how the extracts were made, how many puffs were taken, how much aerosol volume was collected, and how the extract was quantified and/or normalized to a constituent (e.g. nicotine). Without this information, it is difficult to reach meaningful conclusion.

Currently there are no standard protocols for the generation of AqEs for in vitro studies, and various methods are used. Taylor et al. [86] drew 10 puffs from ECs into 20 ml cell culture media under CORESTA CRM81 regime [87]. Other studies include bubbling 200 mg of vaporized e-liquid into 20 ml of cell culture media [55] or 50 ml EC aerosol bubbled through 10 ml cell culture media [88]. Irrespective of how the extract is made, it should be quality checked and assessed for nicotine content as a minimum to enable comparisons across studies and biological effects.

Over the years there have been advances to in vitro exposure systems. These systems have predominately been used to generate, dilute, and deliver aerosols, such as cigarette smoke, environmental particulates, and nanoparticles, to cellular cultures. Cell culture technologies to investigate aerosol properties have also evolved to enable air-liquid interface (ALI) 2D cell and three-dimensional (3D) tissue culture exposures. A number of reviews have outlined the value of commercially available systems, such as the Borgwaldt RM20S and the Vitrocell® VC1 and VC10 systems [89,90], and these tools have been adapted to be used for in vitro assessment of EC aerosol emissions. The problem is that these systems are expensive and as a consequence few entry-level scientists, academics, and new research groups have access to them. Instead, a plethora of poorly standardized, individually

made systems have been used to generate and deliver aerosols instead. The CRM81 regimen [87] has been suggested for EC aerosol generation, but is often overlooked or difficult to implement on a basic aerosol exposure system.

An example of an individually made system is Cervellati et al. [91]. The researchers used an exposure system that draws aerosols over cellular cultures using a vacuum pump, and the amount of aerosol and duration of exposure were not reported. Based on this unreliable procedure the authors conclude that unflavored EC aerosols produced less cytotoxicity than flavored EC aerosols and cigarette smoke. Similarly, Lerner et al [92], used a timer system to control a basic laboratory pump, and they too did not report the dosimetry and robustness of aerosol delivery. They observed an increase in inflammatory and mitochondrial stressors, but due to the basic generation system comparisons cannot be made with consumer usage or data from other reported studies.

Commercially available exposure systems have been used in studies to assess the cellular toxicity of e-cigarettes. When H292 were exposed for 1 hr to EC aerosol using the Borgwaldt RM20S, less cytotoxicity was observed compared to cigarette smoke [61]. The exposures were consistent to human exposures, and with the EC, the maximum concentration delivered was equivalent to a daily dose delivered within one exposure. A limitation of this study is that it focused on only one biological endpoint (cell viability). Other cytotoxicity endpoints could be effected differently.

Thorne et al. [93] reported that cigarette smoke induced DNA damage in BEAS2B at the ALI using a Vitrocell® VC10 system, in a dose dependent manner, whereas short-term exposure with two different ECs did not result in e any DNA damage, even at equivalent or greater doses than cigarette smoke aerosol. Using quartz crystal microbalance technology, nicotine delivery and deposited mass were both assessed at the exposure interface and demonstrated that EC exposures were 12–28 times greater than cigarette smoke. In another study, H292 cells were used to test aerosol from various types of EC devices, or a tank system with different e-liquid flavors, variable nicotine concentrations, and with modified battery output voltage, compared to cigarette smoke [62]. Exposure to EC aerosol resulted in decreased metabolic activity and cell viability and increased inflammatory cytokine levels, but all these factors were more adversely affected by exposure to cigarette smoke.

These studies indicate that product type, battery output voltage, and flavors significantly affected EC toxicity, with strawberry flavor being the most cytotoxic. However, the final flavour in an e-liquid is achieved by the combination of a variety of individual flavor ingredients. This can vary from just a few ingredients in a simple flavour to over a hundred ingredients and constituents in complex flavours. Without information on e-liquid compositions, no conclusions on the relative potency of individual flavour ingredients can be drawn. For the vast bulk of the in vitro papers published in this field, insufficient dose information and lack of information on e-liquid composition does not allow interpretation of the findings to consumer exposures.

Overall, a large number of in vitro studies have been published relating to the cytotoxic effects of vaping products and e-liquids, but we have identified many methodological limitations. The relevance of data obtained from direct e-liquid exposures, instead of aerosol exposures is questionable. Intuitively, aerosol exposure is more relevant to the real-life situation. However, it must be considered that there are no standard procedures for the generation of aerosol extracts (AqEs) or aerosols, and that custom-made exposure systems may not be able to generate consistent and reproducible aerosols. Yet another methodological shortcoming is that the effect of device liquid interactions is generally overlooked, and the device type and make, the e-liquids used, and the device settings are often not fully reported. Given the wide range of devices in the market place, the relevance of outcomes from any one single liquid-device combination cannot be extrapolated to vaping in general.

For robust findings that apply to real life vaping, in vitro exposures need to be contextualized with normal conditions (user exposures) and require the assessment of key dosimetry markers, such as nicotine or glycerol ratio, to 'normalize' exposures. Appropriate comparators must also be incorporated to be able to understand the effects attributed to ECs. Finally, the reliability and reproducibility of test systems need to be considered to ensure that the dynamic range captures EC and cigarette responses appropriately. Despite their limitations, studies on cellular systems and exposure systems offer a vast opportunity for researchers to compare responses to different e-liquids and aerosols and to understand the mechanistic pathways that are associated with biological effects and thus inform the hazard identification and characterization aspect of risk assessment.

4. Effects of EC aerosols on animal models

Despite the opportunities noted above, in vitro models have limitations, as they cannot fully predict the response of the human body to exposures. Although animal models have other shortcomings, they at least represent the complexity found in human bodies and are currently accepted as a reasonable alternative – their use is often required for regulatory toxicological testing. Animal models have been used traditionally to assess both the local and systemic effects of aerosols across a series of exposure durations ranging from hours to weeks. The practicalities, costs, species extrapolation to humans and ethical considerations of using animals makes extensive testing of ECs and their flavorings difficult.

For assessing inhalation toxicology, there are a number of regulatory accepted methods that include acute (OECD TG 403 and 436) [94,95], 28-day sub-acute (6 h per day, 5 days per week for 28 days) (OECD TG 412) [96], and 90-day sub-chronic (6 h per day, 5 days per week for 90 days) (OECD TG 413) [97] inhalation studies employing the controlled use of rodents for nose-only or whole-body exposures use various protocols. In addition to these methods, a variety of custom

methods have been commonly used in animal exposure models. Animal studies have recently investigated the toxicology of EC constituents or whole aerosols and have reported various effects, including minimal irritative responses, oxidative stress, inflammation, and impairment in the lung's immune defense against infection. These studies must be examined for their dosimetry and the appropriate exposures for the species, and, most importantly, how these extrapolate to realistic human doses and exposures.

For example, Phillips et al. [98] studied the toxicity of nicotine and nicotine and pyruvic acid aerosols in a 28-day rat inhalation study (OECD 412). Rats exposed to nicotine had decreased body weight and concentration-dependent increases in liver weight. The respiratory tract effects from nicotine exposures were localized in the larynx and limited to 'adaptive changes'. This study reported no toxicity with observed minimal changes to respiratory tract organs, suggesting minor biological effects on the lung related to nicotine aerosols. However, in this study the authors did not test e-liquids aerosols, which are more chemically complex than nicotine and nicotine and pyruvic acid aerosols on their own.

Waldum et al. [99] studied the longer-term in vivo effects of inhaled nicotine. In a 2-year study of chronic repeated exposure, rats exposed to inhaled nicotine at concentrations twice that found in the plasma of heavy smokers showed no resultant harmful effects. There were no increases in mortality, atherosclerosis, or increased frequency of tumors in treated rats compared with sham exposure controls, with only decreases in the body weight of nicotine-exposed rats reported. There were no attempts to measure markers of lung injury in this study.

Several studies have examined the systemic effects of EC excipients. The effect of inhaled PG was reported by Suber et al. [100] in a 90-day rat inhalation study. No significant differences in respiratory rates, minute volumes, or tidal volumes were observed between any of the groups. Body weights were generally not affected, with only females receiving the highest dose showing reduced body weights from day 50. Slight differences were observed between the treated and control groups in hematological and blood chemistries, but these did not show a dose-response relationship. However, there was an observed increase in nasal goblet cell numbers and mucin production with medium and higher doses of PG aerosol and nasal hemorrhage and ocular discharge with the highest dose. These findings are consistent with more recent data from mice exposed to PG aerosol for 20 min/day for 3 weeks [101] but inconsistent with in vitro results discussed earlier [74], further emphasizing caution in the interpretation of in vitro results. The study of Suber et al [100] suggests that sub-chronic exposures to PG resulted in dehydration and mucosal/tissue irritation, with no obvious signs of toxicity. In contrast, Glynos et al. [102] found that exposing C57BL/6 mice to EC aerosol increased bronchoalveolar lavage fluid (BALF) cellularity, MUC5AC levels, lung oxidative stress markers, airway hyperresponsiveness and pulmonary mechanics at least comparably if not more than tobacco cigarette smoke. However, an excessive 8 puff/min protocol – which equates to an unrealistic pattern of use of one puff every 7.5 seconds and the continuous running of their vaping machine throughout the whole session suggest that the experimental protocol did not reflect realistic exposure under normal conditions of use. Moreover, some study measurements in particular IL levels and respiratory mechanics, were adversely affected only after 3 days of exposure but not after 4 weeks of exposure, indicating temporary airway irritation that resolves over time.

Garcia-Arcos et al. [103] delivered aerosolized VG or PG, with or without nicotine, in A/J mice for 4 months. Exposure to inhaled nicotine-containing VG or PG stimulated the development of COPD-like effects, such as cytokine expression, airway hyper-reactivity, and emphysema-like tissue destruction. However, A/J mice are particularly susceptible to pulmonary emphysema (COPD-like effects) and lung tumors [104–106]. Increased mucin production and lung tissue destruction were seen with nicotine containing PG/VG but not with PG/VG alone, suggesting that nicotine itself causes lung toxicity. This is inconsistent with the rat inhalation study of Waldum et al. described earlier [99].

Another rat study by Salturk et al. [107] assessed the effects of EC aerosols on rats following 28-day exposures and compared outcomes to those in an untreated control group with eight rats per group. Two cases of hyperplasia and four of squamous metaplasia of the laryngeal epithelium were reported in the EC-exposed rats, but these changes were not statistically significant. Notably, there were no differences in epithelial distribution and inflammation in the laryngeal mucosa between the two groups. The study lacked a relevant comparator (i.e. tobacco smoke, which is known to cause consistent hyperplasia and squamous metaplasia in rats), used an unreasonable procedure for the generation of EC aerosol emissions, and overexposed animals to aerosols. In a longer-term exposure study, Werley et al. [108] reported only minor increase in BALF lactate dehydrogenase, total protein, alveolar macrophages, and neutrophils in treated rats following 42 days' recovery after 90 days of EC aerosol inhalation (with and without nicotine and flavors). However, Lerner et al. [60] reported an increase in inflammatory cytokine levels in BALF and reduced glutathione concentrations in the lungs of C57BL mice after three days of whole-body exposure to a similar low-power cigalike EC. Similarly, Sussan et al. [109], following 2 weeks of exposure to another popular cigalike model, reported increased lung lipid peroxidation and inflammation and increased susceptibility of mice to infection with influenza A and Streptococcus pneumoniae. However, the nicotine doses the animals were exposed to were at levels where acute toxicity in mice can be anticipated. Additionally, the control mice were not subjected to the same stress-inducing regime, namely, 1.5-hour, twice daily incarceration in a small box. The combined adverse effects of these factors were visible in the reduction in body weight in the test group versus the control sample. Stress is known to adversely affect the immune system in mice and is thus likely to be at least partially, if not fully, responsible for the increased susceptibility to infection.

Direct intratracheal instillation of e-liquids has also been employed in an asthma-like mouse model (e.g. ovalbumin sensitization) investigating respiratory allergic responses in pre-sensitized mice. Following 10-week intratracheal instilla-

tion of e-liquids, increases in pro-inflammatory cytokine levels in BALF and airway hyper-responsiveness to methacholine challenge were observed [110]. However, in this study as well, the nicotine dose used was higher than levels known to cause acute toxicity in mice. The effects described are consistent with the generic well-known increased sensitivity of 'asthmatic' lungs to inhaled respiratory irritants and do not indicate an e-liquid specific effect. This points to the importance of the inclusion of a reference group of animals exposed to tobacco smoke or instilled with tobacco smoke extracts resulting in equivalent nicotine doses, as a comparator. Such a reference group was missing in all of the animal studies discussed above.

Balancing the dosing of the comparison group is also an issue, Husari et al. [111] exposed mice to laboratory air, EC aerosols or cigarette smoke for 6 h per day for 3 days, and lung injury was assessed. EC aerosols, despite being delivered at higher doses than cigarette smoke (over eight times higher particulate and four times higher nicotine concentration), resulted in lower levels of lung inflammation. In comparison, cigarette smoke exposure resulted in significant increases in IL-1β, IL-6, TNF-α expression and oxidative stress in the lung and BALF, indicating that, despite higher exposure conditions, EC aerosols exhibited less toxic effects on the lungs of experimental animals when compared to cigarette smoke.

The aforementioned in vivo studies have reported effects in response to EC whole-aerosol and aerosol constituent exposures: adaptive responses to whole-aerosol exposure, dehydrating and irritative effects, localized inflammation and hyperplasia in the laryngeal and nasal epithelia, oxidative stress, and impairment in immune defense. However, these responses need to be put into context. The dosing and exposure of rodents to the various materials need to be considered, and have in some cases been higher than weight-adjusted daily doses in humans. It is questionable how reliable the specialist mouse models are; some strains of mice are predisposed to lung disease etiologies, such as emphysema and matrix remodeling, which must be considered when reporting data from these models. Finally, some of these studies have other limitations as they have not compared findings with conventional cigarette smoke exposure responses; when the latter is accounted for, the comparative degree of response from the EC aerosol or constituent may well be much reduced.

5. Effects of EC use on respiratory health

In vitro human cell systems and animal models are not robust indicators of the potential health risks of using ECs. The outcomes of clinical studies in most fields of medicine demonstrate how limited the value of these preclinical models are. When addressing the concern about health effects of ECs, human studies become extremely relevant, particularly when the test EC under normal conditions of use. Only prospective studies of large numbers of well-characterized EC users followed-up for several years can provide clear answers about the long-term health effects of ECs. Given the challenge of conducting multi-year studies, realistic alternatives can be the detection of early changes in subclinical injury in 'healthy' smokers switching to ECs with highly sensitive functional tests and biomarkers of lung inflammation and injury, and as well as modifications of more robust health effect indicators in EC users with pre-existing diseases. Additionally, epidemiologic survey data may provide useful information about the impact of EC use on respiratory health.

For acute reactions, some smokers switching from cigarettes to EC have self-reported transient throat irritation, dry cough, and other symptoms of respiratory irritation [22,23]. The acute changes detected with sensitive respiratory functional tests reported by some authors [112,113] indicates that the human respiratory tract enacts reflex defensive responses when exposed to non-specific stimuli such as hyperosmolar EC aerosols, with asthmatics exhibiting more intense (and efficient) reflex responses. Whether such acute irritation could translate into clinically meaningful lung disease remains unknown, but there is no evidence to suggest that such irritation may lead to clinically significant adverse lung effects. Another effect, the small increase in peripheral flow resistance immediately after EC use, is of questionable relevance to health outcomes [112,113], particularly given that in the same studies no significant changes could be detected by standard spirometry immediately after EC use [112,113]. Acute exposure of EC aerosols to 10 healthy individuals caused rapid changes in the biologic responses of small airway epithelium, alveolar macrophages, and lung capillary endothelium [114]. The relevance of such acute effects to clinical lung disease is however questionable, and can only be evaluated by future large scale, long-term studies of individuals who are not ex- or current cigarette smokers who have used only ECs.

Other researchers have confirmed the absence of airflow obstruction after single short-term EC use [115–117]. Furthermore, a 5 days confinement study of 105 healthy smokers reported no significant changes in pulmonary function (FVC, FEV1) in either the arm completely or partially switched from conventional cigarettes to EC or the arm completely discontinued using tobacco and nicotine products [118]. Likewise, in a high quality randomized control trial of 387 healthy smokers, Cravo and coll [119]. reported no significant changes in pulmonary function tests after 12 weeks between participants who switched to EC and those who were randomized to continue smoking. Although no serious acute respiratory symptoms were elicited after exposure to EC aerosols in any of the studies discussed here, the possibility that adverse events may occur in predisposed individuals responding to contaminants or by-products contained in EC aerosol cannot be excluded.

Improvements in pulmonary function tests may be observed after smoking cessation, but they may take months if not years to become clinically relevant and can be elicited only in smokers with preexisting airway obstruction. The impact of switching to ECs on long-term respiratory outcomes is less clear and it has been investigated only in a few studies. No change in pulmonary function tests was observed in a 1-year randomized controlled trial of smokers with normal spirometry at baseline switching to ECs, but improvements in respiratory symptoms (cough and shortness of breath) were reported [120]. Of note, progressive normalization of peripheral airways function (i.e. FEF 25–75%, a sensitive measure of obstruction in the more peripheral airways) among those who

completely gave up cigarette smoking was observed in this study [120].

For clinical trials, nitric oxide (NO) concentration in exhaled breath provides a practical measure of airway inflammation and high levels are generally found in the inflamed airways of asthmatics [121,122]. Low levels of NO [123,124] and high levels of carbon monoxide (CO) [125] are generally found in the exhaled breath of cigarette smokers and are known to normalize soon after quitting. The evidence about exhaled NO levels immediately after EC use is conflicting, with most of the studies showing either negligible or no change [112,113,115,117,126,127]. Switching from conventional cigarettes to combustion-free nicotine containing products (such as ECs) quickly and universally leads to normalization in exhaled CO levels [22,23].

Normalization of exhaled NO and CO levels have been observed among smokers who completely gave up cigarette smoking. In a 1-year randomized controlled trial [128], reversal to within normal non-smoking levels was already noted at 3 months with complete normalization at 6 and 12 months in quitters who stopped using ECs as well as those who were still using ECs. On the other hand, no significant changes were observed in individuals who failed to quit or reduce cigarette consumption. Complete abstention from smoking combustible cigarette is known to reduce toxic levels of exhaled CO to within normal limits; similar reductions in exhaled CO have been observed in acute [129,130] and long-term ECs studies [131,132]. Given that ECs are battery-operated devices that do not rely on combustion to operate, this was not surprising. Also, the reported improvements in exhaled NO and CO levels were associated with attenuations in composite symptom scores (cough, phlegm, shortness of breath, wheeze, tight chest, stuffy nose, sinus pain, and frontal headache), particularly in individuals who completely gave up smoking. These outcomes have been self-reported by a wide variety of vapers in the real world [2,25]. The reversal of inflammatory changes in the upper and lower airways after quitting smoking may be the mechanism for these improvements in symptom scores. When assessing respiratory health, it is however of outmost importance to disentangle health effects driven by chronic exposure to EC aerosol emissions from those related to previous smoking history. In a small cohort of daily EC users who have never smoked in their life, no deterioration in spirometric indices, development of respiratory symptoms, changes in markers of lung inflammation nor signs of early lung damage on HRCT were noted in any of the 9 subjects who completed the 3.5-year follow up [133]. The small sample size, the lack of a control smoking group, and the relatively short duration of the follow up were important limitations of this study.

The studies discussed above involved 'healthy' subjects, and only limited work has addressed health impact of EC use in users with pre-existing pulmonary diseases. The asthmatic smoker is a distinct disease phenotype with increased susceptibility to exacerbations and poor asthma-specific health status [134]. Quitting smoking can reverse the negative impact of tobacco smoke on asthma symptoms and lung function [135], and switching to EC use may produce significant respiratory benefits as well. A retrospective cohort study of regular EC users with mild to moderate asthma did not show any deterioration in respiratory physiology and subjective asthma outcomes [136,137]. On the contrary, smokers with asthma who quit or substantially decreased tobacco consumption by switching to ECs showed progressive significant improvement in the Juniper's Asthma Control Questionnaire (ACQ), FEV_1, FVC, and forced expired flow between 25% and 75% of the FVC (FEF25-75), as well as airway hyper-responsiveness (AHR) to inhaled methacholine [136]. A 2-year follow-up study confirmed that EC use ameliorated objective and subjective asthma outcomes and suggests that these beneficial effects may persist in the long term [137]. Remarkably, similar findings were found in the dual users of ECs and cigarettes. EC use was well tolerated, and exposure to e-liquid aerosol in this vulnerable population did not trigger any asthma attacks. These positive findings are consistent with results from a large internet survey of EC users with asthma [2]. Improvement in asthma symptoms after switching was reported in 65.4% of the respondents. Improved asthma symptoms were more often noted in exclusive EC users, while similar improvements were also described in dual users. Worsening of symptoms after switching was reported only in 1.1% of the asthmatics.

Another disease associated with tobacco smoking is COPD, a progressive disease characterized by a persistent inflammatory and remodeling response of the airways [138,139]. Smoking cessation is the only evidence-based strategy known to favorably modify the course of COPD and reduce mortality [140,141]. Reducing cigarette consumption by switching to EC use may yield considerable respiratory benefits in COPD. A retrospective-prospective study of patients with COPD found no deterioration in respiratory physiology (post-bronchodilator FEV_1, FVC, and %FEV1/FVC) in COPD patients who quit or substantially reduced their tobacco consumption by switching to EC use [142]. In smokers with COPD and irreversible airway obstruction, the lack of significant improvements in spirometric indices after smoking cessation is not unusual [143,144]. Nonetheless, participants in a three-year study experienced significant declines in yearly respiratory exacerbations, much improved overall health status (measured by the COPD Assessment Test [CAT]), and boosted physical activity (measured by the Six-Minute Walk Test) [142]. These improvement in health outcomes have also been reported in an internet survey of regular EC users with COPD [2]. Improvement in respiratory symptoms after switching was reported by 75.7% of the respondents, whereas worsening was reported by only 0.8%. Outcomes self-reported by general vapers also indicate improvement in respiratory symptoms [2,25]. A key finding is that respiratory exacerbations were halved in COPD patients who quit or reduced substantially their tobacco consumption after switching to ECs [142]. Smoking is known to increase susceptibility to respiratory infection to bacterial and viral pathogens and quitting smoking appears to lower the risk of respiratory infection [145–147]. Regular use of EC may reduce pathogens activity [148], probably due to the presence of propylene glycol in its aerosol form, which has antibacterial as well as antiviral activity [149,150]. Antibacterial activity has been recently shown in commercially available e-liquids [151].

Moving from clinical data to surveys, these studies have investigated the impact of ECs on respiratory health by analyzing associations of their use with respiratory symptoms and respiratory illnesses. Although the evidence from clinical studies suggest that EC are unlikely to raise significant health concerns for the respiratory tract, most published surveys have suggested the opposite. Four studies examined respiratory symptoms in adolescents using or who have used EC [152–155] and all show an association between respiratory symptoms and EC use. All these surveys are cross-sectional, relying on inaccurate self-reporting of respiratory symptoms and respiratory illnesses, and failing to take into account relevant key confounders. These studies should be expanded in more appropriate longitudinal cohorts. In particular, the analysis conducted by McConnell and coll [152]. fails to confirm the association between asthma symptoms and EC use when controlling for tobacco smoking and second-hand smoke exposure. The association of EC use and self-reported chronic respiratory conditions (asthma as well as COPD) have been also reported in cross-sectional surveys of adults in the US [156,157], but these cross-sectional studies cannot demonstrate causation, and are not adjusted for baseline confounders such as smoking history. In a recent analysis from two observational cohorts, Bowler and coll [158]. concluded that EC use was associated with poorer respiratory health outcomes in adults at risk for or with COPD, but the study does not measure the frequency of EC use. Another potential confounder with the study is selection bias with the EC users having a more prolonged exposure to cigarettes (i.e. pack/years) which is associated with poorer COPD outcomes. Therefor the study's reported association of EC use and COPD may be in error from the misclassification of the level of EC use, or the differences in baseline cigarette use may have attenuated the negative association in the findings.

Human subject research on EC use and lung function has been conducted at the clinical and population levels. Clinical studies have observed some non-serious acute effects, but whether they result in lung disease is not known. Several studies and EC user surveys have reported beneficial effects after switching to EC use. To the contrary, cross-sectional surveys have indicated a negative association between EC use and lung disease, but these studies are limited because they do not adjust for confounders such as prior smoking history or frequency of EC use. There is a need for more long-term studies and population level epidemiological analysis of medical records.

6. Conclusions

ECs generate respirable aerosols [16–18] containing glycerol, PG and their thermal degradation products (i.e. carbonyl compounds), chemical flavorings, and metals, but at much lower levels than in cigarette smoke [6–9]. EC use (5 g/day) represents a 79.0–96.8% reduction in formaldehyde, 99.5–99.8% reduction in acetaldehyde and 96.0–99.5% reduction in acrolein exposure compared to smoking 20 tobacco cigarettes. Studies on the effect of the inhalation of PG in humans have indicated that it does not appear to pose a significant hazard [20], while noting that exposure to glycerol and PG aerosols has been shown to elicit some irritant effects [21–23]. Innovations in EC design and new technologies have been recently introduced to further minimize any residual harm and to improve user satisfaction. Newer devices with temperature controls prevent overheating and the dry-puff phenomenon that produce excessive formation of carbonyls.

The potential for EC toxicity has been investigated by exposing cell cultures to e-liquids or to aerosol generated by ECs, and our review focused on studies using human airway epithelial cells [61–64]. In real life, exposures from ECs come from aerosols, not e-liquids, therefore exposing the cells and tissues to aerosol is a more appropriate way to investigate the biological responses to ECs. This requires rigorous lab quality standard procedures for the generation of aerosol extracts (AqEs) or aerosols, and these are rarely applied. Another methodological issue with in vitro studies is that the effect of device liquid interactions is generally overlooked, and the device type and make, the e-liquids used, and the device settings are often not fully reported. Finally, with the large number of devices available, findings from any one single liquid-device combination cannot be extrapolated to vaping in general.

Animal studies have recently investigated the toxicology of EC constituents or whole aerosols and have reported various effects: adaptive responses to whole-aerosol exposure, dehydrating and irritative effects, localized inflammation and hyperplasia in the laryngeal and nasal epithelia, oxidative stress, and impairment in immune defense. These findings must be questioned because in some studies the dosing was substantially higher than for weight-adjusted daily doses in humans. Poisoning animals in their cages is not informative of what happens to consumer under normal condition of use. Studies with specialist mouse models are suspect because some strains of mice are predisposed to lung disease etiologies. Finally, some studies did not compare EC findings with conventional cigarette smoke exposure responses.

In vitro human cell systems and animal models are not robust indicators of the potential health risks of using ECs as preclinical studies have limited value. Human studies are the most relevant for addressing the health effects of EC, particularly when they have tested EC under normal conditions of use. For acute reactions, some smokers switching from cigarettes to EC have self-reported transient throat irritation, dry cough, and other symptoms of respiratory irritation [22,23], indicating that the human respiratory tract enacts reflexive defensive responses when exposed to non-specific stimuli [112,113]. There is no evidence to suggest that such irritation may lead to clinically significant adverse lung effects. Likewise, the small increase in peripheral flow resistance immediately after EC use is probably not indicative of negative health outcomes [112,113]. The relevance of acute effect findings is particularly questionable, given that no significant changes could be detected by standard spirometry immediately after EC use [112,113].

For short-term effects, a 5 days confinement study of 105 healthy smokers reported no significant changes in pulmonary function (FVC, FEV1) and a high quality randomized control trial of 387 healthy smokers [118] reported no significant changes in pulmonary function tests after 12 weeks.

Improvements in pulmonary function tests for smokers with preexisting airway obstruction may be observed after smoking cessation, but they may take months if not years to become clinically relevant.

The impact of switching to ECs on long-term respiratory outcomes is less clear. A 1-year randomized controlled trial of smokers with normal spirometry at baseline switching to ECs found no changes pulmonary function tests and reported improvements in respiratory symptoms (cough and shortness of breath) [119]. The study also observed progressive normalization of peripheral airways function (i.e. FEF 25–75%) among those who completely gave up cigarette smoking. Smokers switching from conventional cigarettes to combustion-free nicotine containing products (such as ECs) quickly and universally leads to normalization in exhaled CO levels [22,23]. When assessing respiratory health, it is of outmost importance to disentangle health effects driven by chronic exposure to EC aerosol emissions from those related to previous smoking history.

Only limited work has addressed health impact of EC use in users with pre-existing pulmonary diseases. A retrospective cohort study of regular EC users with mild to moderate asthma did not show any deterioration in respiratory physiology and subjective asthma outcomes [135,136]. Smokers with asthma who quit or substantially decreased tobacco consumption by switching to ECs showed progressive significant improvements [135], and a 2-year follow-up study confirmed that EC use ameliorated objective and subjective asthma outcomes [136]. EC use was well tolerated, and exposure to e-liquid aerosol in this vulnerable population did not trigger any asthma attacks. For smokers with COPD, a retrospective-prospective study determined that there was no deterioration in respiratory physiology in patients who quit or substantially reduced their tobacco consumption by switching to EC use [141].

Several surveys have contradicted these clinical findings, but their cross-sectional design cannot demonstrate causality. Surveys rely on self-report of respiratory symptoms and respiratory illnesses which can be inaccurate, and surveys fail to consider relevant key confounders, particularly smoking history, and other factors such as vaping frequency and duration. Longitudinal cohort studies could provide more robust data; for example, McConnell and coll [151]. failed to confirm the association between asthma symptoms and EC use when controlling for tobacco smoking and second-hand smoke exposure.

In summary, the human subject studies provide the most relevant data on the effects of EC aerosol on human lung function, and several studies demonstrate potential benefits for smokers switching to EC. No studies reported serious adverse events, although the potential for such reactions cannot be completely excluded. Minor acute reactions have been reported, but it is not known if they are indicators of potential future lung disease, and no significant changes in pulmonary function were observed in short term trials. Smokers who substituted EC use for smoking experienced improvements in symptoms (cough, phlegm, etc.) and exhibited lower levels of exhaled CO, particularly for those with complete EC substitution. For smokers with diseases such as asthma and COPD, EC use appears to have a beneficial effect on symptoms. Yet to completely test the effects of EC on lung function, specific data is needed for each of the hundreds of e-liquid flavor combinations and the many different types of devices. This data can be provided by cell studies and animal models, but the current research designs must be substantially improved to yield accurate findings for determining the respiratory health risks and benefits of EC use by smokers. Last but not least, only large long-range prospective studies of vapers who have never smoked can provide definitive data to demonstrate any potential impacts regular use of vaping products may have on long term health.

7. Expert opinion

There is growing evidence to support the relative safety of EC emission aerosols for the respiratory tract compared to tobacco smoke [4,14,159]. Public Health England estimated, on the basis of a review of 185 studies, that vaping an e-cigarette is likely to be at least 95% less harmful than smoking a regular cigarette [13]. In 2016, the Royal College of Physicians reaffirmed this figure, estimating the risk of long-term inhalation of e-cigarette aerosol to be unlikely to exceed 5% of the risk associated with long-term cigarette smoking [12]. This review article shows that although some potential effects on respiratory cell types can be shown in vitro, and low levels of chronic irritation of the respiratory tract can be anticipated at certain levels of vaping, these effects are much less than those of smoking. The clinical evidence confirms that ECs are unlikely to raise significant health concerns for the respiratory tract under normal conditions of use. Former smokers using and smokers intending to use ECs as a substitute for smoking should receive correct information about residual risks and potential benefits of these products. Promoting further access to ECs may offer an opportunity to reduce or prevent some of the otherwise inevitable burden of respiratory morbidity and mortality caused by tobacco smoking [160].

To this end, Public Health Institutions and the Ministry of Health in the UK support ECs use as an integration to the already existing Tobacco Control policy. The National Centre for Smoking Cessation and Training (NCSCT) and the National Health Service (NHS) are now actively supporting EC-based intervention along to their standard tobacco control programs and smoking cessation interventions to local stop smoking services [161,162]. The results of such UK policy have been encouraging, with an accelerated decline of smoking prevalence in the adult population from 19.8% (7.7 millions) in 2011 to 14.9% (6.1 millions) in 2017 [163]. Nevertheless, in most countries there is resistance in accepting the UK model of introducing ECs in smoking cessation clinics.

This review article also draws attention to the potential for misinformation from poorly designed and largely misinterpreted experimental studies. As for the majority of existing observational and epidemiological studies [164], preclinical (i.e. in vitro systems and animal models) and clinical models can be also uninformative or even misleading due to problem with methodology and interpretation of these studies. It is urgent to address common mistakes and to develop robust

and realistic methodological recommendations in order to adequately assess the impact of EC use on human health under normal condition of use.

The adoption of standardised methods will also enable a better understanding and a reliable comparison and extrapolation of results obtained across various studies and research groups. There are a number of initiatives in existence, driven by industry groups and non-governmental agencies. For example, CORESTA, (Cooperation Centre for Scientific Research Relative to Tobacco) has recently recommended a method and puffing regime for the generation and collection of EC aerosols [165]. The Institute of In Vitro Sciences (IIVS) has recently hosted a series of workshops, 'Assessment of In Vitro Chronic Obstructive Pulmonary Disease (COPD) Models for Tobacco Regulatory Science' and 'In Vitro Exposure Systems and Dosimetry Assessment Tools for Inhaled Tobacco Products', bringing together a community of industry, academic and regulatory scientists to support the development, harmonization and standardization of in vitro applications for tobacco product and EC testing [166,167]. The workshops have explored methods and standards supporting these topic areas and are driving in vitro standardization with the support of technical working groups, sharing of data and publication of key findings.

More prospective clinical trials are needed to provide meaningful insights on the effects of EC aerosol on lung health and to generate findings that are most relevant to researchers, policy makers and users. Clinical research has described no serious adverse events, although the potential for such reactions cannot be completely excluded. Minor acute reactions have been reported, but it is not known if they are indicators of potential future lung disease, and no significant changes in pulmonary function were observed in short term trials. Smokers who substituted EC use experienced improvements in smoking symptoms (cough, phlegm, etc.) and exhibited lower levels of exhaled CO, particularly for those with complete EC substitution. For smokers with diseases such as asthma and COPD, EC use may have a beneficial effect on symptoms. Yet to completely test the effects of EC on lung function, specific data is needed for each of the hundreds of e-liquid flavor combinations and the many different types of devices. This data can be provided by cell studies and animal models, but the current research designs must be substantially improved to yield accurate findings for understanding the respiratory health risks and benefits of EC use by smokers.

In an *Expert Review in Respiratory Medicine* article published about 7 years ago [168], we discussed several important research developments and future avenues for e-cigarette science. In the authors' view, those expert opinions have been substantiated by the growing body of evidence. We therefore reiterate our prediction that EC use is the most effective method of substituting tobacco cigarette for those smokers who are unable or unwilling to quit and we are now confident that current vaping products are much less harmful than conventional cigarettes as well as earlier EC designs.

This narrative review has identified many gaps in EC science and identified specific research needs important for advancing current knowledge about health effects from e-cigarette use. In particular it is paramount to improve research methods, data quality and interpretation of study findings. In relation to experimental in vitro and animal models, exposure studies must be representative of human inhalation exposure to e-cigarette aerosols under normal condition of use and include relevant controls. In relation to human behavioral/market research, it is important to develop and standardize new questionnaires for improved assessments of dependence on e-cigarettes, patterns and frequency of use, as well as device characteristics. In relation to clinical and epidemiological studies, it is mandatory to include as comparison groups individuals who continue to smoke, those who try to quit with other evidence-based tobacco cessation treatments, and those who are not users of tobacco products, including e-cigarettes.

Looking into the future, it is likely that the interest among medical community and patients' associations about risk reduction with ECs among COPD patients will grow because poor quality of life in patients with COPD remains an unmet need and medical management is quite unsatisfactory. Anything that can improve quality of life of COPD patients should not be dismissed lightheartedly. Given that many COPD patients continue smoking despite their symptoms, it will be important to substantiate the role of the EC as a viable, much less harmful alternative.

In the next 5 years there will be more evidence supporting the possible trade-off between vaping products as an 'off-ramp' for adult smokers and an 'on-ramp' to nicotine use for youth. Millions of deaths from cigarette smoking are an immediate, stark, and preventable tragedy that should be fully factored in to a rational risk-benefit analysis.

Independent research will become increasingly important. Tolerability, safety, efficiency, and harm reduction potential of these new technologies will have to be endorsed through independent research. Such an approach is strongly needed to provide rigorous feedback to the industry and informed answers to the regulators.

Potential concern on the absolute risk of existing ECs will be resolved by technological innovation in EC design with the creation of superior and much safer new generation products. A clear understanding of the residual risk of these new products will resolve current concerns about long term health effects. Nonetheless, we should not lose sight of the potential benefits of ECs compared to cigarettes as a lot of people still smoke conventional cigarettes and this will be a public health issue for a number of years to come.

More disruption will occur. The critical distinction in public health and consumer policy is that of a fast-moving tech innovation that is obsoleting combustible tobacco products. This is likely to bring more disruption among the enemies of innovation and lovers of status quo in tobacco control. This disruption has been already set in motion; more countries will follow the positive developments in Japan, Korea, England, New Zealand, Canada and Iceland that by promoting a widespread and complete adoption of new technologies it is possible to substantially accelerate declines in smoking prevalence.

Author contributions

All authors revised the article critically for important intellectual content and approved its final version.

Declaration of interest

In relation to his work in the area of tobacco control, R Polosa has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also received support from The Consumer Advocates for Smoke-free Alternatives (CASAA) for publication and open access costs of one paper. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl., and Health Diplomats (consulting company that delivers solutions to global health problems with special emphasis on harm minimization). Lectures fees from a number of European electronic cigarette industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vapers advocacy no-profit organizations. Publication costs for previous work have been met by independent e-cigarette industry including Happy Liquid, Ritchy Europe, Cuts Ice e-Liquid Laboratories and VDLV e-Liquids. R Polosa is the Director of the Center of Excellence for the acceleration of Harm Reduction at the University of Catania (CoEHAR), which has received a grant from Foundation for a Smoke Free World to develop and carry out 8 research projects. R Polosa is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives (CASAA) and the International Network of Nicotine Consumers Organizations (INNCO); Chair of the European Technical Committee for standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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