FDA should prohibit additives and design elements in e-cigarettes known to increase the risk of severe lung injury, but the burden remains with manufacturers to demonstrate that their products are appropriate for the protection of the public health, notwithstanding the fact that their products exclude the prohibited ingredients and designs

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In response to the outbreak of serious lung injuries associated with e-cigarette use or vaping (EVALI) that spiked in the summer 2019, FDA has issued a Request for Information on Vaping Products Associated with Lung Injuries (RFI). The RFI seeks data and information on e-cigarette product design and ways to prevent consumers from modifying or adding substances to those products that were not intended by the manufacturers. Among other things, FDA specifically requests information on specific chemicals, compounds, ingredients, or combinations of ingredients that when inhaled or aerosolized may be associated with EVALI symptoms.

1. **To reduce the likelihood of severe lung injury, FDA should prohibit additives such as vitamin E acetate and flavor compounds that are cytotoxic; only permit the marketing of closed system e-cigarette products; set comprehensive restrictions on device characteristics such as types of coils, resistances, and power settings that generate high coil temperatures and high levels of oxidants; and should ban the sale of compatible components and parts produced by companies to be used in competitors' products.**

There are several regulatory approaches FDA should take that would reduce the likelihood of severe lung injury.

a) **FDA should prohibit additives such as vitamin E acetate and flavor compounds that are cytotoxic.**

Compounds that may be safe to ingest are not necessarily safe to inhale. The literature shows that some flavorants and other additives become lung irritants and potentially dangerous when they are heated and inhaled.

(1) Vitamin E acetate should be prohibited

On September 6. 2019 the New England Journal of Medicine (NEJM) published a report[1] describing 53 cases of severe pulmonary disease associated with the use of vaping products among generally young, healthy persons:

> E-cigarette liquids and aerosols have been shown to contain a variety of chemical constituents that may have adverse health effects. Major declared constituents in nicotine-based e-cigarettes include propylene glycol and glycerin, in addition to nicotine. Identified contaminants include polycyclic aromatic hydrocarbons, nitrosamines, volatile organic chemicals, and inorganic chemicals such as toxic metals. Endotoxins and flavoring compounds such as diacetyl and 2,3-pentanedione have also been detected. The health risks of some constituents remain poorly characterized, and toxicologic assessment of these substances is an active area of ongoing research. In addition to nicotine, e-cigarette devices can be used to deliver a variety of other recreational drugs, including THC-based oils. [citations eliminated]

As of February 18, 2020, a total of 2,807 hospitalized EVALI cases or deaths had been reported to the CDC from all 50 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands, and 68 deaths had been confirmed in 29 states and D.C. Of 2,022 hospitalized patients with data on substance use, 82% reported using THC-containing products, 33% reported exclusive use of THC-containing products, 57% reported using nicotine-containing products, and 14% reported exclusive use of nicotine-containing products.[2] While no single product is linked to all cases of lung disease, vitamin E acetate (tocopheryl acetate), a solvent used in some THC-containing vaping products, has been strongly linked to the EVALI outbreak. In analyzed samples from 51 EVALI cases, Vitamin E acetate was identified in bronchoalveolar lavage (BAL) fluid samples (fluid samples collected from the lungs) from 48 of the 51 EVALI patients, but not in the BAL fluid from the healthy comparison group.[2]

The extent to which vitamin E acetate has been used in e-cigarettes is not known due to a lack of oversight of e-cigarette manufacturing and the ease of product manipulation by retailers and users. The rationale for use of vitamin E acetate in nicotine e-cigarettes is not clear either. Vitamin E acetate is used as a diluent in THC extract-containing vaporizers to increase the volume of extract and boost profit margins. On the other hand, nicotine can be purchase in bulk at low cost. Nicotine is also not a viscous material and does not need to be "thinned" to be used in nicotine e-cigarettes.

Although Vitamin E acetate is not known to be harmful when ingested as a vitamin supplement or when applied to the skin, data on its inhalation effects suggest that its oil-like properties could be associated with the observed pulmonary symptoms.[3] Exogenous lipoid

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[1] Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Final Report. N Engl J Med. 2020;382(10):903–916. doi:10.1056/NEJMoa1911614

[2] Centers for Disease Control and Prevention, Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products (updated February 25, 2020). Available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-information

[3] Sun, LH, Contaminant found in marijuana vaping products linked to deadly lung illnesses, tests show. https://www.washingtonpost.com/health/2019/09/05/contaminant-found-vaping-products-linked-deadly-lung-illnesses-state-federal-labs-show/

pneumonia can occur when an oil is inhaled. Once inhaled into the lungs, the oil can cause an inflammatory reaction, and the severity of the reaction can depend on the length of exposure. Severe inflammation can permanently damage the lungs. Lipid-laden macrophages and acute lung injury associated with e-cigarette inhalation has been reported previously.[4] Evidence also suggests that the pathology of EVALI may be driven by the chemical toxicity of the inhaled products. Based on biopsies from 17 EVALI patients, the authors of the study said, "the histologic changes instead suggest that vaping-associated lung injury represents a form of airway-centered chemical pneumonitis from one or more inhaled toxic substances rather than exogenous lipoid pneumonia as such."[5]

Absent specific evidence demonstrating the safety of aerosolizing and inhaling a specific "oil" in a specific product, FDA should adopt the precautionary principle and prohibit vitamin E acetate and other fatty acids ("oils") in e-cigarettes.

(2) Flavor compounds that are cytotoxic should be prohibited

Many flavor compounds and other additives in e-cigarettes become lung irritants when heated (even if not combusted) and inhaled. Because e-cigarettes produce aerosols for inhalation, when considering flavorants and other additives in e-cigarettes, FDA must not rely on previously established designations that these constituents are "generally recognized as safe" (GRAS) for ingestion. ***Inhalation is a fundamentally different exposure mode than ingestion, so the fact that a substance is GRAS for ingestion provides no useful information regarding safety for inhalation.***

Erythropel et al.'s October 2018 study[6] found flavor aldehyde PG acetals in commercial e-liquids, and concluded that e-liquids are potentially reactive chemical systems in which new compounds can form after mixing of constituents and during storage, and these can have unexpected toxicological effects. Erythropel et al.'s 2019 study[7] reported the presence of flavor aldehyde VG acetals in e-liquids and aerosols, and found that the compounds present in some Juul e-liquids (e.g., crème brulee) are delivered efficiently to the aerosol when heated, exposing users to the PG and VG acetals of vanillin. Appreciable amounts of acetals were present in the aerosol which, if inhaled, may cause irritation and contribute to inflammatory responses. This study demonstrates that e-cigarette liquids can be chemically unstable, with reactions occurring between flavorant and solvent components immediately after mixing at room temperature. The resulting compounds have toxicological properties that differ from either the flavorants or

[4] Masayuki I, Kazutetsu A, Yoriko H, et al., Lung injury associated with electronic cigarettes inhalation diagnosed by transbronchial lung biopsy. Respirology Case Reports, 6 (1), 2018, e00282, doi: 10.1002/rcr2.282

[5] Butt YM, Smith ML, Tazelaar HD, et al. Pathology of Vaping-Associated Lung Injury. N Engl J Med. 2019;381(18):1780–1781. doi:10.1056/NEJMc1913069

[6] Erythropel HC, Jabba SV, deWinter TM, et al., Formation of flavorant–propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids, *Nicotine & Tobacco Research*, Volume 21, Issue 9, September 2019, Pages 1248–1258, https://doi.org/10.1093/ntr/nty192

[7] Erythropel HC, Davis LM, deWinter TM, et al., Flavorant-Solvent Reaction Products and Menthol in JUUL E-Cigarettes and Aerosol. Am J Prev Med. 2019 Sep;57(3):425-427. doi: 10.1016/j.amepre.2019.04.004. Epub 2019 Jul 27.

solvent components. ***These findings suggest that the reporting of manufacturing ingredients of e-liquids (including the reporting of HPHCs) is not alone sufficient for a safety assessment. Rather, to effectively analyze the risks, FDA should require companies to establish an analytical workflow to detect newly formed compounds in e-liquids and their potential toxicological effects.***[7]

Omaiye et al.[8] studied the flavor chemical and nicotine concentrations in 8 currently marketed Juul e-cigarette pods to evaluate the cytotoxicity and potential health impacts. They identified 59 flavor chemicals in Juul pod fluids, and found that all pod fluids were cytotoxic at a 10% dilution, and most aerosols were cytotoxic at concentrations between 0.2 and 1.8%. The study demonstrated that not only are the Juul flavor pods attractive to youth, but the concentrations of nicotine and some flavor chemicals (e.g., ethyl maltol) are high enough to be cytotoxic in acute *in vitro* assays, suggesting that Juul products could lead to adverse health effects with chronic use.

Jabba and Jordt found[9] that mint- and menthol-flavored e-cigarettes contain extremely high levels of pulegon. Pulegone, a constituent of oil extracts prepared from mint plants, is a carcinogen that causes hepatic carcinomas, pulmonary metaplasia, and other neoplasms in rodents, and can also cause liver and kidney failure. Although the FDA banned synthetic pulegone as a food additive in 2018 and the chemical is banned in the European Union and in the state of California, substantial amounts of pulegone have been detected in mint- and menthol-flavored e-cigarette liquids and smokeless tobacco products.

Jabba and Jordt's analysis measured daily pulegone exposure from e-cigarettes and smokeless tobacco at higher levels compared with exposure from menthol cigarettes and compared the risk associated with pulegone content in combustible menthol cigarettes to the pulegone content in mint- and menthol-flavored e-cigarettes and smokeless tobacco. The margin of exposure (MOE) is the measure used by the FDA and other regulatory agencies for cancer risk assessment of food additives, and cancer risk is inversely proportional to the MOE, with values of 10,000 or below requiring mitigation strategies. Jabba-Jordt's study found that the MOE for all the products that were analyzed are below the accepted MOE threshold of 10,000 for carcinogens. This suggests that users of mint- and menthol-flavored e-cigarettes are exposed to pulegone levels higher than the FDA considers unacceptable for intake of synthetic pulegone in food, and higher than in smokers of combustible menthol cigarettes. Omaiye's study[7] found that mint-, menthol-, and cucumber-flavored Juul pods, not studied in the Jabba/Jordt analysis, also contain pulegone.

[8] Omaiye EE, McWhirter KJ, Luo W, Pankow JF, Talbot P. High-Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations. *Chem Res Toxicol.* 2019;32:1058-1069.

[9] Jabba SV, Jordt SE, Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. JAMA Intern Med. 2019 Sep 16. doi: 10.1001/jamainternmed.2019.3649. [Epub ahead of print]

Because these findings establish health risks associated with pulegone intake, especially in connection with use of mint- and menthol-flavored e-cigarettes, FDA should prohibit pulegone in e-cigarettes.

Further, a study by Khlystov and colleagues suggests that flavors are major contributors to emissions of toxic aldehydes from e-cigarettes.[10]

These findings build on a 2016 study[11] that investigated the cellular effects of exposure to e-cigarette aerosol and the impact of various product characteristics on potential inhalation toxicity of e-cigarette products. The researchers found that exposure to e-cigarette aerosol resulted in decreased metabolic activity and cell viability, and flavors in e-liquids can have an acute cytotoxic effect on respiratory cells. In this study, menthol, coffee, and strawberry flavors had a significant impact on overall cytotoxicity of e-cigarette products. However, the study did not identify which of the flavoring compounds caused this cytotoxicity and release of inflammatory mediators, and only one e-liquid product was tested for each flavor name. The study also confirmed that increasing the device power by increasing battery output voltage resulted in significantly higher overall toxicity of e-cigarette aerosol.

Earlier studies had already found that inhalation of complex mixtures like flavored e-cigarette aerosols can cause a wide range of adverse health effects, ranging from simple irritation to systemic diseases.[12] Cinnamon flavorings in refill fluids were found to be linked to cytotoxicity, which could adversely affect e-cigarette users.[13]

Clapp et al showed that inhalation of cinnamaldehyde in flavored e-cigarette liquids may increase the risk of respiratory infections in e-cigarette users.[14] Gerloff et al showed that flavorings such as acetoin (butter), diacetyl, pentanedione, maltol (malt), ortho-vanillin (vanilla), coumarin, and cinnamaldehyde in some flavored e-cigarette liquids and aerosols can cause significant loss of epithelial barrier function and proinflammatory response in lung cells.[15] Muthumalage et al found that commonly used e-cigarette flavoring chemicals, including diacetyl, cinnamaldehyde, acetoin, pentanedione, o-vanillin, maltol and coumarin, can trigger an inflammatory response in monocytes and increased oxidative stress, and mixing a variety of flavors results in greater cytotoxicity and oxidative stress and may be more harmful to users,

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[10] Khlystov A, Samburova V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. Environ Sci Technol. 2016;50(23):13080-5.

[11] Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). Tob Control. 2016;25(Suppl 2):ii81–ii87. doi:10.1136/tobaccocontrol-2016-053205

[12] Hayes A, Bakand S. Inhalation Toxicology. In: Luch A, editor. Molecular, Clinical and Environmental Toxicology. Basel, Switzerland: Birkhäuser; 2010. pp. 461–88

[13] Behar R, Davis B, Wang Y, et al. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. Toxicol In Vitro. 2014;28:198–208. doi: 10.1016/j.tiv.2013.10.006

[14] Clapp PW, Lavrich KS, van Heusden CA, et al., Cinnamaldehyde in flavored e-cigarette liquids temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. Am J Physiol Lung Cell Mol Physiol 2019 Mar 1;316(3):L470-L486. doi: 10.1152/ajplung.00304.2018. Epub 2019 Jan 3.

[15] Gerloff J, Sundar IK, Freter R et al. Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography-mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. Appl Vitro Toxicol 2017; 3(1): 28–40

providing insights into potential pulmonary toxicity and tissue damage in e-cigarette users.[16] Park et al found that two widely used e-cigarette flavoring chemicals, diacetyl (often used in butter flavors) and its substitute 2,3-pentanedione, impair the cilia function in airway epithelium and likely contribute to the adverse effects of e-cigarettes in the lung.[17]

b) FDA should only permit the marketing of closed system e-cigarette products and should prohibit the sale of refillable tanks and e-liquid refills.

FDA should not authorize the marketing of any new e-cigarette product unless it is a truly tamper-proof, closed system. To this end, manufacturers seeking PMTA authorization must demonstrate with sufficient scientific/engineering evidence that their proposed new e-cigarette products cannot be modified to add new components, cartridges, or e-liquid refills that are not intended by the manufacturer for use with its product.

Refillable tanks and e-liquid refills must therefore be prohibited. FDA should only authorize through the PMTA process the sale of prefilled cartridges, closed tanks, and pods that have obtained specific FDA review and authorization for use with a particular product.

c) **FDA should set comprehensive restrictions on device characteristics such as types of coils, resistances, and power settings that generate high coil temperatures and high levels of oxidants**

The power supplied to heat the e-liquid is a function of the voltage from the battery and the resistance of the coil/atomizer ($P = V^2/R$, where P is electrical power, V is voltage, and R is resistance). The degree to which the e-liquid is heated, which influences aerosol production as well as generation of thermal breakdown products, depends on both the electrical characteristics of the e-cigarette (voltage, resistance) and e-liquid properties, such as mass of e-liquid and specific heat capacity of the e-liquid, as shown in the equation below.

$$Temperature\ rise = \frac{Power \times Time}{Mass \times Specific\ heat\ capacity}$$

FDA has to place limits on allowable power of e-cigarettes, but to be effective, regulation can't be done in a 'one size fits all' approach. Given the variation in metals, coil sizes and shapes, and resistance of atomizers on the market, the effect of power on heating the e-liquid is device-specific. Any effort to regulate these variables, and it is important to note that they should be regulated, should be done in a comprehensive manner, taking into consideration all the variables that influence temperature rise of e-liquids when activated. Any effort to simply limit the power of e-cigarettes in the absence of the context of the resistance and gauge of the coils would likely be ineffective.

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[16] Muthumalage T., Prinz M., Ansah K.O., Gerloff J., Sundar I.K., Rahman I. Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine. Front. Physiol. 2017;8:1130. doi: 10.3389/fphys.2017.01130.

[17] Park HR, O'Sullivan M, Vallarino J, Shumyatcher M, Himes BE, Park JA, et al. Transcriptomic response of primary human airway epithelial cells to flavoring chemicals in electronic cigarettes. Sci Rep. 2019;9(1):1400. doi: 10.1038/s41598-018-37913-9

d) **FDA should ban the sale of compatible components and parts produced by companies that are intended to be used in competitors' products**

Some popular e-cigarettes, such as JUUL, foster creation of accessories, components and parts by entities separate from the manufacturers of these popular products. For example, there are several JUUL-compatible pods on the market.[18] There are also devices that can be attached to the mouthpiece of devices such as JUUL pods. The website of one product describes the product as, "a set of rubberized silicone pod attachments, affixing to the top of the pod as a mouthpiece, delivering additional flavor through the crush-able flavor capsule within the silicone skin."[19] It is not known what chemicals are used as flavorants in these products.

FDA should immediately ban the sale of these compatible pods, accessories, components, and parts.

2. Although FDA should prohibit certain ingredients and design characteristics in e-cigarettes that are currently known to pose clear risks to lung health, FDA should not consider such a list as exhaustive; rather, e-cigarette manufacturers seeking PMTA authorization have the burden of demonstrating that their products are appropriate for the protection of the public health.

Manufacturers seeking marketing authorization for new e-cigarettes have the legal burden of demonstrating that their products are "appropriate for the protection of the public health" (APPH).[20] As described above, there are several ingredients and design characteristics in e-cigarettes that can clearly pose a risk for serious lung injury and should be prohibited by FDA. However, any FDA-created list of prohibited e-cigarette ingredients and/or design components associated with EVALI should set a floor, not a ceiling, for establishing that a proposed new e-cigarette product is APPH because known toxicants and dangerous designs are absent. E-cigarette manufacturers must not consider such a list a safe harbor or how-to manual for product design, and FDA must not automatically authorize the marketing of proposed new e-cigarettes solely because they do not contain ingredients or use design elements that are specifically prohibited on such a list.

FDA's marketing order[21] for IQOS provides an example of how this could happen. FDA's order was based largely on its finding that IQOS contained reduced levels of some chemicals on its list of Harmful and Potentially Harmful Constituents (HPHC).[22] However, independent analyses of Philip Morris International's modified risk tobacco product application showed that IQOS presented other potential dangers, including potential cardiovascular

[18] https://ziipstock.com/collections/all-juul-compatible-pods
[19] https://puffecig.com/puff-krush/#description
[20] Family Smoking Prevention and Tobacco Control Act, §910, Pub. L. No. 111-31, 123 Stat. 1776 (2009).
[21] FDA, Marketing Order, FDA Submission Tracking Numbers (STNs): PM0000424-PM0000426, PM0000479, 30 April 2019. Available at: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders
[22] FDA, PMTA Coversheet: Technical Project Lead Review (TPL), 29 April 2019. Available at: https://www.fda.gov/media/124247/download

impairment,[23] pulmonary and immunosuppressive effects,[24] cytotoxic effects,[25] and hepatotoxic effects,[26] and that the product's potentially misleading labeling,[27] appeal to youth,[28] and the product's likely dual use and impact on non-users were not adequately considered.[29] In issuing its IQOS marketing order, FDA was wrong to prioritize the absence of some HPHCs and exclude consideration of other dangerous aspects of IQOS. Similarly, when reviewing future premarket tobacco product applications for new e-cigarettes, FDA should not consider the fact that ingredients or design features that are specifically prohibited should alone be enough for a determination that the product is APPH.

In determining whether a proposed new product is APPH, FDA is required to consider whether the manufacturer submitted sufficient evidence showing an increased likelihood that existing users of tobacco products will stop using, and a decreased likelihood that nonusers of tobacco products (including youth) will start using tobacco products. Unfortunately, FDA's IQOS authorization demonstrates that it may permit companies who meet a set minimum standard to market products that will later be found to contain dangerous constituents, or that may increase the usage of tobacco products through dual usage, marketing tactics, appeal to youth, and/or other factors.

It must be understood that manufactures whose e-cigarette products comply with such a list would meet necessary, but not sufficient, steps in demonstrating that their proposed products are appropriate for the protection of the public health.

3. FDA should make premarket tobacco product applications (PMTAs) available for public inspection and comment.

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[23] Nabavizadeh P, Liu J, Havel CM, et al. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. Tob Control. 2018;27(Suppl 1):s13–s19. doi:10.1136/tobaccocontrol-2018-054325

[24] Moazed F, Chun L, Matthay MA, Calfee CS, Gotts J. Assessment of industry data on pulmonary and immunosuppressive effects of IQOS. Tob Control. 2018;27(Suppl 1):s20–s25. doi:10.1136/tobaccocontrol-2018-054296

[25] Leigh NJ, Tran PL, O'Connor RJ, Goniewicz ML. Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. Tob Control. 2018;27(Suppl 1):s26–s29. doi:10.1136/tobaccocontrol-2018-054317

[26] Chun L, Moazed F, Matthay M, Calfee C, Gotts J. Possible hepatotoxicity of IQOS. Tob Control. 2018;27(Suppl 1):s39–s40. doi:10.1136/tobaccocontrol-2018-054320

[27] McKelvey K, Popova L, Kim M, et al. IQOS labelling will mislead consumers. Tob Control. 2018;27(Suppl 1):s48–s54. doi:10.1136/tobaccocontrol-2018-054333

[28] McKelvey K, Popova L, Kim M, et al. Heated tobacco products likely appeal to adolescents and young adults. Tob Control. 2018;27(Suppl 1):s41–s47. doi:10.1136/tobaccocontrol-2018-054596

[29] Max WB, Sung HY, Lightwood J, Wang Y, Yao T. Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product. Tob Control. 2018;27(Suppl 1):s82–s86. doi:10.1136/tobaccocontrol-2018-054572

The Tobacco Control Act[30] requires FDA to make modified risk tobacco product applications (MRTPAs) publicly available, to request public comments on the information contained in the MRTPA, and to refer submitted MRTPAs to the Tobacco Products Scientific Advisory Committee (TPSAC). Although the Tobacco Control Act[31] does not *require* FDA to make PMTAs available for public inspection or comment, ***FDA is free to use its discretion to refer the PMTAs to TPSAC and thereby make the applications available for public comment by independent scientists.***

Doing so would allow the public the opportunity to assess whether permitting a new tobacco product to be marketed would be appropriate for the protection of the public health, and to give FDA input about the potential health or safety issues with the proposed new product. Following this process would underscore the responsibility of tobacco companies to design products that benefit the public health, rather than shifting that burden to the FDA (and, by extension, to the public through the FDA's RFI process) to set a minimum standard that would prohibit only the most dangerous hazards that are known at the time that standard was set.

Conclusion

E-cigarettes and other vaping products are complex tobacco products that can be engineered with selective components to achieve a manufacturer's desired goals (e.g., making a product that is more addictive, has a smoother throat hit, produces more aerosol, or offers a sweeter flavor). Indeed, from the 1950s through the 1970s, the cigarette companies demonstrated in internal, largely unpublished research that they could substantially reduce selective substances in cigarette smoke, but the result was the increase in other components.[32] By the mid-1970s, they had abandoned the effort as technologically impossible and legally and politically dangerous. In 2009 the Tobacco Control Act was enacted with a key provision that requires ***companies*** to demonstrate that their products that are "appropriate for the protection of the public health (APPH)"[33] before they can obtain FDA authorization to market their tobacco products (including e-cigarettes).

The legal burden is on the companies, not on the public or FDA, to design products that meet the APPH standard. In the case of e-cigarettes and other vaping products, ***this law requires manufacturers to demonstrate, among other things, not only that their proposed products would not cause EVALI, but also that their products are otherwise APPH. The importance of this requirement has been made even more starkly evident with the COVID-19 outbreak, since damage to the lungs from vaping can lead to more severe COVID-19 symptoms.***

[30] Family Smoking Prevention and Tobacco Control Act, §911(e) and (f), Pub. L. No. 111-31, 123 Stat. 1776 (2009).
[31] Family Smoking Prevention and Tobacco Control Act, §910, Pub. L. No. 111-31, 123 Stat. 1776 (2009).
[32] Glantz SA, Slade J, Bero LA, et al. The Cigarette Papers. University of California Press,1996. Chapter 4: The Search for a "Safe" Cigarette. Available at: https://publishing.cdlib.org/ucpressebooks/view?docId=ft8489p25j&chunk.id=d0e3989&toc.depth=1&toc.id=d0e3989&brand=ucpress
[33] Family Smoking Prevention and Tobacco Control Act, §910, Pub. L. No. 111-31, 123 Stat. 1776 (2009).

Further, the FDA exercise its discretion and make e-cigarette (and other new tobacco product) PMTA's available to the public and the scientific community for public comment so that they can advise the FDA on the specifics of any product application.