

FDA should reject the tobacco industry’s efforts to guide e-cigarette manufacturing standards and instead formulate their own science-driven tough regulations to protect public health

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Section 906(e) of the Family Smoking Prevention and Tobacco Control Act provides that FDA must prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, preproduction design validation, packing, and storage of tobacco products conform to current good manufacturing practice to assure that the public health is protected. The law explicitly provides that “the regulations may differ based on the type of tobacco product involved.” In January 2012, a number of tobacco industry stakeholders submitted recommendations for good manufacturing practice (GMP) requirements for tobacco products already subject to FDA’s tobacco authority. In May 2016, FDA published its final “Deeming Rule” that deemed new products, including e-cigarettes, to be subject to FDA’s regulatory authority under the Tobacco Control Act. Subsequently, in June 2017, a group of 13 companies (including RAI Services Company on behalf of R.J. Reynolds Tobacco Company and R.J. Reynolds Vapor Company; Altria Client Services LLC on behalf of Nu Mark LLC; Fontem

US, Inc.; Council of Independent Tobacco Manufacturers; Purbacco USA, LLC; Sky Marketing Corporation dba Hometown Hero Vapor; Baker White, Inc.; S.E. Box Mods LLC; EL-O-QUENET E-Juice LLC; Global Vapor Standards Association; Ballantyne Brands, LLC; Five Pawns Inc.; and Cosmic Fog Vapors LLC, collectively referred to as the “Companies”, submitted to FDA a supplement to the January 2012 GMP proposal entitled “Proposed Good Manufacturing Practices Regulation to Account for FDA’s Deeming Regulation (Docket No. FDA-2013-N-022)” that purports to account for the differences in manufacturing newly deemed products, in particular e-cigarettes.

We applaud the industry for recognizing that differences in the manufacturing of e-cigarettes demand different manufacturing regulations, and for agreeing that there is a need for tobacco product standards to protect public health. However, it is important that while the FDA critically considers the industry’s proposal, the FDA should follow its own independent, science-driven process to formulate strong and effective e-cigarette manufacturing standards.

E-cigarettes are manufactured and sold in a variety of designs, and their effectiveness as nicotine delivery devices varies.¹ While e-cigarettes are commonly perceived as less toxic than combustible tobacco cigarettes, there is likely a continuum of risk across e-cigarettes, with some having low toxicity and others with significant toxicity.² Toxicants include volatile organic compounds such as acrolein and formaldehyde, metals, tobacco specific nitrosamines, and some chemical additives which serve as flavorants. In general, toxicants in e-cigarette aerosol are at

¹ St Helen G, Havel C, Dempsey DA, Jacob P, 3rd, Benowitz NL. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. *Addiction*. 2016;111(3):535-544. PubMed PMID: 26430813; PubMed Central PMCID:4749433.

² Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. *Tobacco Control*. 2017;tobaccocontrol-2017-053808.

lower levels than combustible cigarette smoke³ but there can be considerable variability between products, highlighting the need for manufacturing standards. Toxicants (other than nicotine and carrier liquids, vegetable glycerin and propylene glycol) in e-cigarettes are either present in the e-liquid as contaminants, leach from e-cigarette components such as coils into the e-liquid/aerosol, or are generated from e-liquid components during the heating process and given off in the aerosol. Some flavorants are also toxic. In order to protect public health, manufacturing standards must be broad, with the objective of eliminating or significantly reducing contaminants in e-liquids as well as control over conditions under which toxicants are formed when e-cigarettes are being used.

Identifying the source of toxic substances in e-cigarettes or aerosol is critical to formulating effective manufacturing standards. Exposure to many of the toxicants in e-cigarettes are largely avoidable with appropriate manufacturing and/or product standards. The primary sources of metals, such as nickel, copper, zinc, and chromium, are the metal coils/atomizers and soldering used in electric circuits.^{4,5} Reactive volatile organic compounds such as acetaldehyde, formaldehyde, and acrolein are generated in a temperature-dependent manner from glycerin and propylene glycol.⁶ Flavorants also generate reactive aldehydes when they are heated.⁷ Some

³ Goniewicz, M. L., J. Knysak, M. Gawron, L. Kosmider, A. Sobczak, J. Kurek, A. Prokopowicz, M. Jablonska-Czapla, C. Rosik-Dulewska, and C. Havel. 2014. "Levels of selected carcinogens and toxicants in vapour from electronic cigarettes." *Tobacco Control* 23(2): 133-39.

⁴ Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PloS one*. 2013;8(3):e57987.

⁵ Mikheev VB, Brinkman MC, Granville CA, Gordon SM, Clark PI. Real-Time Measurement of Electronic Cigarette Aerosol Size Distribution and Metals Content Analysis. *Nicotine & Tobacco Research*. 2016:ntw128.

⁶ Sleiman M, Logue JM, Montesinos VN, Russell ML, Litter MI, Gundel LA, Destailats H. Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals. *Environmental Science & Technology*. 2016;50(17):9644-9651.

⁷ Khlystov A, Samburova V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. *Environmental Science & Technology*. 2016;50(23):13080-13085.

contaminants are present in the e-liquids, likely during manufacturing. These include tobacco alkaloids and carcinogenic tobacco-specific nitrosamines.^{8,9}

Other concerns include battery safety and consistency in nicotine content across batches. E-cigarettes have exploded and caused severe burns to users.¹⁰ Inconsistencies in nicotine content between and within batches of e-cigarettes have also been reported,¹¹ as well as incongruence between nicotine content on the label and the actual levels in the e-liquid.¹²

The Companies should only refer to their proposed regulation as “tobacco product manufacturing practices” and not “good manufacturing practices.”

It is important to note that while section 906(e) of the FD&C Act refers to “good manufacturing practices,” FDA uses “tobacco product manufacturing practices” to refer to regulations that can be issued under section 906(e). The distinction between “good manufacturing practices (GMP)” and “tobacco product manufacturing practices (TPMP)” is significant. There is no risk-free tobacco product, including e-cigarettes. As such, the term “good manufacturing practices” should not be applied to these products. Although the Companies

⁸ Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control*. 2014;23(2):133-139.

⁹ Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical composition and evaluation of nicotine, tobacco alkaloids, pH, and selected flavors in e-cigarette cartridges and refill solutions. *Nicotine & Tobacco Research*. 2015;17(10):1270-1278.

¹⁰ Kumetz, E. A., Hurst, N. D., Cudnik, R. J., & Rudinsky, S. L. (2016). Electronic cigarette explosion injuries. *The American journal of emergency medicine*, 34(11), 2252-e1.

¹¹ Cheng T. Chemical evaluation of electronic cigarettes. *Tobacco Control*. 2014;23(suppl 2):ii11-ii17.

¹² Etter J-F, Bugey A. E-cigarette liquids: Constancy of content across batches and accuracy of labeling. *Addictive Behaviors*. 2017;73:137-143.

adopted TPMP instead of GMP in the text of their new proposal, they should also refer to their proposal as TPMP in the title and when addressing the public.

The scope of the TPMP regulations should apply to manufacturers of every component and part of e-cigarettes.

The Companies wrote that they believe “that the scope of the TPMP regulations should apply to ENDS product manufacturers but exclude manufacturers/suppliers of accessories and manufacturers/suppliers of components and parts that are used to make ENDS products by ENDS manufacturers.... [M]anufacturers of components and parts such as battery cells and control circuitry supplied to ENDS products manufacturers would not be within the scope of the TPMP regulations.” It would be a grave mistake for the FDA to accept this proposal.

Components and parts are defined in the deeming rule as “any software or assembly of materials intended or reasonably expected: 1) to alter or affect the tobacco product’s performance, composition, constituents or characteristics; or 2) to be used with or for the human consumption of a tobacco product.” Components and parts are deemed as tobacco products and are subject to FDA regulation. Components and parts are critical for the function and performance of e-cigarettes. They are determinants of the safety and toxicity of e-cigarettes. Battery safety is an important consideration, as batteries have been known to explode, causing burns. The content of metals used in atomizers and coils is also critical, as these are likely sources of metal exposure. If the manufacturer is producing these components and parts specifically for use in e-cigarettes, why should they not be subject to TPMP regulations? **The FDA should ensure that all manufacturers of components and parts of e-cigarettes are included in TPMP regulations.**

The FDA should not allow the tobacco industry to leapfrog its own regulation-forming process.

Several of the major tobacco companies manufacture and sell e-cigarettes. RAI's proposed regulation is just one example of the industry's direct interest and active involvement in attempting to define the e-cigarette regulatory environment. We strongly advise that the FDA not cede any ground to the industry in its regulation of tobacco products. It is unlikely that the Companies, whose products will be regulated, will propose regulations that are strong enough to protect public health. But this is essentially what the Companies have claimed in their letter: "The Companies believe that the following supplement, in conjunction with the January 2012 proposed GMP regulations, provide sufficient direction for the establishment of adequate manufacturing controls for ENDS products."

Even as the Companies make the claim that the proposed regulations are 'adequate' and 'provide sufficient direction,' the Companies are also asking FDA to form regulations that 'allow for flexibility' or in other words, regulations that are not too stringent. Throughout the text, the Companies use ambiguous phrases such as, "where appropriate," "as appropriate," and "of appropriate accelerated studies." These phrases are open to the stakeholder's interpretation and do allow the 'flexibility' the Companies are requesting. **Instead, the FDA should propose specific product standards and tests to evaluate product performance and safety.** These proposed tests and standards should be science-based, with the goal of protecting public health as the sole determinant. Examples include: mandate e-liquids contain no detectable levels of tobacco specific nitrosamines; mandate that e-liquid nicotine content is reproducible between batches and is in agreement with labeled nicotine levels; mandate that e-cigarette aerosol is metal-free; and, mandate that e-cigarette performance and emissions are tested under a wide

range of conditions (topography, power settings) to capture the wide variability of user topography and use patterns.

The FDA should require that all e-cigarette manufacturers use USP grade nicotine.

Contaminants in e-cigarettes/e-liquids are potential sources of toxicity or increased abuse liability of e-cigarettes. These include low levels of carcinogenic tobacco-specific nitrosamines, metals, and other tobacco alkaloids, among others. To minimize the health risks of e-cigarettes, all manufacturers should be required to use USP grade nicotine, the recognized standard for nicotine, in their products. The Companies' proposals did not call to standardize the use of USP grade nicotine used in their products. FDA should also implement regulations that ensure that the nicotine, vegetable glycerin, and propylene glycol content listed on the label matches the actual e-liquid content.

The FDA should standardize e-cigarette testing protocols

Currently, there is no established testing protocol for e-cigarette emissions. The FDA must ensure that a testing protocol is included as part of its TPMP regulations. In addition, the unit of measurement of e-liquid and emission constituents should also be standardized by regulation. This will allow comparability between products from different companies.

In summary, the effort by the tobacco and e-cigarette industries to define e-cigarette manufacturing standards should be viewed critically by the FDA and certainly not accepted

wholesale. The FDA should not allow the industry to leapfrog its regulatory process. Instead, the FDA should formulate its own science-driven TPMP regulations with protecting the public health as the goal. In particular, FDA should include manufacturers of components and parts in TPMP regulations, mandate the use of USP grade nicotine in all e-liquids, and standardize e-cigarette testing protocols.