



December 22, 2017

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0227

The undersigned organizations submit these comments in the above-designated docket, which provides interested parties the opportunity to submit comments on a proposal for a “Good Manufacturing Practices Regulation to Account for FDA’s Deeming Regulation” made by various manufacturers of tobacco products in this docket on June 7, 2017. *See* 82 Fed. Reg. 55613 (November 22, 2017).

*Summary of Arguments*

1. The Tobacco Control Act requires FDA to establish regulations governing the design and manufacture of e-cigarettes.
2. FDA has long experience establishing regulations for current good manufacturing practices for a wide range of regulated products and should itself establish such regulations rather than adopting self-serving regulations developed by the regulated industry.
3. FDA should explicitly identify the objectives of such regulations.
4. The standards suggested by the RAI letter are inadequate to protect the public health.
5. Extensive evidence demonstrates that the absence of such regulations unnecessarily exposes consumers to products that are both hazardous and addictive.
6. Good manufacturing practices should include requirements that products be consistently produced to specifications. Prompt promulgation of good manufacturing practices is particularly important to protect consumers during the several years before the new deadline for submission of premarket applications.
7. Good manufacturing practices should prohibit the use of flavorings that may contribute to the presence of toxins and carcinogens in the final product.

8. Good manufacturing practices should require consistent and accurate nicotine content and delivery in e-cigarette products.
9. Good manufacturing practices should require that e-cigarettes claiming to be nicotine-free actually contain no nicotine.
10. Good manufacturing practices should require basic quality standards for e-cigarette devices and their components.
11. Good manufacturing practices should require specific responsibilities for qualified personnel to effectively design, produce, enforce quality control, ship, handle, and store products.
12. Good manufacturing practices are especially important for products, such as e-cigarettes and e-liquids, that are predominantly manufactured abroad, particularly in China, where production standards may not be adequate and regulations not adequately enforced.
13. The fact that some small manufacturers may be required to become resellers rather than manufacturers is not a valid objection to promulgation of good manufacturing practice requirements.

### *Discussion*

#### **1. The Tobacco Control Act requires FDA to establish regulations governing the design and manufacture of e-cigarettes.**

Section 906(e) of the Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act of 2009 (“the Act”), *requires* the Secretary to prescribe regulations “. . .requiring that the methods used in, and the facilities used for, the manufacture, preproduction design validation (including a process to assess the performance of a tobacco product), packing and storage of a tobacco product conform to current good manufacturing practice, or hazard analysis and critical control point methodology. . .to ensure that the public health is protected and that the tobacco product is in compliance with [the provisions of the Act].”

In 2013 FDA sought comments on recommendations for “good manufacturing practices” (GMP) for products then subject to regulation by the Center for Tobacco Products and the undersigned organizations submitted comments on May 20, 2013. These comments concluded that FDA should set standards for manufacturing practices for such products. Despite the statutory requirement and despite the 2013 submission of comments, FDA has taken no further steps to establish standards for manufacturing practices for such products. The undersigned continue to urge FDA to follow the recommendations made in their previous comments filed in this docket with regard to tobacco products regulated by FDA in 2013.

Section 906(e) also unconditionally requires FDA to prescribe manufacturing process standards for the newly deemed tobacco products and a failure to do so would be inconsistent with FDA's obligation to protect the public health. The establishment of such standards has been an integral part of FDA's regulatory program for other products subject to regulation under the Food, Drug, and Cosmetic Act. FDA has promulgated regulations establishing current good manufacturing practices for food products (21 CFR § 110); drugs (21 CFR § 210 ff.); medical devices (21 CFR § 820); blood and blood components (21 CFR § 606 ff.); food for animals (21 CFR § 507 ff.); infant formula (21 CFR § 106 ff.); dietary supplements (21 CFR § 111 ff.); and other regulated products. For instance, for drugs FDA has stated that the purpose of such current good manufacturing practices is to

provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.<sup>1</sup>

Although the standard applicable to tobacco products is different from the standards applicable to other products regulated by FDA, the need to prevent "contamination, mix-ups, deviations, failure, and errors" exists for tobacco products as well and the absence of any such standards with regard to e-cigarettes is a cause for concern. As noted in more detail below, in the absence of such requirements, a consumer can have no assurance about the level of nicotine in any e-cigarette product or even whether such a product actually contains nicotine; no assurance about the existence or the level of toxins or carcinogens in the product she is consuming; no assurance about the measures taken by the manufacturer to ensure that toxins or carcinogens are not present in the product or, if they are, at what levels; no assurance that the product was manufactured in accordance with an established protocol designed to ensure that it conforms to specification; no assurance that there even are specifications for such product; no assurance that there is a validation process for quality control; no assurance that the batch from which a product is drawn has the same constituents as a prior batch; and no assurance that the product has been stored or distributed in a manner consistent with any standard.

These concerns are not abstract problems: consumers actually face every one of these uncertainties. In the absence of regulation, thousands of e-cigarette products have been marketed

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<sup>1</sup> Facts About Current Good Manufacturing Practices (CGMPs), <https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/unc169105.htm>.

without any regulatory control and consumers have no greater assurance about the contents of the products, the method of their manufacture, the level of contaminants and hazardous substances, and the level of nicotine than they did before FDA asserted jurisdiction. Moreover, by virtue of FDA's extension of the deadline for the filing of applications for marketing by e-cigarette manufacturers, these uncertainties will continue to threaten the public health for years to come. Under these circumstances, the prompt promulgation of standards for manufacturing practices for e-cigarette products, while not a substitute for premarket review, can contribute to the protection of the public health by establishing minimum requirements for keeping products on the market prior to the deadlines for submission of marketing applications.

Requirements for good manufacturing practices should extend to all phases of the manufacturing process, including product design; design, construction and maintenance of manufacturing facilities; procedures for quality control; testing facilities and procedures; distribution; storage; and employee qualification and training. The detailed systems FDA has required for other products subject to its jurisdiction can be adapted for application to the manufacture of e-cigarette products. The prompt adoption of such systems is particularly important in light of the addictiveness of the product, the proliferation of such products, the ease by which potentially unqualified manufacturers have entered the market, consumers' lack of information about the sources of such products, and the inability of consumers to distinguish between the relative hazards posed by different products.

## **2. FDA should itself establish the substantive content of GMP regulations.**

FDA itself should establish strict GMP<sup>2</sup> regulations rather than adopting regulations previously developed by industry participants. The 2012 industry proposal for the establishment of good manufacturing practices suggested that FDA adopt standards developed by manufacturers. The undersigned organizations opposed the manufacturers' 2012 proposal, arguing that the regulations proposed by the industry were grossly inadequate and that the establishment of such regulations was appropriately the role of FDA, not of the regulated entities.<sup>3</sup> Moreover, the undersigned organizations specifically objected to the narrow scope of the regulations urged by the industry, which virtually ignored the inherent lethality of cigarettes and would have done nothing to protect the public health.

When FDA establishes current good manufacturing practices for e-cigarettes, it is important for it to do so independently and not merely provide validation for an industry proposal. FDA has long experience and expertise in fashioning regulations establishing such practices and should not depend on self-interested regulated entities to supply the substance of

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<sup>2</sup> It has been suggested that describing any manufacturing practices for tobacco products as "good" is inherently contradictory. For ease of reference, this comment uses the term "good manufacturing practices" or "GMP," which term is also used in the Tobacco Control Act, without taking a position on whether a different characterization of such manufacturing practices would be preferable.

<sup>3</sup> A copy of the May, 2013 comment submitted by the undersigned organizations is attached. The undersigned organizations reiterate those comments.

such regulations. As recommended by Dr. Gideon St. Helen in separate comments on this docket, FDA should set “standards and tests to evaluate product performance and safety” that are “science-based, with the goal of protecting public health as the sole determinant.”

The undersigned organizations note that the manufacturers have offered to meet and work with FDA in the establishment of such regulations. The undersigned organizations strongly believe that in developing any such regulations FDA also should meet and work with representatives of the public health community. Industry representatives should not be the only non-governmental parties who contribute to the development of such regulations.

### **3. FDA should identify the objectives of GMP regulations.**

The objectives of GMP regulations should include all of the following:

- To ensure that products are designed to minimize the presence of toxins and carcinogens in such products, including but not limited to metals, tobacco-specific nitrosamines (TSNAs) and other harmful or potentially harmful components;
- To ensure that manufacturing facilities are designed, maintained, and operated in a manner that makes possible the manufacture of products while minimizing toxins or carcinogens;
- To ensure that specifications exist for all such products;
- To ensure that procedures are established and actually implemented to validate the conformity of products and product components to specifications;
- To ensure that the manufacturing process results in batches that consistently conform to specifications;
- To ensure that a specification exists for nicotine content and delivery, and that it is met;
- To ensure that personnel responsible for design, production, quality control, shipping, handling and storage of such products are qualified to perform their duties and actually do so effectively.

### **4. The standards suggested by the tobacco product manufacturers in their June 7, 2017 letter are inadequate.**

The standards for good manufacturing practices suggested by the tobacco product manufacturers in their June 7, 2017 letter (the “RAI letter”) are inadequate to meet the objective of protecting the public health. The inadequacy of their proposal becomes evident when that proposal is compared to the standards for good manufacturing FDA has established for drugs and devices. In this connection, it is important to note that good manufacturing practices for drugs and devices already accord manufacturers ample flexibility. There is no reason why standards

for good manufacturing practices for e-cigarettes should accord even more flexibility. The following specifics are representative of this failing.

The first bullet in the RAI letter concerns design requirements and specifications. The analogous quality system (QS) regulation for medical devices, 21 CFR 820.30, contains provisions about design review, validation, and verification requirements that are missing from the RAI letter. Also, the RAI letter focuses on “changes” to a specification, process, or procedure, whereas the QS regulation also concerns controls of the design specifications and processes, not just changes thereto. Also, this bullet refers to “qualifying” changes, not “validating” them as in the regulations. The use of “qualification” rather than “validation” occurs throughout the RAI letter. The original 2012 preamble (at p. 8) noted that the word choice was intentional, clearly meant to set a lower bar without identifying any justification for such a departure. The RAI letter also does not justify requiring only “qualification” for methods, processes, and specifications for e-cigarettes.

The second bullet appears analogous to 21 CFR 820.70 and 820.75 to address when “results of a process cannot be fully verified.” In that circumstance, the QS regulation (820.75(a)) requires process validation “with a high degree of assurance,” a standard that has been eliminated, without explanation, by the recommendation in the RAI letter.

The third bullet, concerning “procedures for controlling and verifying the acceptability of process capability and product characteristics,” is analogous to 21 CFR 820.250. However, the existing regulation requires “valid statistical techniques.” And rather than a “documented rationale” in the RAI letter, the regulation requires a “valid statistical” rationale. In addition, the regulation requires that changes to sampling plans must be “reviewed and documented;” the RAI letter says only that they must be “reviewed.”

The fifth bullet refers to testing of samples from each product batch. The FDA regulation for drugs (21 CFR 211.110) refers to a statistical sampling and testing plan to ensure conformance to product specifications. Moreover, 21 CFR 211.165 refers to statistical quality control criteria. The RAI letter appears clearly designed to lower the bar, requiring only conformance “within reasonable, demonstrable manufacturing variance.” The RAI letter provides no justification for this departure.

The seventh bullet concerns the volume and retention period of product samples. The RAI letter proposes retention of “an appropriate number” for the expected shelf-life of the product. The drug GMP regulation (211.170) says the manufacturer should retain at least two times the quantity needed to conduct tests to determine conformity to specifications, and directs retention for a period after the expiration date that is linked to the shelf-life. Again, the RAI letter appears to be a watered-down version of existing standards and provides no justification for such a departure.

**5. Establishment of good manufacturing practices is needed to minimize the presence of hazardous constituents and contamination that has been documented in currently available e-cigarettes.**

Evaluation of products and aerosol from products has shown that some e-cigarettes expose users to a variety of toxicants and carcinogens, including carbonyl compounds (such as formaldehyde, acetaldehyde, and acrolein), volatile organic compounds, metals, and even tobacco-specific nitrosamines. There is no reason why the presence of such substances in e-cigarette products should not be minimized or eliminated and establishment of appropriate good manufacturing practices would do so.

Presentations made to FDA when the agency held workshops in December 2014, March 2015, and June 2015, clearly demonstrated that e-cigarettes and components contained and produced toxicants and carcinogens. At FDA's December workshop, Dr. Michael Trehy of FDA's Center for Drug Evaluation and Research accurately stated, "There are product quality issues in the marketplace, which the consumer would have difficulty identifying."<sup>4</sup>

One presentation to FDA showed high levels of nickel in e-cigarette aerosol, as well as tin, which could be traced back to poor solder joints in the device.<sup>5</sup> Other research presented to FDA showed the presence of highly toxic ethylene glycol, a compound found in antifreeze, in varying amounts of the solvents used for e-liquids.<sup>6</sup> These are just a few examples of how defective manufacturing can unnecessarily expose users to toxicants and they underscore the need for strong manufacturing practices, which should prohibit and prevent dangerous contamination.

Newer research confirms that metals continue to be present in e-cigarettes and aerosol, and that contamination is often due to manufacturing issues. A recent study found nickel, chromium, manganese, and lead in the liquid of cigalike products, which varied within and between brands. Nickel is a class 1 carcinogen, chromium is associated with lung disease such as emphysema and in a carcinogen in some forms, manganese is a strong neurotoxicant, and lead harms many organs and body systems. The researchers noted that consumers would have a hard time determining which products would provide less exposure to toxic metals.<sup>7</sup> These problems demonstrate why strong manufacturing standards are needed to protect consumers against dangers that otherwise would not be apparent to them.

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<sup>4</sup> Trehy, ML, *Nicotine, Nicotine Related Impurities and Additives in E-Cigarette Cartridges and Refills*, Presentation at the FDA "Electronic Cigarettes and the Public Health: A Public Workshop," December 10, 2014.

<sup>5</sup> Williams M, *Metals and Silicates Identified in Electronic Cigarette Fluid and Aerosol*, Presentation at the FDA "Electronic Cigarettes and the Public Health: A Public Workshop," December 10, 2014; Williams, M, et al., "Metal and Silicate Particles Including Nanoparticles Are Present in Electronic Cigarette Cartomizer Fluid and Aerosol," *PlosOne*, 8(3), March 2013.

<sup>6</sup> Hutzler, C, "Chemical hazards present in liquids and vapors of electronic cigarettes," *Archives of Toxicology* 88(7):1295-308, July 2014.

<sup>7</sup> Hess, CA, et al., "E-cigarettes as a source of toxic and potentially carcinogenic metals," *Environmental Research* 152:221-225, 2017.

Another study discussed how silicate glass threads in the sheath and wick of disposable e-cigarettes and e-hookah may become damaged during manufacturing or common use of the product; copper wire and clamps releasing copper nanoparticles; tin, again, from soldered joints; lead also from soldered joints; and zinc from brass clamps or other sources can end up in the aerosol inhaled by users. Each of these elements can cause health problems such as kidney or liver damage, respiratory irritation, decreased pulmonary function, and in the case of lead, which is classified as a carcinogen, cancer. Twenty-one of the 35 metals and elements found in the tested disposable e-cigarettes and e-hookahs were not found in cigarette smoke, and some of the metals and elements were measured at significantly higher levels than in cigarette smoke.<sup>8</sup> Changes to the design and manufacturing can help eliminate or minimize the metals that get into the aerosol,<sup>9</sup> but manufacturers must be required to use those methods.

Toxicant levels are not always consistent across the use of the products, and can vary by the user. One study looking at metals in aerosols emitted from disposable e-cigarettes and e-hookah found that the mix of elements were different between the first 60 puffs of the products and the last 60 puffs. Even more, concentrations of some elements fluctuated within the same brand of product. The authors warned, “Users of EC/EH [e-cigarettes/e-hookah] products, who do not normally have a method to identify ECs/EHs with high concentrations of elements/metals, should be aware of these variations in concentrations between and within brands.” They also advised, “Improvements in manufacturing and design could make element/metal emissions in EC/EH aerosols more uniform within a brand and reduce those that are relatively high in concentration.”<sup>10</sup>

It is also important to note that although some of the harmful substances detected in e-cigarette liquid and aerosol were identified in very low concentrations, we do not know the effect of intense and chronic exposure – with 200-300 daily inhalations – over decades of use.<sup>11</sup> In addition, the safety of the combination of harmful substances has yet to be evaluated.<sup>12</sup>

## **6. Promulgation of good manufacturing practices for e-cigarettes is important to remedy threats to the public health caused by FDA’s blanket extension of the deadline for premarket review.**

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<sup>8</sup> Williams, M, et al., “Elements including metals in the atomizer and aerosol of disposable electronic cigarettes and electronic hookahs,” *PLoS ONE* 12(4):e0175430, 2017. See also, Williams, M, et al., “Strategies to Reduce Tin and Other Metals in Electronic Cigarette Aerosol,” *PLoS ONE* 10(9):e0138933, 2015.

<sup>9</sup> Williams, M, et al., “Strategies to Reduce Tin and Other Metals in Electronic Cigarette Aerosol,” *PLoS ONE* 10(9):e0138933, 2015.

<sup>10</sup> Williams, M, et al., “Elements including metals in the atomizer and aerosol of disposable electronic cigarettes and electronic hookahs,” *PLoS ONE* 12(4):e0175430, 2017.

<sup>11</sup> Pisinger, C & Dossing, M, “A systematic review of health effects of electronic cigarettes,” *Preventive Medicine* 69:248-260, 2014.

<sup>12</sup> Pisinger, C & Dossing, M, “A systematic review of health effects of electronic cigarettes,” *Preventive Medicine* 69:248-260, 2014.

FDA's suspension of premarket review of e-cigarette products until 2022 permits all e-cigarette products on the market on August 8, 2016 to stay on the market until at least August, 2022 and likely much longer. This extension will permit thousands of unregulated and untested products that likely could not pass muster under any reasonable criterion to stay on the market and continue to threaten the public health for years to come. Some e-cigarette products currently on the market are manufactured by entities that lack the capability to produce products consistently to specification, to assure consistency from one batch to another, or to ensure that the product does not contain or produce harmful constituents. No such products could possibly satisfy the requirements for premarket review and a policy that leaves them on the market to threaten public health for years before they are removed serves no valid purpose. Prompt imposition of requirements for good manufacturing practices could be used to mitigate some of the damage done by FDA's unwarranted blanket extension of the deadline for submission of premarket applications.

Although establishment and enforcement of regulations for current good manufacturing practices can serve an important role in eliminating products that would have no chance of satisfying requirements for the grant of a premarket application, such regulations are not a substitute for premarket review to determine if their marketing is appropriate for the public health. The marketing of a product that met the current good manufacturing practices would still not be appropriate for the protection of the public health unless the manufacturer can meet the statutory public health standard. However, FDA could undo a considerable portion of the damage done by the extension of the application deadline for e-cigarette products by promptly establishing and enforcing current good manufacturing practices.

## **7. Establishment of good manufacturing practices should prohibit the use of flavorings that may contribute to the presence of toxins and carcinogens in the final product.**

In the absence of regulatory constraints, e-cigarette manufacturers have created unjustifiable levels of risk by introducing flavorings that themselves increase consumers' exposure to toxic and carcinogenic substances. With more than 7,000 flavors of e-cigarettes and e-liquids on the market at last count,<sup>13</sup> FDA must set parameters to rein in the potential risks presented by flavor additives.

Evidence establishes that many of the flavorings used in e-cigarette products either contain toxins or carcinogens or can contribute to the presence of toxins or carcinogens in the aerosol of e-cigarettes.<sup>14</sup> Such flavorings include the following: diacetyl, which makes e-liquids taste buttery or creamy, has been shown to cause severe and irreversible obstructive lung disease

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<sup>13</sup> Zhu, S-H, et al., "Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation," *Tobacco Control* 23: iii3-iii9, 2014.

<sup>14</sup> Klager, S, et al., "Flavoring chemicals and aldehydes in e-cigarette emissions," *Environmental Science & Technology* 51(18):10806-10813, 2017. Barrington-Trimis, JL, Samet, JM, & McConnell, R, "Flavorings in Electronic Cigarettes: An Unrecognized Respiratory Health Hazard?," *Journal of the American Medical Association*, doi:10.1001/jama.2014. 14830, published online November 10, 2014.

when inhaled in high doses;<sup>15</sup> cherry-flavored products containing high levels of benzaldehyde, which can cause eye pain, conjunctiva redness, burning sensations in the nose and throat, cough and breathing difficulty;<sup>16</sup> and cinnamon flavoring has increased the cytotoxicity of some products.<sup>17</sup> FDA should establish good manufacturing practices that prohibit the use of any such flavorings or additives that could produce those chemicals through aerosolization of the liquid.

Flavor additives can not only contain harmful chemicals, but they also can change the addictiveness and appeal of e-cigarettes. Flavor additives have been found to alter the pH of e-liquids<sup>18</sup> in a way that could impact nicotine absorption.<sup>19</sup>

One study found that high concentrations of menthol improved ratings of liking/wanting e-cigarettes by study subjects, including when paired with high concentrations of nicotine. The authors suggested that among youth, high concentrations of menthol could “increase the rewarding effects of higher concentrations of nicotine, which we hypothesize could promote the development of nicotine dependence.” In addition, even low levels of menthol could increase the appeal of e-cigarettes among youth.<sup>20</sup>

These findings reinforce previous conclusions from FDA and TPSAC on the impact of menthol on cigarette smoking. For instance, FDA’s TPSAC concluded that “[t]he evidence is sufficient to conclude that it is biologically plausible that menthol makes cigarette smoking more addictive.”<sup>21</sup> In its own report, FDA also found that “the data indicate that menthol in cigarettes is likely associated with greater addiction”<sup>22</sup> and “the weight of evidence supports the conclusion

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<sup>15</sup> Barrington-Trimis, JL, Samet, JM, & McConnell, R, “Flavorings in Electronic Cigarettes: An Unrecognized Respiratory Health Hazard?,” *Journal of the American Medical Association*, doi:10.1001/jama.2014.14830, published online November 10, 2014. Farsalinos, KE, et al., “Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins,” *Nicotine & Tobacco Research* 17(2):168-174, February 2015.

<sup>16</sup> Goniewicz, M, *Toxicants in E-Cigarette Refill Solutions and Vapor*, Presentation at the FDA “Electronic Cigarettes and the Public Health: A Public Workshop,” December 10, 2014. Kosmider, L, et al., “Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde,” *Thorax* 71(4):376-377, 2016.

<sup>17</sup> Goniewicz, M, *Toxicants in E-Cigarette Refill Solutions and Vapor*, Presentation at the FDA “Electronic Cigarettes and the Public Health: A Public Workshop,” December 10, 2014, citing Bahl, V. et al., “Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models,” *Reproductive Toxicology* 34:529-537, 2012.

<sup>18</sup> Lisko, JG, et al., “Chemical Composition and Evaluation of Nicotine, Tobacco Alkaloids, pH, and Selected Flavors in E-Cigarette Cartridges and Refill Solutions,” *Nicotine & Tobacco Research* [Advance Access], doi:10.1093/ntr/ntu279, 2015.

<sup>19</sup> St.Helen, G, et al., “Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes,” *Drug and Alcohol Dependence* 178:391-398, 2017.

<sup>20</sup> Krishnan-Sarin, S, et al., “Studying the interactive effects of menthol and nicotine among youth: An examination using e-cigarettes,” *Drug and Alcohol Dependence* 180:193-199, 2017.

<sup>21</sup> FDA TPSAC, *Menthol Report*, <https://wayback.archive-it.org/7993/20170405201750/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM247689.pdf>, 2011, at p. 28.

<sup>22</sup> FDA, *Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes*, 2013, at p. 6.

that menthol in cigarettes is likely associated with increased dependence.”<sup>23</sup> Good manufacturing practices for flavorings should not allow flavor constituents that enhance the addictiveness of the product (such as increasing the absorption of nicotine).

The importance of establishing good manufacturing practices for flavorings is underscored by the preference for flavored e-cigarettes by youth. The most recent data available found that 81 percent of youth aged 12-17 who had ever used e-cigarettes had used a flavored e-cigarette the first time they tried the product, and that 85.3 percent of current youth e-cigarette users had used a flavored e-cigarette in the past month. Moreover, 81.5 percent of current youth e-cigarette users said they used e-cigarettes “because they come in flavors I like.”<sup>24</sup>

## **8. Establishment of good manufacturing practices should require consistent and accurate nicotine content and delivery in e-cigarette products.**

The vast majority – one study found 99% – of electronic cigarettes sold in traditional retail channels in the U.S. contain nicotine at various levels.<sup>25</sup> The nicotine delivery to the user also varies. However, the differences are not always intentional. FDA’s own review of the research literature on nicotine levels found in e-cigarette cartridges, refill solutions, aerosols and environmental emissions found that “[e]-cigarette brands and models differ in the efficacy and consistency of nicotine yields, and the delivery of nicotine is not uniform either from puff-to-puff or across products of the same brand.”<sup>26</sup> There also is substantial evidence that the level of concentration of nicotine in e-liquids fluctuates considerably from the level identified on the label, including some cases where products labeled as non-nicotine actually contain nicotine.<sup>27</sup> In the absence of a provision for good manufacturing practices that would require that manufacturers demonstrate that they can manufacture their products consistently to specification, users cannot be sure about the level of nicotine in the product they are using, nor the amount of nicotine that he or she is getting, despite what is on the label.

In contrast to the inconsistent levels of nicotine that have been found in e-liquids, FDA-approved nicotine replacement therapy products have been shown to deliver a consistent dose of

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<sup>23</sup> FDA, *Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes*, 2013, at p. 6.

<sup>24</sup> Ambrose, BK, et al., “Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014,” *Journal of the American Medical Association*, published online October 26, 2015.

<sup>25</sup> Marynak, KL, et al., “Sales of Nicotine-Containing Electronic Cigarette Products: United States, 2015,” *American Journal of Public Health* 107(5):702-705, May 2017.

<sup>26</sup> Cheng, T, “Chemical evaluation of electronic cigarettes,” *Tobacco Control* 23:ii11-ii17, 2014, at ii12.

<sup>27</sup> Cheng, T, “Chemical evaluation of electronic cigarettes,” *Tobacco Control* 23:ii11-ii17, 2014, at ii12. Lisko, JG, et al., “Chemical Composition and Evaluation of Nicotine, Tobacco Alkaloids, pH, and Selected Flavors in E-Cigarette Cartridges and Refill Solutions,” *Nicotine & Tobacco Research* [Advance Access], doi:10.1093/ntr/ntu279, 2015. Davis B, et al., “Nicotine Concentrations in Electronic Cigarette Refill and Do-It-Yourself Fluids,” *Nicotine & Tobacco Research* 17(2):134-41, February 2015. Salt Lake City Health Department, *Analysis of Nicotine Content in E-Liquid Samples*, December 2014.

nicotine.<sup>28</sup> This experience demonstrates that it is possible for manufacturers to comply with standards that produce uncontaminated and uniform products.

## **9. FDA should establish good manufacturing practices that ensure that e-cigarette products manufactured to be nicotine-free actually are in fact nicotine-free.**

Importantly, FDA’s responsibility to protect the public health also requires it to establish procedures to verify that e-cigarette products that are manufactured with the intention of being nicotine-free actually are in fact nicotine-free. The importance of preventing such errors should be clear: Examination of e-cigarettes and e-liquids on the market in the absence of regulation has demonstrated that some products labeled as nicotine-free are not. As a result, users may unwittingly be trapped into addiction while using products they believe to be non-addictive. The most recently published Monitoring the Future survey reports that nearly 52% of underage e-cigarette users believe the products they are using had “just flavoring” without nicotine,<sup>29</sup> despite the fact that the overwhelming majority of e-cigarette products actually sold do contain nicotine.<sup>30</sup>

An e-cigarette labeled nicotine-free that in fact contained nicotine would be a misbranded tobacco product within the meaning of 21 U.S.C. § 387c. While FDA does not have jurisdiction to regulate products that are not derived from tobacco (such as e-cigarettes that do not contain nicotine), FDA has indicated that they would determine on a case-by-case basis whether a product falls under its jurisdiction.<sup>31</sup> In order to fulfill its obligation to protect the public health, FDA must establish mechanisms to ensure that products labeled and advertised as containing no nicotine are in fact nicotine-free and that products that do contain nicotine are appropriately labeled and regulated to ensure that consumers understand that they are using an addictive product. FDA clearly has authority to require manufacturers of e-cigarette products that claim to be nicotine-free to demonstrate that such claims are true, including the authority to require prior approval of statements made on the label of a tobacco product to ensure that such statements do not violate the misbranding requirements. 21 U.S.C. § 387c(b).

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<sup>28</sup> Trehy, ML, *Nicotine, Nicotine Related Impurities and Additives in E-Cigarette Cartridges and Refills*, Presentation at the FDA “Electronic Cigarettes and the Public Health: A Public Workshop,” December 10, 2014.

<sup>29</sup> National Institute on Drug Abuse (NIDA), *Vaping popular among teens; opioid misuse at historic lows*, Press Release, December 14, 2017, <https://www.drugabuse.gov/news-events/news-releases/2017/12/vaping-popular-among-teens-opioid-misuse-historic-lows>.

Another smaller study found that nearly as high a percentage of high school students who had used e-cigarettes in the past 30 days believed they were nicotine-free. Goldenson, NI, et al., “Associations of Electronic Cigarette Nicotine Concentration With Subsequent Cigarette Smoking and Vaping Levels in Adolescents,” *JAMA Pediatrics*, doi:10.1001/jamapediatrics.2017.3209, published online October 23, 2017.

<sup>30</sup> Marynak, KL, et al., “Sales of Nicotine-Containing Electronic Cigarette Products: United States, 2015,” *American Journal of Public Health* 107(5):702-705, May 2017, finding that 99% of e-cigarettes sold in retail commercial outlets contain nicotine.

<sup>31</sup> FDA, *Commonly Asked Questions: About the Center for Tobacco Products*, last updated December 7, 2017, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts/ucm378205.htm#14>.

## 10. Establishment of good manufacturing practices should require basic quality standards for e-cigarette devices and their components.

At FDA's December 2014 Workshop, a presentation described common device malfunctions that put users at risk, including leakage of e-liquid through the mouthpiece, leaching of compounds from the materials used to construct the e-cigarette (e.g., metals, polymers, silica and ceramics) into the e-liquid, material degradation over time, and leaking, overheating or exploding batteries.<sup>32</sup> Studies released since those workshops continue to highlight burns and other injuries resulting from e-cigarette malfunctions.<sup>33</sup>

These problems are common in even the most popular devices available. A recent news article featured product issues experienced by users of the brand JUUL, owned by Pax Labs, including "pods leaking into the device and ... mouth" and "devices clogged with spilled liquid." The article also mentioned actions the company was taking to try to fix these malfunctions, including "improving the machinery." However, Pax Labs plans to increase production and expand its sales, which could again compromise the quality of the products.<sup>34</sup>

Standards for manufacturing e-cigarette devices can be set to require products that perform consistently and as marketed. One study comparing the devices made by the major tobacco companies with those from independent companies found that the number of puffs that the device could produce were uniform among products made by the major tobacco companies and those products that used a button to activate use.<sup>35</sup>

Design and manufacturing standards for e-cigarette devices and components are also important because components can interact with the liquid to produce harmful chemicals delivered to the user. As discussed earlier, improperly soldered parts can leak tin into the e-liquid, which ends up in the aerosol, and silica from fibers can emit silica nanoparticles into the aerosol. Further, higher battery voltage can increase temperature of certain liquids to levels that produce various levels of nicotine, as well as formaldehyde and other volatile aldehydes that are harmful to health.<sup>36</sup> Some of these issues can be addressed through establishment of basic

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<sup>32</sup> Gad, SE, *Material Hazards Associated with E-Cigarettes*, Presentation at the FDA "Electronic Cigarettes and the Public Health: A Public Workshop," December 10, 2014.

<sup>33</sup> Toy, J, et al., "Alarming increase in electronic nicotine delivery systems-related burn injuries: A serious unregulated public health issue," *American Journal of Emergency Medicine*, doi: 10.1016/j.ajem.2017.05.029, 2017. Brownson, EG, et al., "Explosion Injuries from E-Cigarettes," *New England Journal of Medicine* 375(14):1400-1402, 2016.

<sup>34</sup> LaVito, A, "JUUL e-cigs' growth in popularity strains supply chain," CNBC, October 30, 2017, <https://www.cnbc.com/2017/10/30/juuls-popularity-exposes-the-challenges-of-making-a-mass-market-e-cig.html>.

<sup>35</sup> Williams, M, et al., "Comparison of the Performance of Cartomizer Style Electronic Cigarettes from Major Tobacco and Independent Manufacturers," *PLoS ONE* 11(2):e0149251, 2016.

<sup>36</sup> Logue, JM, et al., "Emissions from Electronic Cigarettes: Assessing Vapers' Intake of Toxic Compounds, Secondhand Exposures, and the Associated Health Impacts," *Environmental Science & Technology* 51:9271-9279, 2017. Bitzer, ZT, et al., "Solvent and Temperature Effects on Free Radical Formation in Electronic Cigarette Aerosols," *Chemical Research in Toxicology*, doi: 10.1021/acs.chemrestox.7b00116. [Epub ahead of print], December 8, 2017. Jensen, RP, et al., "Hidden Formaldehyde in E-Cigarette Aerosols," *New England Journal of*

manufacturing standards such as requiring devices to limit temperatures, which some of the newer devices can do.<sup>37</sup>

### **11. Establishing good manufacturing practices should require specific responsibilities for qualified personnel to effectively design, produce, enforce quality control, ship, handle, and store products.**

It is not enough to require that the products themselves do not contain or produce toxins and carcinogens, or are free from contamination. Good manufacturing practices must also require that all personnel assembling the products – liquids and devices, and other components – are adequately trained to do so and follow protocols to ensure the products consistently meet quality standards.

Some vape shops mix their own e-liquids rather than selling pre-made products. In these stores, the staff may not be properly trained to mix chemicals, which could result in incorrect proportions (i.e., wrong nicotine level), contamination, or product inconsistency. This could also leave staff – or worse, unsuspecting customers – vulnerable to injuries if, for instance, safety measures are not followed.

An observational study of vape shops in Los Angeles found that liquid spills occurred frequently and safety equipment were not available. Researchers found that “[s]ome of the employees interviewed received no training at all in handling of Nicotine containing products, and most were not informed of the dangers of nicotine-containing e-liquids.” In addition, nearly a quarter of those interviewed said that customers could mix the liquids themselves, which presents an additional safety hazard.<sup>38</sup>

### **12. Establishing good manufacturing practices is especially important for a product that is predominantly produced outside the United States, particularly in China.**

In establishing appropriate good manufacturing practices for e-cigarettes and their components, it is especially important for FDA to take account of the fact that the manufacture of most of these products takes place outside the United States and in countries in which comparable standards do not exist or are not effectively enforced. The predominance of China as a supplier of e-cigarettes<sup>39</sup> presents a challenge for FDA to develop good manufacturing practices that can actually be enforced there. For instance, one study found that, although China

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*Medicine* 372(4):392-394, 2015. Brown, CJ & Cheng, JM, “Electronic cigarettes: product characterisation and design considerations,” *Tobacco Control* 23 Suppl 2:ii4-10, 2014.

<sup>37</sup> Bitzer, ZT, et al., “Solvent and Temperature Effects on Free Radical Formation in Electronic Cigarette Aerosols,” *Chemical Research in Toxicology*, doi: 10.1021/acs.chemrestox.7b00116. [Epub ahead of print], December 8, 2017.

<sup>38</sup> Garcia, R, et al., “Employee and customer handling of nicotine-containing e-liquids in vape shops,” *Tobacco Prevention & Cessation* 2(Supplement):7, 2016.

<sup>39</sup> U.S. Department of Health and Human Services (HHS), *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016, at 14, 152.

officially bans the use of lead in solder, the presence of lead in e-cigarette aerosol indicated that this ban is not being strongly enforced and that manufacturers freely use it, to the detriment of users.<sup>40</sup>

Both importers of such products and components and companies that manufacture or assemble finished products in the United States should be held responsible for ensuring that the products and components that are included in products they sell meet the same standards applicable to U.S. manufacturers. If they are unable to do so, they should not be permitted to continue selling such products in the United States.

### **13. Objections that establishment of good manufacturing practices for e-cigarette products may force some small manufacturers to become resellers are not a valid reason for failing to adopt such requirements.**

Some manufacturers may object to establishing good manufacturing practices on the grounds that small manufacturers with limited resources could not afford to adhere to them and that some manufacturers will have to cease manufacturing and go out of business or become resellers. The short answer to this objection is that these requirements are necessary to protect consumers from unnecessarily hazardous products and any manufacturer that is unable to satisfy minimum GMP requirements should not be selling addictive and potentially harmful products to the public. Just as FDA would not permit a drug manufacturer incapable of meeting minimum GMP requirements to sell drugs to the public, so it should not permit the sale e-cigarettes by manufacturers who are incapable of meeting GMP requirements.

Moreover, as FDA itself established in the discussion accompanying the deeming rule, the fact that some manufacturers of e-cigarettes would have to cease manufacturing does not mean that they will go out of business. Rather than continuing to manufacture e-cigarette products, such entities could purchase pre-mixed e-liquids and devices from manufacturers who have the resources to comply with good manufacturing practices and become resellers.<sup>41</sup> The use of master files, as detailed in the discussion accompanying the deeming rule, could reduce burdens and enable such companies to continue supplying products to consumers while adhering to regulatory requirements.<sup>42</sup>

In addition, the fact that e-cigarette present a different risk of disease than combusted products is no reason not to establish good manufacturing practices for them. As long as e-cigarette products present any risk to the public health it is appropriate for FDA to establish good manufacturing practices. In developing sound manufacturing practices, the criterion that should be applied is whether the product is more hazardous than a properly manufactured e-cigarette, not whether it is any more or less hazardous than a combusted tobacco product.

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<sup>40</sup> Williams, M, et al., “Elements including metals in the atomizer and aerosol of disposable electronic cigarettes and electronic hookahs,” *PLoS ONE* 12(4):e0175430, 2017.

<sup>41</sup> 81 Fed. Reg. at 29044.

<sup>42</sup> 81 Fed. Reg. at 29002, 29045.

Respectfully submitted,

American Cancer Society Cancer Action Network

American Heart Association

American Lung Association

Campaign for Tobacco-Free Kids

Truth Initiative