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www.AEMSA.org

1-877-68-AEMSA(23672)

Info@AEMSA.org

This document was submitted to OMB/OIRA as part of AEMSA's meeting pursuant to Executive Order 12866 to discuss the Food and Drug Administration's "Deeming Regulation" which proposes to deem certain products as regulated tobacco products subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act Rule (RIN: 0910-AG38).

AEMSA

OMB Meeting – Summary of Positions

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The American E-Liquid Manufacturing Standards Association (AEMSA) appreciates this opportunity to meet with the Office of Management and Budget (OMB), Office of Information and Regulatory Affairs (OIRA) to discuss the Food and Drug Administration's (FDA or Agency) Notice of Proposed Rulemaking (NPRM) for the "Deeming Regulation" (Docket No. FDA-2014-N-0189; RIN 0910-AG38), which proposes to deem currently unregulated tobacco and nicotine-containing products as regulated tobacco products pursuant to the Food, Drug and Cosmetic Act (FDCA), as amended by the Family Smoking Prevention and Tobacco Control Act of 2009 (the Tobacco Control Act).

I. Background on AEMSA

AEMSA is the first and only manufacturers' trade association completely dedicated to creating responsible and sustainable standards for the manufacturing of e-liquids used in e-vapor devices (commonly referred to as electronic cigarettes). AEMSA is an all-volunteer 501(c)(6) organization, formed by U.S. manufacturers of e-liquids, to promote safety and responsibility through self-regulation. Our Members believe we have a responsibility to self-regulate the e-liquid manufacturing process using professional criteria. One of AEMSA's primary goals is to provide consumers and government regulators with confidence that our members' products are manufactured in a professionally responsible and safe manner until such time as FDA promulgates Good Manufacturing Practices (GMPs) for e-liquids. In this regard, AEMSA has developed manufacturing standards for e-liquids which may be downloaded from our website at: <http://www.aemsa.org/standards/> and are attached hereto as **Appendix I**. AEMSA supports reasonable, responsible and science-based regulation of e-vapor products, including open-system refillable personal vaporizers and the e-liquids used in those products.

In 2014 AEMSA established the E-Research Foundation (www.e-researchfoundation.org), a 501(c)(3) non-profit foundation designed to be a collective funding portal to advance independent medical/scientific research targeted for peer-review and publication. The sole mission and focus of the E-Research Foundation is the advancement of independent medical/scientific research subject to the scrutiny of peer-review and publication by the professional medical/science community. In addition to funding scientific research, one of the unique features of the E-Research Foundation is our dedication to making available independently verifiable non-industry expert presentations from various conferences around the world (*e.g.*, TMA and Global Forum on Nicotine). Typically, only conference attendees have access to and are aware of this valuable information. To make this valuable information more readily available to the public, the E-Research Foundation obtained permission from the respective organizations to re-post expert panels and presentations, which are available here:

- <http://e-researchfoundation.org/direct-from-the-experts/gfn-2014/>;
- <http://e-researchfoundation.org/direct-from-the-experts/tma-2014/>;



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- <http://e-researchfoundation.org/gfn-2015/>; and
- <http://e-researchfoundation.org/tma-2015/>.

We note that although e-liquid and e-vapor products manufactured by AEMSA's Member companies may have the corollary benefit of helping tobacco cigarette smokers quit smoking or nicotine use altogether, these products are not intended to be smoking cessation devices or nicotine replacement therapies (NRTs) (and are not marketed as such), but rather are recreational use products. Although the available evidence demonstrates that most current e-vapor users are using these products as an aid to help them quit or cut down on their use of traditional cigarettes, no claims to this effect are being made by AEMSA or any of its Member companies about their products.

AEMSA is providing this document to the OMB/OIRA on behalf of its e-liquid manufacturing Members.

II. FDA and OMB/OIRA Obligations Under Executive Order 12866

Executive Order 12866 establishes the guiding principles federal agencies must follow when developing regulations, including encouraging the use of cost-benefit analysis, risk assessment, and performance-based regulatory standards. The executive order also delegates authority to OIRA to coordinate agency rulemaking efforts with the regulatory priorities of the President. Executive Order 12866 also expands the roles of OIRA in rulemaking through a centralized review of regulations, whereby OIRA acts as gatekeeper for the promulgation of all significant rulemakings.

FDA's proposed Deeming Regulation violates many of the guiding principles of regulation set forth in Executive Order 12866. Accordingly, OIRA must review the Deeming Regulation with FDA's shortcomings in mind and require FDA to consider all of the relevant costs and benefits of the Deeming Regulation, as well as the feasibility of simpler, less burdensome regulatory alternatives, some of which are discussed herein. Below we detail each of the ways FDA has violated Executive Order 12866 in the proposed Deeming Regulation, and what OIRA must require of FDA in order to ensure the Deeming Regulation is in line with the regulatory philosophy set forth in Executive Order 12866.

The driving force of Executive Order 12866 is the idea that an agency must assess all of the costs and benefits of available regulatory alternatives and select the approach that maximizes the net benefits. Section 1(b)(6) of Executive Order 12866 requires an agency to consider the costs and benefits of a regulation and adopt a regulation only upon a "reasoned determination that the benefits of the intended regulation justify its costs." The Deeming Regulation, as proposed, does not account for all of the costs associated with the regulation, and therefore, it cannot be said to be the product of a reasoned determination that the regulation's benefits justify its costs. Some market impacts that the FDA failed to consider are:



- Market growth rate, both domestically and globally, and potential market impacts if it continues to grow or negative economic impacts of industry elimination post-Deeming;
- Domestic manufacturing and the volume of products exported, and the money generated from these activities;
- The potential for job creation or elimination with implementation of the Deeming Regulation; and
- The burden of taxation, *i.e.*, wholesale taxes and excise taxes, both built into sales prices, with sales tax added on top of sales price.

FDA also failed to consider the costs associated with the Deeming Regulation's impact on development of reduced harm nicotine-containing products and innovation in the e-vapor industry. FDA did not consider the costs of the decreased availability of e-vapor products on the market, and in particular, the impact of removal of these products on current smokers, who may have used e-vapor products to quit and, as a result of the proposed rule, would be dissuaded and/or precluded from continuing to use them, or former smokers who did in fact quit smoking using e-vapor products (many for several years now away from much more harmful combustible tobacco smoking) who now face having these products removed from the market. Even if FDA had accounted for the full range of costs associated with the Deeming Regulation, the benefits of the Deeming Regulation to the public health are so minimal that they could not be said to be justified by the costs. For example, under the proposed Deeming Regulation, Premarket Tobacco Product Applications (PMTAs) would be required of all e-vapor products, while combustible cigarettes, a product significantly more dangerous to both users and non-users, are mostly "grandfathered" and exempt entirely from premarket authorization. We further discuss the impact of the e-vapor industry on the public health in Section VII of this comment, below.

Section 1(b)(11) of Executive Order 12866 requires an agency to tailor a regulation to "impose the least burden on society, including individuals, businesses of differing sizes, and other entities." FDA grossly underestimated the number of e-vapor products currently available and the number of small businesses currently operating in the e-vapor industry in the proposed Deeming Regulation, as detailed in AEMSA's May 2014 Paperwork Reduction Act comments to OMB. Only the billion-dollar tobacco companies will be able to afford the costly and lengthy PMTA process in order to continue marketing their products, while smaller e-vapor businesses will be forced out of the market. Rather than impose the complex PMTA process on e-vapor products, FDA could have introduced, for example, mandatory safety standards to mitigate risks specific to e-vapor products, which would give businesses both large and small an opportunity to continue on the market while putting in place measures to protect the public. An approach like this would also be much easier for the industry to understand, as Executive Order Section 1(b)(12) requires. As proposed, the Deeming Regulation would require each e-vapor business to work with scientists across many disciplines not only to understand the chemistry and toxicological concerns of each e-vapor product, but to answer questions pertaining to marketing, human behavior, and epidemiology (for which any and all evaluations would be inherently subjective and therefore impossible to meet any "objective" compliance requirements).



Requiring such voluminous submissions for each PMTA would be confusing, burdensome, and expensive for those submitting the filing, resource-intensive for FDA, and is likely to result in inefficient (and ineffective) decision-making. As e-liquid products primarily all contain essentially the same four ingredients, such exhaustive analysis and evaluations of each and every product would also be exhaustively duplicative (for both applicants and the FDA) with negative economic impacts for all parties involved.

Further deviating from the spirit of Executive Order 12866, FDA did not adequately consider a less burdensome regulatory framework for e-vapor products (several such frameworks were described in AEMSA's comments to FDA). Section 1(b)(8) of Executive Order 12866 requires agencies to consider alternative forms of regulation, such as objectively defined and evaluated specific performance standards, in lieu of "specifying the behavior of manner of compliance that regulated entities must adopt." FDA could have developed objectively defined and evaluated product-specific performance standards, such as safety standards for e-liquids, in lieu of requiring all e-vapor products to produce the voluminous data required by the PMTA process. Such an alternative, unlike the proposed Deeming Regulation, would also conform with Section 1(b)(5), which requires an agency's regulatory action to be the most cost-effective way to achieve the regulatory objective. The proposed Deeming Regulation imposes not only a huge cost burden on the e-vapor industry, but also on the FDA itself, which must utilize a tremendous amount of resources to review PMTAs once the Deeming Regulation is effective. The less costly approach for both industry and FDA would be to mandate objectively delineated specific performance standards for these products, which would allow the Agency to utilize resources only to the extent necessary to verify and enforce such standards.

OMB/OIRA plays a critical role in ensuring that the regulatory burden imposed by FDA on the industry is not overly burdensome and overreaching, but rather is commensurate with the true harm posed to the public – which, in this case, is minimal. Moreover, it is OMB/OIRA's duty to ensure that the Agency has followed the mandates set forth in Executive Order 12866 when developing the Deeming Regulation. By failing to properly account for all the costs associated with the proposed Deeming Regulation, making the proposed Deeming Regulation complicated and difficult to understand, imposing tremendous burdens (predominantly on small businesses) to produce voluminous, expensive filings that will require significant FDA resources for review, and failing to consider alternative regulatory frameworks, FDA has violated the regulatory intent and philosophy in Executive Order 12866; therefore, OIRA must compel FDA to rework the proposed Deeming Regulation to address these issues.

III. Economic Impact of AEMSA Members

A. Industry Size

The e-vapor industry has grown rapidly since these products first entered the U.S. market in 2007-2008, roughly doubling in size *every year* since the products first started being



commercially distributed.¹ Sales in 2008 were approximately \$50 million; in 2015 sales are expected to exceed over \$3.5 billion (all product categories).²

With respect to the refillable e-liquid industry alone, the available evidence indicates that there are at least **8,500**³ and possibly up to **15,000** individual manufacturers and retailers

¹ We note, however that these gross underestimates are not miscalculations on FDA's part, but rather based on the assumption that most of these small companies will not be able to comply with the burdensome and costly regulations, and thus will be forced to exit the industry. Indeed, FDA's own *Regulatory Impact Analysis* for the proposed rule acknowledges that the regulatory burdens of the rule will result in most companies exiting the industry, but failed to estimate the value of this loss of consumer choice. See Preliminary Regulatory Impact Analysis, April 2014, available at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/UCM394933.pdf>. Specifically, FDA states in the impact analysis that

In addition, we assume that the per-product (or per-UPC) costs of this proposed rule, including labeling changes and premarket tobacco product applications (PMTAs) are costly, and if there are no valid predicate products for substantial equivalence submissions, electronic cigarettes would necessarily be marketed through the premarket tobacco application pathway. There are currently a large number of electronic cigarette products being marketed, some of which have very little market share while others represent product variation among larger market players. Products that do not have sufficient sales to justify incurring the costs of complying with the proposed rule would exit. Products with larger sales will more likely bear these costs to come into compliance with any final rule, but we expect some reduction in the variety of products offered even among larger players. Therefore, we expect that considerable product consolidation and exit would occur, as well as the entry, exit, and consolidation that would be expected to occur in an emerging market and that would occur under baseline conditions.

We note, however, that while many of these companies are small, they are entrepreneurial and are continuing to grow, and intend to comply with FDA's regulations. To propose a rule that assumes up to 99.99% of the thriving advanced e-cigarette vaporizers and e-liquid manufacturing companies will be eliminated is obdurate beyond reason. Rather, FDA should use the enforcement discretion envisioned by Congress to implement appropriate regulatory requirements tailored to these products.

² See Wells Fargo Securities, April 22, 2014, "NATO E-Cig and Vape Panel, Key Trends Facing the Industry," available at: <http://natoshow.ramamc.com/media-assets/uploads/2014/08/NATO-2015-Marking-E-Cig-Territory-Herzog-Panel.pdf>



producing and/or selling e-liquid products in the U.S., nearly all of which are small businesses (*i.e.*, less than 350 employees), including vape shops. Specifically, we note that:

- The Smoke Free Alternatives Trade Association, a trade association representing small and mid-sized businesses in the vapor industry, including vape shops, manufacturers, importers and distributors, has estimated that there are 1,200 e-liquid manufacturers that make their own e-liquid and 15,000 vape shops in the United States (many of whom also mix their own e-liquids), representing over 65,000 jobs. This estimate is based on internal data collected from manufacturer and distributor members, as well as insurance researchers. See www.sfata.org.
- Prominent Wall Street Securities Analyst Bonnie Herzog of Wells Fargo estimates that that are 5,000 to 10,000 vape shops in the United States.⁴
- The Vapor Search USA online portal, available at <http://www.vaporsearchusa.com/>, has over 5,000 e-liquid producers throughout the United States listed in its database.
- The Electronic Cigarette Forum (ECF), an online community for e-cigarette consumers and stakeholders (available at <http://www.e-cigarette-forum.com/forum/>) has nearly 1,700 e-cigarette and e-liquid businesses (including U.S.-based manufacturers and foreign importers) on record.⁵

These estimates are only for the e-liquid industry, and do not include the hundreds of companies that are manufacturing the various hardware components used in advanced e-cigarette vaporizers (*i.e.*, “mod” or device components including adapters, atomizers, cartomizers, clearomizers, batteries, chargers, tanks, endcaps, tubing, internal microprocessors/motherboards, springs, o-rings, drip-tips/mouth pieces, wicking materials, and other device components such as internal connectors, buttons, casings, gaskets, seals, internal charging circuitry components, etc.).⁶

³ See Tripp Mickle, “FDA Cloud Hangs Over Vape Shops,” The Wall Street Journal, July 7, 2015, *available at*: <http://www.wsj.com/articles/SB10130211234592774869404581088451777513530>.

⁴ See Wells Fargo Securities, Equity Research, April 14, 2014, “Vape Shops – Springing Up Across The Country,” *available at*: http://www.vaporworldexpo.com/PDFs/Tobacco_%20Vape_Shop_Visit_Apri_2014.pdf.

⁵ Only those who apply and pay for recognized vendor status on ECF are listed here.

⁶ Further, each of these components can come in many models, sizes or be made from different raw materials.



B. Survey of AEMSA Member Companies (16 Respondents)

Category	2013	2014	2015
Sales and Customers			
Retail - Number of Customers	105,033	225,206	292,050
Retail - Value of Sales	\$11,029,838	\$21,731,582	\$19,352,410
Wholesale (excluding Export) - Number of Customers	463	3,581	5,056
Wholesale (excluding Export) - Value of Sales	\$3,898,784	\$9,656,348	\$11,090,073
Export - Number of Customers	54	104	103
Export - Value of Sales	\$261,491	\$2,473,151	\$5,188,264
Value of All Sales (including, but not limited to above)	\$25,349,091	\$49,593,174	\$58,482,177
Average Value per Sale	\$64	\$185	\$277
Employment			
Number of Employees - Total	209	431	707
Manufacturing			
Variable Costs and Supplies – Total	\$10,916,134	\$25,161,928	\$21,752,494
Number of Contract Manufacture Customers	6	68	368
Value of Contract Manufacture Sales	\$150,000	\$1,850,000	\$13,380,336
Number of SKUs (E-liquids)	59,642	47,636	49,562
Number of SKUs (non E-liquids)	4,270	8,282	11,179
Facilities			
Number of Locations (Owned)	16	33	46
Number of Locations (Owned, Wholesale, Franchise)	19	57	110
Total Square Footage of Locations	48,800	136,050	272,700
Quality Assurance			
Amount Spent on Product Testing and Analysis	\$20,390	\$175,524	\$345,783



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Taxes

Total Sales Taxes Collected	\$719,040	\$1,214,946	\$970,570
Total Business Taxes Paid	\$1,043,912	\$2,788,834	\$3,431,380 ⁷
Total Real Estate Taxes Paid	\$10,615	\$23,714	\$52,174

Various potential economic impact projection variations (depending on assumptions) can be extrapolated from this data. To delineate merely one set of examples, consider the number of e-liquid SKUs relative to various estimated PMTA application costs (per SKU):

16 AEMSA member respondents, spanning the spectrum of entrepreneurial e-liquid manufacturers (from smallest with only a few employees to some of the largest in the US), report a total of 49,562 e-liquid SKUs. Assume an average per member: $49,562/16=3,097$ e-liquid SKUs per member. PMTA cost has been estimated to range anywhere from \$330,000 to \$3 Million per SKU

- at \$330,000 for 3,097 SKUs, application cost per average member:
\$1,022,010,000.00
- at \$1,000,000 for 3,097 SKUs, application cost per average member:
\$3,097,000,000.00
- at \$3,000,000 for 3,097 SKUs, application cost per average member:
\$9,291,000,000.00

IV. AEMSA Position on E-Vapor as “Tobacco” Products

The e-vapor device is a revolutionary technology that has the ability to greatly benefit the public health, as it provides the first viable recreational alternative to tobacco for cigarette smokers. As detailed in AEMSA’s comments to the NPRM for the Deeming Regulation (FDA Docket No. FDA-2014-N-0189) available online⁸, our position is that e-vapor products are *technology* products, not tobacco products, and that Congress never intended the Tobacco Control Act to apply to novel, tobacco-free products. Rather, the legislative history of the Tobacco Control Act makes clear that the law was only intended to apply to agricultural-based products that actually contain tobacco-leaf. In particular, the onerous PMTA process was designed to make it nearly impossible for tobacco companies to introduce new, *more* harmful tobacco-leaf products, particularly combusted products, to the market – not to effectively ban an entirely novel category of products that has the potential to greatly reduce tobacco-related disease and death.

⁷ Only 8 respondents reported total business taxes paid through November 1, 2015.

⁸ See Comment ID FDA-2014-N-0189-81140 and tracking number 1jy-8dol-z5ml, available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-0189-81140>.



Accordingly, Congress should pass separate legislation specifically giving FDA authority over these products and their e-liquid components separate from the Agency's tobacco and drug authorities under the FDCA. Such legislation could appropriately establish and delineate **objective** regulatory and product evaluation criteria specific to e-vapor products rather than trying to force-fit the square peg (e-vapor products) into the round hole (TCA). We believe that attempting to force the Tobacco Control Act's requirements onto these products is neither an effective nor efficient regulatory strategy, and one that could actually harm the public health, as e-vapor products have proven to be an effective tool for tobacco harm reduction, as discussed below. Nevertheless, for purposes of these comments, we assume, *arguendo*, that e-vapor and e-liquid products that contain nicotine derived from tobacco will be subject to the Tobacco Control Act requirements once the Deeming Regulation becomes effective.

V. Purpose of the Tobacco Control Act

The primary purpose of the Tobacco Control Act is to reduce *tobacco* related disease and death in the United States by making it nearly impossible to bring new, harmful tobacco leaf-containing products – and particularly those that are combusted – to the market. It is well established that traditional tobacco products, and cigarettes in particular, are detrimental to the health of individual consumers as well as to the public (*i.e.*, net population) health. According to the U.S. Centers for Disease Control and Prevention (CDC):⁹

- Smoking is the leading cause of preventable death.
- Cigarette smoking is responsible for more than 480,000 deaths per year in the United States, including 42,000 deaths resulting from secondhand smoke exposure. This is about one in five deaths annually, or 1,300 deaths every day.
- More than 16 million Americans are living with a disease caused by smoking.
- Smoking causes cancer, heart disease, stroke, lung diseases, and chronic obstructive pulmonary disease (COPD), which includes emphysema and chronic bronchitis.
- The percentage of U.S. adults aged 18 years or older who were current cigarette smokers in 2014 was 16.8% (40 million people).

When Congress passed the Tobacco Control Act it set out ten purposes underlying the legislation. These purposes include not only reducing “the social costs associated with tobacco-related diseases” and ensuring “that consumers are better informed”¹⁰—but also continuing “to

⁹ See Centers for Disease Control and Prevention, Smoking & Tobacco Use, Fast Facts, available at: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/.

¹⁰ The Deeming Regulation runs contrary to this purpose in several ways. Requiring PMTAs of e-vapor products will drastically diminish the number of e-vapor products on the



permit the sale of tobacco products to adults” and providing effective oversight of the “industry’s efforts to develop, introduce, and promote less harmful tobacco products.”¹¹

It is clear from the plain language of the statute itself as well as its legislative history that, because of these well-known health consequences of tobacco use, the Tobacco Control Act was intended to apply to products that actually contain tobacco leaf, and to make it very difficult for the *tobacco industry* to bring such new products to the market.¹² As the Supreme Court found in *Brown & Williamson v. FDA*, 529 U.S. 120 (2000), traditional tobacco products are *inherently* unsafe, and it was well known that products produced by the *tobacco industry* had become more harmful and addictive over the years. For this reason, Congress sought to ensure that such traditional tobacco products did not become even more harmful or addictive by requiring any “new” tobacco products – defined as any tobacco product modified in any way or introduced into

market, making it difficult for consumers to customize their vaping experience. In addition, by deeming e-vapor products as tobacco products and subjecting them to all the same requirements of other tobacco products, even the e-vapor manufacturers who manage to make it through the PMTA process will be severely limited in what they can say about their products due to the limitations of marketing language to the language used to market cigarettes prior to March 21, 2000, *i.e.*, precisely the types of “Big Tobacco” language the e-vapor industry tries to avoid associating with. See AEMSA’s November 2015 comments to the Notice of Proposed Rulemaking: Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses”; Docket No. ID: FDA–2015–N 2002, available at: <http://www.aemsa.org/wp-content/uploads/2015/12/AEMSA-Comment-FDA%20AD2015%20ADN%20AD2002.pdf>.

¹¹ See 21 U.S.C. 387 et seq.

¹² For example, the following sections of the Tobacco Control Act are clearly designed to only apply to tobacco-leaf products, not tobacco-derived products:

- Section 102 of the only applies to specific products that contain tobacco (e.g., cigarettes, smokeless tobacco, etc.);
- Section 201 and 202 transferred authority over labeling and advertising from the Federal Trade Commission to FDA for cigarette and smokeless tobacco (which require unique language for those products specifically);
- Section 907 characterizing flavor ban only applies to cigarettes;
- Section 919 only requires user fees for manufacturers of designated products like cigarettes;
- Section 904 (submission of health information) focuses on tobacco product manufacturers to include tobacco, paper, filter (no mention of vapor); and
- Section 904 (HPHC) focuses on things like smoke constituents (no mention of vapor).



the market after the February 15, 2007 “Grandfather Date” – to go through rigorous premarket authorization.

Specifically, before being able to bring such a new product to the market, tobacco product companies have the heavy burden of demonstrating that such product is either (1) “substantially equivalent” to a predicate product that was on the market as of the Grandfather Date, or (2) obtain marketing authorization through the onerous PMTA process. The PMTA requires tobacco companies to demonstrate that their new product is “appropriate for the protection of the public health”. This is a very high standard that requires considering the product’s risks and benefits to the *population as a whole*, including users and non-users of the tobacco product, and taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products (*i.e.*, cessation), and the increased or decreased likelihood that those who do not use tobacco products will start using such products (*i.e.*, initiation). Data that must be submitted in a PMTA include the following:

- full reports of all investigations of health risks;
- a full statement of the components, ingredients, additives and properties, and principles of operation of the tobacco product;
- a full description of methods of manufacturing and processing;
- an explanation of how the product complies with any applicable tobacco product standards;
- samples of the product and its components;
- specimens of proposed labeling; and
- other information that FDA may require.

FDA has also issued a draft PMTA Guidance document that further details the types of extensive non-clinical (*e.g.*, genotoxicity, cytotoxicity, etc.) studies, clinical (human) studies, consumer perception studies, labeling studies, computational/mathematical modeling, nationwide consumer surveys, focus groups, comprehensive toxicity literature reviews, and much more will likely be needed to meet the very high public health standard for PMTAs.¹³ The guidance makes clear that, in general, non-clinical studies will not be enough to support the conclusion that a product is appropriate for the protection of the public health - clinical studies of each product are generally necessary. **Estimated costs to develop all of the data needed to support a PMTA range from \$2,000,000 to \$10,000,000 per SKU, as reported in the Wall Street Journal.**¹⁴ Additionally,

¹³ See FDA Guidance for Industry, *Applications for Premarket Review of New Tobacco Products*, available at: <http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM273425.pdf>.

¹⁴ See Tripp Mickle, “FDA Cloud Hangs Over Vape Shops,” *The Wall Street Journal*, July 7, 2015, available at:



FDA has not yet proposed regulations establishing conditions for exempting investigational e-vapor products from certain FDCA requirements (such as premarket authorization) so that they may be used in clinical trials needed to get through the PMTA process.

Even more untenable than the PMTA process is the modified risk tobacco product (MRTP) application process set forth in Section 911 of the Tobacco Control Act. FDA has also issued a Draft Guidance document on the information the Agency suggests be submitted in support of a MRTP.¹⁵ To obtain authorization to make a “modified risk” claim about a product, even one with obvious and scientifically verified reduced harm like an e-vapor product, the applicant must demonstrate that the product, as actually sold to consumers, will:

- (1) significantly reduce harm and risk of tobacco-related disease to individual tobacco users; and
- (2) benefit the health of the population as a whole (taking into account both users of tobacco products and persons who do not currently use tobacco products).

In determining the latter (*i.e.*, the public health benefit), the statute identifies five factors that FDA will consider (Section 911(g)(4)) (emphasis added):

- the *relative health risks* to individuals of the MRTP;
- the increased or decreased likelihood that *existing users* of tobacco products who would otherwise stop using such tobacco products will switch to using the MRTP;
- the increased or decreased likelihood that *persons who do not use tobacco products* will start using the MRTP;
- the *risks and benefits* to persons from the use of the MRTP *compared to smoking cessation products* approved to treat nicotine dependence; and
- comments, data, and information submitted by interested persons.

In addition, Sections 911(g)(1) and (2) specify the requirements that must be demonstrated before FDA will issue an order that a MRTP may be commercially marketed in the U.S. A commercial marketing order granted pursuant to Section 911(g)(1) is a “Risk Modification Order,” which would authorize claims that the product “presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco

<http://www.wsj.com/articles/SB10130211234592774869404581088451777513530>, discussed in <http://tobaccoanalysis.blogspot.com/2015/07/wall-street-journal-article-predicts.html>.

¹⁵ See FDA’s Draft Guidance for Industry, “Modified Risk Tobacco Product Applications” (March 2012), available online at: <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf>.

products.” A Section 911(g)(2) commercial marketing order, on the other hand, is an “Exposure Modification Order,” which would authorize only reduced-exposure claims, *e.g.*, claims that the use of the tobacco product results in less exposure to particular substances. We note at the outset that, in our opinion, obtaining a Section 911(g)(2) Exposure Modification Order is **impossible**, as it requires demonstrating through actual consumer perception studies that the reduced exposure claims will not *mislead* consumers into believing the product (1) is or has been demonstrated to be less harmful, or (2) presents or has been demonstrated to present less of a risk of disease than other commercially marketed tobacco products.¹⁶ In other words, an applicant must prove that its reduced exposure claims will not cause consumers to believe that the product is actually less harmful than other tobacco products – which, some might argue, defeats the purpose of making the claim. **Just as with the PMTA, the population-level assessment required for MRTPs would cost millions of dollars to complete, making it virtually impossible for e-vapor products, which are demonstrably reduced-harm products compared to cigarettes, to obtain MRTP marketing authorization. To date, not a single product has obtained MRTP authorization from FDA.**

The high burden for introducing new harmful *tobacco* products actually makes sense if the goal is to reduce tobacco-related disease and death – but **not** if it prevents significantly less harmful cigarette alternatives from entering the market. Indeed, it would go explicitly against Congressional intent to place this same burden on manufacturers of e-vapor products considering, as discussed below, that these products are (1) substantially less harmful to the health of smokers than cigarettes, (2) as a product category, have demonstrated a net-positive public health impact, as evidenced by the continuing declining cigarette smoking rate, and (3) all scientific evaluations so far show minimal to no second-hand exposures risks (some indicate urban air is worse).¹⁷ Congress did not intend the implementation of the Tobacco Control Act to effectively ban products that have the potential to greatly reduce the burden on society of tobacco-related disease.

Moreover, retroactively applying the PMTA requirements to the existing market of e-vapor products will result in the vast majority of, if not all, such products being forced off the market. If the Deeming Regulation is implemented as proposed and the likely insurmountable burden of demonstrating the population-level impact (completely subjective and impossible to objectively satisfy) is placed on e-vapor product manufacturers, we do not believe the industry will survive. This would clearly go against Congress’ intent to reduce harm from tobacco-

¹⁶ See Section 911(g)(2)(B)(iii).

¹⁷ Furthermore, businesses are still free to enact bans on the use of e-vapor products or establish vape-friendly policies, just as consumers may still opt to patronize businesses that either are tolerant of vaping or enact vaping bans. Thus, despite an absence of evidence of second-hand exposure risks, individuals can choose whether or not to subject themselves to vaping.



related disease through the promotion of less harmful products. The evidence suggests that Congress understood that the Tobacco Control Act was not intended to bring the tobacco industry to a grinding halt; rather, it sought only to establish “appropriate regulatory controls”¹⁸ over tobacco products.¹⁹ FDA should take a similar approach in the Deeming Regulation to establish appropriate regulatory controls over e-cigarette and e-liquid products, as discussed in Section VIII of this comment, below.

In summary, Congress intended the PMTA process for dangerous tobacco products to be insurmountable by design, and for good reason. Cigarettes kill nearly half a million people and cost the US \$300 billion in economic costs every year. An expensive, onerous and time-consuming PMTA process was put in place to make it harder to introduce new smoking products that are known to kill. The PMTA, however, will paradoxically be the death of the harm reducing vapor industry. The paradox, of course, is that killing the vaping industry will have the opposite effect on the ultimate goal of the Tobacco Control Act – to prevent smoking and the death and disease associated with it. This will leave millions of vapers, the vast majority of whom are former smokers, to either turn to a black market or revert back to deadly combustible tobacco.

VI. Concerns with the Proposed Deeming Regulation

A. FDA Should have Published an Advanced Notice of Proposed Rulemaking

In promulgating a Notice of Proposed Rulemaking rather than an *Advanced* Notice, FDA acted hastily in attempting to promulgate a rule without first gathering adequate information and data. The FDA held three Public Workshops in an effort to gather relevant scientific data but did not hold these data gathering workshops until *after* the NPRM was executed. The notice for the proposed Deeming Regulation was unique in that its *preamble* makes clear that that FDA is still seeking much information regarding e-cigarettes and how such products should be regulated. Specifically, the preamble poses a number of questions regarding how it should regulate newly deemed products, such as:

¹⁸ An example of an appropriate regulatory control for the e-vapor industry would be implementing a licensing scheme for vape shops (akin to bar licenses) and registration or licensing for e-liquid manufacturers. This approach would give government oversight over operations while giving businesses the opportunity to continue to operate upon meeting licensing standards.

¹⁹ For example, Congress gave FDA the authority to establish nicotine yields in Section 907 of the Act, but prohibited FDA from reducing the levels of nicotine in a product to zero, presumably because doing so would result in a de-facto ban on cigarettes, cigars, smokeless tobacco and roll-your-own tobacco products.



- Whether, and, if so, how FDA should consider a different regulatory mechanism for newer proposed deemed tobacco products that cannot, as a practical matter, use the SE pathway.
- Should FDA consider a different compliance policy for proposed deemed tobacco products that cannot, as a practical matter, use the SE pathway? If so, what should the compliance policy entail and would it benefit public health? Instead of, or in addition to, such a policy, should FDA consider ways to expedite the review of some or all premarket applications for proposed deemed products?
- What other FDA actions or regulatory approaches, if any, should FDA consider for proposed deemed tobacco products that are “new tobacco products” under section 910(a)(1) of the FD&C Act and why?

FDA also notes several areas in which the Agency lacks sufficient data regarding e-cigarettes and e-liquids and requests comment on, among other things:

- The effects e-cigarettes and e-liquids have on the public health.
- How e-cigarettes should be regulated based on the continuum of risk for various nicotine-delivering products and the potential benefits associated with e-cigarettes.
- The impact of e-cigarettes and e-liquid products either on reducing usage of cigarettes or in possibly prolonging usage of cigarettes while continuing to expose users to the harmful carcinogens in combustible tobacco products.

Inherent in these questions and requests for data is the recognition that there are several novel considerations that must be weighed in determining whether and how to apply the Tobacco Control Act requirements to e-cigarettes and e-liquids – products that Congress never even considered when drafting the legislation. When the Agency is seeking background information to support and inform a regulation in this manner, it typically issues an *Advanced* Notice of Proposed Rulemaking (ANPRM), rather than a NPRM, as FDA did here. ANPRMs are often promulgated when the Agency needs early public input on key issues before proposing a new rule.

FDA took the ANPRM approach to determine whether it should take steps to regulate menthol in cigarettes.²⁰ In that advanced notice, FDA requested stakeholders to comment on unique regulatory options it might consider with respect to the use of menthol in cigarettes, including potentially establishing tobacco product standards. The advanced notice was designed to inform the Agency on the available science and data and to help FDA determine what types of studies are needed to address outstanding questions about the public health implications of

²⁰ See Menthol in Cigarettes, Tobacco Products; Request for Comments, Advance Notice of Proposed Rulemaking, 78 Fed. Reg. 44484 (July 24, 2013), *available at*: <http://www.gpo.gov/fdsys/pkg/FR-2013-07-24/pdf/2013-17805.pdf>.



menthol use in tobacco products. The menthol ANPRM was made available for public comment for a total of 120 days. The Agency is now considering all comments, data, research, and other information submitted to the docket to determine what, if any, regulatory action with respect to menthol in cigarettes is appropriate. If the FDA decides to propose a rule, the next step would be a notice of proposed rulemaking, which would give the public an opportunity to weigh in on the specifics of the proposed rule.

Given the rapidly evolving science and technology here, FDA should have initiated an advanced rulemaking to gather data necessary to propose a notice of proposed rulemaking for the Deeming Regulation.

B. Alternative Frameworks for Regulation

The proposed Deeming Regulation would not do any of the things necessary to immediately safeguard the public health such as, for example, establishing quality control standards and good manufacturing practices, ingredient standards, nicotine concentration limits, clean room requirements, temperature limits, child and tamper proof packaging, or other safety features. Rather, the proposed rule would simply “deem” these products to be regulated tobacco products if they contain nicotine derived from tobacco, and would *retroactively* apply the premarket authorization requirements to products that are already on the market providing a comparatively safer alternative to smokers and contributing to declining smoking rates. While we understand that FDA would need to go through separate rulemaking procedures to create any specific regulations, there is a good chance there will be no industry left to regulate in a few years if the proposed rule becomes final.

Rather than simply “pigeon-holing” e-vapor products into all of the same statutory requirements that currently apply to cigarettes, we believe that FDA has the legal authority (as detailed in our Deeming Regulation comments to FDA) to modify the final rule in a manner that would not result in a *de facto* ban of e-vapor products.²¹ For example, FDA has the authority and an obligation to promulgate regulations that make sense and protect the public health. In this

²¹ As noted in Section VI(A), the preamble to the proposed Deeming Regulation demonstrates how FDA lacks an understanding of the e-vapor industry. The e-vapor industry was born out of concerns about combustible tobacco and consumer desires for reduced harm tobacco products. The e-vapor industry, through organizations like AEMSA, has pushed itself to innovate and create standards for e-vapor products in the absence of direct regulation. This unique industry needs a window of potential, meaning the ability to present options to consumers who desire recreational tobacco products without combustion and space to innovate. Instead, FDA proposes to impose a grandfather date that would disregard the industry (or at least, the most meaningful innovation in the industry) entirely and render most manufacturers unable to comply with the vigorous PMTA process, which would eliminate many if not all options from the market, to the consumer’s detriment.



regard, FDA should (1) amend the Grandfather Date for deemed products coupled with baseline product standards, and (2) create an expedited/streamlined PMTA process for new e-vapor products which removes the population impact burden from manufacturers and focuses on compliance with baseline product standards.

Regarding the Grandfather Date, FDA not only has the enforcement discretion to amend the Grandfather Date for deemed products, but an affirmative obligation to do so based on Congress' intent in creating the Tobacco Control Act. In Section VIII(A)(2) of this comment, we suggest a number of potential common-sense grandfather dates for e-vapor products, the most appropriate of which is the effective date of the final Deeming Regulation.

Additionally, the notion that retroactive application of the PMTA requirement to the existing e-vapor industry is necessary to protect the public health is false. FDA already has the authority to prevent adulterated and misbranded products from being sold without retroactively applying the PMTA. Specifically, the FDCA already prohibits the interstate delivery of adulterated (unsafe or contaminated) or misbranded (misleading) tobacco products.²² In the event of a violation of a prohibited act, FDA holds broad authority to bring a variety of administrative, civil, and criminal sanctions, including monetary damages and injunctions, against the offending company.²³ This being the case, for new products introduced after the amended Grandfather Date (*e.g.*, effective date of the Deeming Regulation), FDA should create a streamlined/expedited PMTA process for e-liquids and e-vapor devices, considering their vastly different risk profile compared to combustible tobacco products. This streamlined process would remove the burden of the population-level analysis from individual companies. FDA should use its enforcement discretion and its notice and comment rulemaking authority and find that the *category* of e-vapor products are “appropriate for the protection of the public health”. FDA can initiate a separate rulemaking process to determine whether the category of products meets this requirement. We further discuss this in Section VII(B)(1) below.

VII. Impact on the Public Health

In the 7+ years that e-vapor products have been on the market, and over 25 million global vapors, we are not aware of any consumers developing any serious adverse acute health effects, much less dying, from using these products as intended. While e-vapor products are not marketed as completely “harmless” and should only be used by adults, there is no doubt that compared to tobacco-leaf products, and especially those that are combusted, e-cigarettes and the e-liquids used in them are dramatically less harmful for individual tobacco users, especially

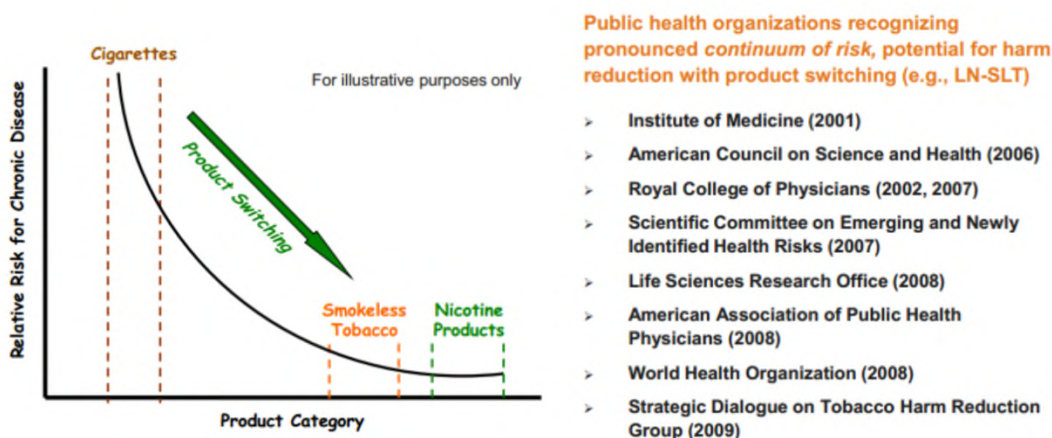
²² See Federal Food, Drug, and Cosmetic Act (FDCA) §§301(a) and (b), 21 U.S.C. § 301 et seq. (2015).

²³ See, *e.g.*, 21 U.S.C. §§ 331, 332, 333 (2015); 21 C.F.R. §§ 17.1, 17.5-17.51 (2015).

cigarette smokers. The risk disparity between tobacco and e-vapor products can be viewed on the “Continuum of Risk”.

A. Understanding the Continuum of Risk

The continuum of risk of nicotine-containing products is a way to visualize the risk disparity between different categories of products. The product categories that pose the greatest harm and risk of tobacco-related disease (*i.e.*, the traditional, combustible tobacco cigarette) are on one end of the continuum, and new product forms (such as e-vapor) that do not contain or combust tobacco are on the other end, as depicted in the following diagram²⁴:



Combusted tobacco products are the most harmful and dangerous products on the continuum and should be treated as such (*i.e.*, by requiring PMTAs for new cigarettes as Congress intended). It is well established, for example, that the more pyrolyzed tobacco constituents a user inhales from a combustible cigarette the greater the risk of tobacco-related disease that product poses.²⁵ Of the approximately 5,300 chemicals identified in cigarette smoke, at least 60 are known human carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs).²⁶ E-vapor products are far less risky to individual users than combustible cigarettes because they do not result in the inhalation of pyrolyzed chemicals.

²⁴ See FDLI, Embracing the Continuum of Risk, Presentation by RAI Services, (2013) available at: <http://www.fdpi.org/docs/default-document-library/6---tobacco---combined.pdf?sfvrsn=0>.

²⁵ See R.R. Baker, et al., The pyrolysis of tobacco ingredients, 71 J. Anal. Appl. Pyrolysis 223-311 (2004).

²⁶ See Rodgman, A. and Perfetti, T.A., The Chemical Components of Tobacco and Tobacco Smoke, Boca Raton, FL: CRC Press (2009).



The American Legacy Foundation (now the Truth Initiative), a not-for-profit organization dedicated to preventing teen smoking and encouraging smokers to quit, published a position statement on e-cigarettes, in which it stated: “Legacy recognizes that, on an individual level, there is a continuum of risk across tobacco products with combustible products (*e.g.*, cigarettes, cigars, hookah) posing the most danger and Food and Drug Administration (FDA) approved nicotine replacement therapies (NRT’s) posing the least harm. Harm reduction is a valuable public health strategy with the potential to reduce, although not eliminate, the preventable disease and death caused by tobacco. Electronic cigarettes may hold great promise in this regard. While they are not without risk, initial scientific evidence suggests that, for the individual smoker, they are likely less harmful than smoking cigarettes, and they likely have significant lower levels of known tobacco toxicants than combusted tobacco products.”²⁷ Indeed, public health experts from around the world have come out in support of tobacco harm reduction through the use of e-cigarettes. For example, more than 50 tobacco and nicotine and public health specialists from 15 countries recently sent a letter to the World Health Organization (WHO) Director General Margaret Chan emphasizing the importance of tobacco harm reduction through the use of “low risk non-combustible tobacco products (which includes e-cigarettes). These products “could be among the most significant health innovations of the 21st Century—perhaps saving hundreds of millions of lives.”²⁸

Most recently, Public Health England (PHE) calculated the level of harm caused by different nicotine delivery systems, from cigarettes to cigars, pipes, nicotine patches and e-cigarettes. PHE took into account a wide range of risks, from the effect of addiction on people’s incomes to fatal lung damage to accidental poisoning, and ultimately found that e-cigarettes are 95% less harmful than conventional cigarettes.²⁹ PHE also found that a comprehensive review of the evidence determined that almost all of the 2.6 million adults using e-cigarettes in England are current or ex-smokers, most of whom are using the devices to help them quit smoking or to prevent them going back to cigarettes. The report indicates that very few adults and young people who have never smoked are becoming regular e-cigarette users (less than 1% in each group). Despite these benefits, the review raised concerns that increasing numbers of people

²⁷ See Legacy, *E-cigarette policy: the FDA should promptly exercise regulatory authority over e-cigarettes*, (2014), available at: http://tobacco.cleartheair.org.hk/wp-content/uploads/2015/09/LEG-Policy_Statement-ECigarette-JAN2014.pdf.

²⁸ See David Abrams *et al.*, *Statement from specialists in nicotine science and public health policy*, (2014), available at: <http://www.nicotinepolicy.net/documents/letters/MargaretChan.pdf>.

²⁹ See “E-cigarettes: an evidence update,” A report commissioned by Public Health England, August 2015, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf.



think e-cigarettes are equally or more harmful than smoking (22.1% in 2015, up from 8.1% in 2013: ASH Smokefree GB survey) or don't know (22.7% in 2015, ASH Smokefree GB survey).

For a comprehensive list of already existing peer-reviewed and published research citations related to e-vapor products, please visit the E-Research Foundation's "Direct from the Experts" page available at: <http://e-researchfoundation.org/direct-from-the-experts/>. Of particular relevance, we highlight Dr. Derek Yach's keynote address at the GFN 2015 conference, also available on the E-Research Foundation's website. Dr. Yach led the development of the Framework Convention on Tobacco Control at the World Health Organization (WHO), and is currently Executive Director of the Vitality Institute, a think tank focusing on health promotion and chronic disease prevention. Dr. Yach has focused his career on advancing global health and tackling tobacco control at national and international levels. He leads the Vitality Institute, an evidence-driven and action-oriented research organization founded by Discovery Holdings and dedicated to health promotion and the prevention of chronic disease to build a culture of health. **At GFN 2015, Dr. Yach highlighted the importance of harm reduction as the way forward and embracing e-vapor products.**

When developing regulatory requirements for deemed products, including e-cigarettes and e-liquid, FDA must consider how the different product types compare to each other in terms of risk disparity. As demonstrated above, not all nicotine-containing products are equally harmful. Indeed, FDA Center for Tobacco Products Director Mitch Zeller has stated on numerous occasions that while people may smoke for the nicotine, they die from the tar and smoke. Treating all products the same by establishing a "one-size-fits-all" regulatory scheme as FDA has proposed would do considerably more harm than good.³⁰ Rather, as AEMSA outlined in its comments to the proposed Deeming Regulation, FDA should use its enforcement authority to establish appropriate regulatory requirements and procedures for the different types of deemed products that are commensurate with the harm that requires regulation.

³⁰ Further evidence that it does not make sense to group e-vapor and conventional tobacco products under a one-size-fits-all approach is seen in FDA's own comments to the proposal by the French standardization agency AFNOR for ISO to create a new technical committee for e-vapor products to develop product standards. In support of the proposal, FDA noted that a new, separate ISO technical committee for e-vapor products is needed to facilitate the development of standards that are attuned to the technology of e-vapor products. There is no logical connection between e-vapor products and tobacco and tobacco products other than the fact that both products involve the consumption of nicotine (and e-vapor products do not always contain nicotine). FDA's comments were in line with AEMSA's own, which argued that e-vapor products are more akin to medical devices than conventional cigarettes, and that the development of appropriate product standards requires expertise that the existing ISO tobacco technical committee simply does not have.



As noted above, e-vapor products are far less risky to individual users than combustible tobacco cigarettes because they do not result in the inhalation of pyrolyzed chemicals. Rather, the safety of the ingredients used to formulate e-liquids is well known. We discuss the safety of these substances below.

1. Safety of E-Liquid Ingredients

Standard e-liquid ingredients include excipients (carriers) such as propylene glycol and/or vegetable glycerin (glycerol), nicotine, and flavorings. Although the media often portrays e-liquids as containing “unknown” toxins, the safety of many of these ingredients is well established.³¹

a) Nicotine

The safety and toxicological profile of nicotine has been studied extensively in both animals and man, and a comprehensive survey of this literature will not be presented here. We do note that, importantly, nicotine itself is not a carcinogen. The long-term inhalation effects of nicotine have been studied over a two-year period in 68 female Sprague-Dawley rats (34 control animals).³² After being exposed to pure nicotine aerosol for 20 hours a day for five days a week for over two years, no tumorigenic effects of nicotine were found in any organ in the body. No tumors were detected on either microscopic or macroscopic examination of the lungs. There were also no changes evident in the macroscopic examination of the hearts, including atherosclerotic lesions (although some nicotine-exposed animals did develop pituitary tumors).

Studies on the long-term use of nicotine-replacement therapies (NRTs) have similarly made clear that nicotine is also not a carcinogen in humans. Specifically, a connection between nicotine and cancer was not found in a 5-year study of 5,887 subjects.³³ In that study, the researchers concluded that “[t]he absence in general of a relation between nicotine replacement therapy and cancer across the models adds credence to our conclusion that nicotine replacement therapy does not cause cancer.” FDA itself has confirmed this in its Notice of Findings

³¹ Furthermore, with over three years of active verifications, AEMSA has proven that it is easy to verify (in a cost-effective manner) the nicotine quality and accuracy of content of e-liquids, as well as diluents quality, appropriately clean mixing environments, packaging, appropriate labeling and warnings, limited product exposure in the manufacturing/mixing environment with controlled chain of custody, etc.

³² See Waldhum, H.L. et al., *Long-term effects of inhaled nicotine*, 58(16) Life Sciences 1339-1346 (1996).

³³ See Murray, R.P et al., *Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study*, Nicotine Tob Res. 2009 Sep; 11(9): 1076–1082, available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725009/>.



published in 2013 for “Modifications To Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use”.³⁴ In that notice, FDA cites a growing body of evidence that demonstrates the safety of long-term nicotine use as well as that NRT products sold over-the-counter (OTC) do not appear to have significant potential for abuse or dependence. Considering this, FDA requested NRT manufacturers to submit supplemental New Drug Applications to change the labeling of their current NRT products to make clear that, among other things, it is safe for consumers to use such products beyond the 8-12 weeks on the label in order to quit smoking.

Of course, we recognize that nicotine does pose some acute hazards if swallowed or absorbed through the skin and, as a result of the increasing market share of refillable open-system vaporizers, the growing presence of e-liquids on the marketplace, and in the home, expands the population that may be inadvertently exposed to nicotine at levels that pose an acute toxicity risk. But it is first important to recognize that, contrary to popular belief, the lethal dose of nicotine for adults (when ingested) is between 500-1000 mg (not 50-60 mg as many still believe).³⁵ Nevertheless, risks associated with these hazards can be controlled by careful attention to how these products are packaged. AEMSA fully supports the safe handling of nicotine-containing e-liquids by adults through the use of child-resistant packaging and other means.

It is also critical to understand the context of the potential harm. Recent media reports about the rising dangers of nicotine exposures from e-liquids greatly exaggerate the level of harm. According to the National Poison Data System (NPDS), e-cigarettes account for only 0.1% of exposures reported to Poison Control Centers (*i.e.*, 200 of 194,500 monthly calls). In 2012, there were 2,275,141 exposures reported to Poison Control Centers, or 189,595 exposures per month.³⁶ Considering this in light of the CDC’s announcement in 2014 that up to 200 e-cigarette calls per month were being reported to Poison Control Centers, it is clear that e-cigarettes account for only a tiny fraction (0.1%) of reported exposures (*i.e.*, 200 of 189,595 monthly calls).³⁷ Other common household goods result in far more reported poisoning cases.

³⁴ See 78 Fed. Reg. 19718 (April 2, 2013).

³⁵ See Farsalinos, KE, *Nicotine lethal dose in humans: a common argument by regulatory authorities, based on poor science*, available at: <http://ecigarette-research.com/web/index.php/2013-04-07-09-50-07/132-nicotine-lethal-dose-in-humans>.

³⁶ See James Mowrey *et al.*, *2012 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 30th Annual Report*, (2013), available at: https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2012_NPDS_Annual_Report.pdf.

³⁷ See CDC, *Notes from the Field: Calls to Poison Centers for Exposures to Electronic Cigarettes — United States, September 2010–February 2014*, (2014), available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6313a4.htm?s_cid=mm6313a4_e.

According to NPDS's annual report from 2012, the top five substance classes most frequently involved in all human exposures were analgesics (11.6%), cosmetics/personal care products (7.9%), household cleaning substances (7.2%), sedatives/hypnotics/antipsychotics (6.1%), and foreign bodies/toys/miscellaneous (4.1%). Analgesic exposures as a class increased the most rapidly (8,780 calls/year) over the last 12 years. The top five most common exposures in children aged 5 years or less were cosmetics/personal care products (13.9%), analgesics (9.9%), household cleaning substances (9.7%), foreign bodies/toys/ miscellaneous (7.0%), and topical preparations (6.3%).³⁸

b) Propylene Glycol and Vegetable Glycerin

Like nicotine, the safety and toxicological profile of both propylene glycol and vegetable glycerin, the most common e-liquid excipients, have been studied extensively in both animals and man, and a comprehensive survey of this literature will not be presented here. Both of these substances are used in a variety of pharmaceuticals (as a solvent in many oral, topical, and injectable formulations), tobacco products (as a humectant), consumer products (including pet food, candy, personal lubricants), and are Generally Recognized as Safe (GRAS) by FDA for direct use in food.³⁹ Neither of these substances are carcinogenic or genotoxic. The publicly available summaries of the toxicity of these substances has been published, for example, through the "Screening Information Data Set" (SIDS) program operated under the auspices of the Organization for Economic Cooperation and Development (OECD), whose reports are available online.⁴⁰ In particular, propylene glycol is one of the most commonly used solvents, intermediates, or carrier molecules used in consumer products. It has been subject to animal toxicology studies dating back to the 1940s. Results consistently demonstrate very low oral, dermal or inhalation toxicity.⁴¹ With respect to inhalation, the route of exposure of interest here, we note that a comprehensive review of the toxicological profile of a condensation aerosol of

³⁸ See Mowry, *et. al.*, 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report, 51(10), Clin. Toxicol. 949-1229 (2013). See CDC, 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report.

³⁹ See 21 C.F.R. §§ 182.1320 ("Glycerin") and 184.1666 ("Propylene glycol").

⁴⁰ Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) program, *available at*: <http://www.chem.unep.ch/irptc/sids/OECDIDS/57-55-6.pdf>; and <http://www.chemicals.moew.government.bg/chemical/site/File/registers/profile/56815p.pdf>.

⁴¹ See LaKind, J.S., McKenna, E.A., Hubner, R.P., Tardiff, R.G., 1999. A review of the comparative mammalian toxicity of ethylene glycol and propylene glycol. *Critical Reviews in Toxicology*, 29, 331–365.

propylene glycol under conditions where the inhaled aerosol was targeted to produce deep lung delivery was conducted by Werley and colleagues and published in 2011.⁴²

c) Flavorings

E-liquids come in a variety of flavors. In Section VII(B)(2) of this comment, we discuss why flavored e-liquids are appropriate for the protection of the public health. In this section we discuss the safety of the flavors themselves, as there has been growing concern about potential dangers associated with the inhalation of certain compounds found in some e-liquid flavors.

Specifically, two substances which have been identified in some e-liquid flavors as being of concern when inhaled are diacetyl and acetyl propionyl (2,3-pentanedione), a common replacement for diacetyl. A recent study from researchers at Harvard on the levels of these compounds in e-liquids has been getting much media attention.⁴³ That study reported finding diacetyl in 39 of 51 flavors of e-liquids tested, with levels ranging from below the level of quantification to 239 µg/e-cigarette. Acetyl propionyl and acetoin were detected in 23 and 46 of the 51 flavors tested at concentrations up to 64 and 529 µg/e-cigarette, respectively. The study authors concluded that “[d]ue to the associations between diacetyl, bronchiolitis obliterans and other severe respiratory diseases observed in [microwave popcorn factory] workers, urgent action is recommended to further evaluate this potentially widespread exposure via flavored e-cigarettes.” The potential presence of these substances in e-liquid flavors, however, has been known for some time. In fact, researchers led by Dr. Farsalinos published a study earlier this year in the journal *Nicotine and Tobacco Research* which evaluated the presence of diacetyl and acetyl propionyl in 159 e-liquid samples.⁴⁴ The study found that 74.2% of the samples contained either diacetyl or acetyl propionyl, with more samples containing diacetyl.

While these substances appear to be present in many flavors, it is critical to understand the context of the levels observed relative to the identified workplace/occupational hazard, as well as cigarette smoking. Specifically, the levels in the Farsalinos study were on average slightly lower than currently-established safety limits (set by the National Institute of

⁴² See Werley, M.S. (2011). Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. *Toxicology*, 287, 76–90.

⁴³ See Allen JG, *et al.* Flavoring chemicals in e-cigarettes: Diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environmental Health Perspectives*. Published online December 8, 2015: <http://ehp.niehs.nih.gov/15-10185/>.

⁴⁴ See Farsalinos, K., *et al.*, Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins, *Nicotine Tob Res* (2015) 17 (2): 168-174, available at: <http://ntr.oxfordjournals.org/content/17/2/168>.



Occupational Safety and Health (NIOSH)). It is also important to note that tobacco cigarette smoke contains both compounds, at levels significantly higher when compared to the average daily exposure from e-cigarette vapor. Dr. Michael Siegel, a professor in the Department of Community Health Sciences, Boston University School of Public Health, noted that studies have demonstrated that, on average, cigarette smoke contains diacetyl at levels 750 times higher than in e-vapor aerosol.⁴⁵ This is based on a study by Fujioka and Shibamoto which measured the diacetyl exposure from active smoking.⁴⁶ They found that the average diacetyl content of the cigarettes tested was 335.9 µg/cigarette. Assuming that a smoker consumes one pack per day (20 cigarettes), the average daily inhaled dose of diacetyl associated with smoking is therefore 6,718 µg. Another study conducted by Pierce *et al.*, found that the maximum inhaled daily diacetyl dose associated with smoking was 20,340 µg, whereas for vaping it was only 239 µg. In short, it is clear that the levels of these substances in cigarette smoke is generally far greater than in e-vapor aerosol.

Moreover, as detailed below, although no specific health risks have been established from the use of these substances at the levels present in some e-liquids, AEMSA has been working with its Members to ensure that their products are tested, and has encouraged its Members work to eliminate diacetyl and acetyl propionyl from their products.⁴⁷

With respect to the toxicity of diacetyl, exposure to diacetyl by ingestion has been fully evaluated by experts and determined to be safe for uses resulting in very low exposures in food.⁴⁸ Indeed, diacetyl occurs naturally in foods such as apples, beans, butter, is present in alcoholic beverages (as a byproduct of fermentation), and is commonly employed as a flavoring agent to

⁴⁵ See Tobacco Analysis, “New Study Finds that Average Diacetyl Exposure from Vaping is 750 Times Lower than from Smoking,” December 10, 2015, *available at*: <http://tobaccoanalysis.blogspot.com/2015/12/new-study-finds-that-average-diacetyl.html>.

⁴⁶ See “The Chemical Constituents in Cigarettes and Cigarette Smoke: Priorities for Harm Reduction – A Report to the New Zealand Ministry of Health,” March 2000, *available at*: [http://www.moh.govt.nz/moh.nsf/pagescm/1003/\\$File/chemicalconstituentscigarettespriorities.pdf](http://www.moh.govt.nz/moh.nsf/pagescm/1003/$File/chemicalconstituentscigarettespriorities.pdf).

⁴⁷ See American E-liquid Manufacturing Standards Association, “AEMSA Recommends Flavor Testing,” September 11, 2014, *available at*: <http://www.aemsa.org/aemsa-recommends-flavor-testing/>.

⁴⁸ See FDA’s food additive regulations, 21 CFR § 184.1228 (2014) (“Diacetyl”); *available at*: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1278&SearchTerm=diacetyl>. This regulation affirms the generally recognized as safe (GRAS) status of diacetyl as a direct human food ingredient when used as a flavoring agent and adjuvant at levels not to exceed current GMP.



impart a buttery taste, as well as for other purposes. With respect to inhalation, exposure to large amounts of inhaled diacetyl in certain work-place settings (*e.g.*, the microwave popcorn production and flavor manufacturing industries) has been documented to be associated with bronchiolitis obliterans, a severe respiratory illness.⁴⁹ It is important to recognize that while additional studies are necessary, no specific health risks have been established for diacetyl (or acetyl propionyl) at the levels typically present in some e-liquid flavors which, again, are substantially lower than the levels of these substances found in tobacco smoke.

In fact, despite high levels of diacetyl, cigarette smoking has *not* been associated with popcorn lung.⁵⁰ Cigarette smoke consists of a complex mixture of chemical constituents including a variety of potentially carcinogenic compounds. FDA has established a list of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke.⁵¹ The list includes many commonly recognizable chemicals, such as acrylamide, benzene, formaldehyde, and styrene, as well as many substances that are less-recognizable to the common citizen. In total there are 93 substances on FDA's list of HPHCs. The list also classifies each substance as to whether it is perceived to be a carcinogen, a respiratory toxicant, a cardiovascular toxicant, and reproductive or developmental toxicant, or addictive. **Notably diacetyl and acetyl propionyl are both absent from this list.**

Nevertheless, AEMSA agrees that precautionary measures should be taken to assure that consumer risk to these effects is minimized. With these concerns in mind, AEMSA encouraged and provided guidance to its Members to have their e-liquid products tested using third-party accredited labs using appropriate and scientifically verified analytical detection limits and procedures. AEMSA has worked with its scientific Subject Matter Experts to ensure that appropriate methodologies with low limits of detection are used consistently.

AEMSA believes that the e-liquid industry should focus on the presence of potentially harmful substances in the flavor components used in e-liquids. We encourage all e-liquid manufacturers to have their flavors independently tested and learn more about appropriate testing

⁴⁹ NIOSH, *Diacetyl and 2,3-Pentanedione Criteria Document*, "Occupational Exposure to Diacetyl and 2,3-Pentanedione," External Review Draft at ix, (August 12, 2011) (hereinafter "NIOSH Criteria Document"), available at:

<http://www.cdc.gov/niosh/docket/archive/pdfs/NIOSH-245/0245-081211-draftdocument.pdf>.

⁵⁰ See Pierce, J.S., Abelmann, A., Spicer, L.J., Adams, R.E., and Finley B.L., "Diacetyl and 2,3-pentanedione exposures associated with cigarette smoking: implications for risk assessment of food and flavoring workers" May 2014, 44(5).

⁵¹ See "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List" available at: <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm297786.htm>.



methodologies and detection limits. It is critical for the e-liquid industry to work together with FDA to establish effective testing protocols to ensure substances which may pose a health or safety concern when inhaled are not present in flavors. FDA should work with organizations such as AEMSA and the U.S. Pharmacopeia to establish certification procedures for e-liquid ingredients (in addition to nicotine, which can be USP-certified), as well as analytical testing methods and limits of detection for impurities of concern.

d) Concerns Regarding Formation of Aldehydes in E-Vapor

We note that one area of concern for e-liquids is the potential formation of aldehydes (*e.g.*, formaldehyde and acetaldehyde) during use. Although these substances are not intentionally added ingredients, some studies have shown that at excessively high temperatures propylene glycol and vegetable glycerin in e-liquids can decompose to low molecular carbonyls compounds, including harmful aldehydes. It is important to understand, however, that during actual e-cigarette use, the potential for human exposure to these substances is quite low because (1) consumers are unlikely to allow their devices to reach such high temperatures and (2) more devices are incorporating temperature-control and other safety mechanisms to prevent excessive heat generation.

The excessive heat required to generate these harmful compounds results in what is known as the “dry puff” phenomenon – the immediate unpleasant, burning taste experienced by the user when the heater coil overheats – which makes the vapor uninhalable. Because a user can immediately detect and avoid dry puffs when vaping (by decreasing puff duration and increasing the inter-puff interval, or refilling the tank if the e-liquid level is low) the potential for exposure to any generated carbonyls is low. Under normal vaping conditions, the aldehyde emission levels are minimal and by far lower than the levels found in tobacco cigarette smoke.

In a letter recently published in the *New England Journal of Medicine*,⁵² researchers highlighted the risk of formaldehyde exposure from certain e-cigarette devices. Specifically, the researchers obtained a variable voltage e-cigarette device, and applied 3.3 and 5.0 volts to an (unnamed) atomizer for 4 seconds per puff. At 3.3 volts they found no formaldehyde, while at 5.0 volts they found formaldehyde levels up to 15 times higher than in tobacco cigarette smoke. But this study had some serious flaws, as summarized by leading e-vapor researcher and AEMSA Subject Matter Expert (SME), Dr. Konstantinos Farsalinos⁵³:

⁵² See *Hidden Formaldehyde in E-Cigarette Aerosols*, *N Engl J Med* 2015; 372:392-394. January 22, 2015 DOI: 10.1056/NEJMc1413069, available at: http://www.nejm.org/doi/full/10.1056/NEJMc1413069?query=featured_home.

⁵³ See Farsalinos, K., “The deception of measuring formaldehyde in e-cigarette aerosol: the difference between laboratory measurements and true exposure,” January 21, 2015, available at: <http://www.ecigarette-research.com/web/index.php/2013-04-07-09-50-07/2015/191-form-nejm>.



For start, the authors did not find formaldehyde but formaldehyde hemiacetals. This is a combination of formaldehyde and alcohols (formaldehyde-propylene glycol or formaldehyde-glycerol). The authors characterized them as formaldehyde-releasing agents, providing a reference to a study evaluating contact dermatitis from such agents. However, looking at the study referenced, it is clear that those formaldehyde-releasing agents have nothing to do with formaldehyde hemiacetals found in e-cigarette aerosol. Moreover, there is absolutely no evidence that hemiacetals are toxic or carcinogenic. In fact, it is possible that the formation of hemiacetals might protect against damage induced by formaldehyde. Nevertheless, the authors considered the risk equal to formaldehyde and calculated the risk of cancer.

There are many other major issues in that study. The authors fail to realize that voltage levels provide no information about the thermal load of an e-cigarette device. It seems that both the researchers and the reviewers who approved the study for publication missed that energy should be expressed in watts. As a result, we do not know how many watts were applied to the atomizer. However, there is a way to approximate this, through the information provided about liquid consumption per puff. The authors report that 5mg of liquid were consumed at 3.3 volts. Based on measurements I have performed, such consumption is observed at about 6-7 watts at 4-second puffs. Thus, the atomizer resistance is probably 1.6-1.8 Ohms. This means that at 5 volts the energy was around 14-16 watts. That would be an extremely high value for most commercially-available atomizers (excluding some rebuildables which can withstand such high wattage levels). Thus, it is more than obvious that once again the atomizer was overheated, which of course will result in very high levels of formaldehyde production. What the authors ignore is that these conditions, commonly called dry-puff phenomenon (which is explained in detail in one of my published studies), are easily detected by the vapers. In fact, overheating results in an unpleasant taste that none can withstand. As a result, no vaper is ever using the e-cigarette at such conditions and, thus, will never be exposed to such levels of formaldehyde. The story published in New England Journal of Medicine is similar to finding carcinogens in an overcooked piece of meat that none can ever eat. Of course the findings are true, but none will be exposed to the levels found.

I am concerned that we will very often see stories like this. The scientific community must realize that variable wattage devices cannot be used at any wattage levels with any available atomizer. Even for naïve users, the harsh taste of the dry puff phenomenon is unbearable. I would suggest scientists to try themselves an e-cigarette at dry puff conditions (it is very easy, just use an atomizer without enough liquid), and they will find out themselves. In fact, it is



very easy to produce as much aldehydes as you want in the lab with an e-cigarette device. However, this has nothing to do with exposure from e-cigarette use.

Dr. Farsalinos and his team recently completed a study (which is currently being peer-reviewed for publication in the journal *Addiction*) to identify the dry-puff temperature (using actual consumer volunteers) and to evaluate the levels of aldehydes released at those temperatures, as well as in temperatures associated with conventional vaping. In that study, two customizable atomizers were prepared so that one had a double wick (A1) resulting in high liquid supply and lower chance of overheating at high power levels, with the other was a conventional single-wick atomizer (A2). Seven users took four puffs at various power settings (6.5 W, 7.5 W, 9 W and 10 W) using both atomizers and were asked to report whether dry puffs were generated. The atomizers were then attached to a smoking machine and the aerosol was trapped. The levels of formaldehyde, acetaldehyde, acetone and acrolein were measured in the aerosol. The users all identified dry puff conditions at the higher 9 W and 10 W power settings with the A2 atomizer, while the A1 atomizer was used at all power levels without generating the dry puff taste.

The results of the aldehyde measurements, reported per 10 puffs, are as follows:

	Formaldehyde (ug/10 puffs)	Acetaldehyde (ug/10 puffs)	Acetone (ug/10 puffs)	Acrolein (ug/10 puffs)
6.5 watts				
A1	6.5	ND	ND	ND
A2	3.7	0.8	ND	0.2
7.5 watts				
A1	6.1	ND	ND	ND
A2	ND	0.8	ND	1.3
9 watts				
A1	9.5	3.5	ND	0.8
A2 [dry puff]	119.2	58.9	4.6	48.4

	Formaldehyde (ug/10 puffs)	Acetaldehyde (ug/10 puffs)	Acetone (ug/10 puffs)	Acrolein (ug/10 puffs)
10 watts				
A1	11.3	4.5	ND	1.0
A2 [dry puff]	344.6	206.3	22.5	210.4
Tobacco cigarettes ⁵⁴ (Health Canada Intense puffing regime)	74.0	1240.3	641.9	120.4

As demonstrated in the table above, minimal levels of aldehydes were found at all power levels with A1 and at 6.5 W and 7.5W with A2. These levels were significantly lower compared to smoking.⁵⁵ However, at the power levels where dry puff conditions were experienced by the users (9 W and 10W with A2), emissions were raised by 30 to 250 times for formaldehyde, acetaldehyde and acrolein. Acetone was detected only in the aerosol generated by A2 at power levels associated with dry puff conditions.

These results confirm that while it is possible for e-vapor products to generate high levels of aldehydes, this is only observed during dry puff conditions. On the other hand, minimal amounts of aldehydes were released to the aerosol under normal vaping conditions, with the levels being far lower compared to tobacco cigarette smoke. Aldehyde release was associated with the efficiency of the atomizer design to accommodate the high power levels through effective e-liquid supply to the wick. In other words, during normal temperature conditions of use, high power levels are not associated with exposure to significant levels of toxic aldehydes.

Accordingly, aldehyde emissions in e-vapor aerosol are directly related with dry puff conditions. At normal vaping conditions, the aldehyde emission levels are minimal and by far lower than the levels found in tobacco cigarette smoke. At the dry puff conditions, aldehyde release is significantly elevated, but consumers are not expected to be exposed to such levels during normal e-vapor use.

⁵⁴ See Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoking composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions Regul Toxicol Pharmacol 2005; 41:185-227.

⁵⁵ *Id.*



B. Assessing the Population-Level Impact of E-Vapor Products

1. FDA's Authority to Initiate a Separate Rulemaking Procedure to Assess Population-Level Impact of E-Vapor Products

The proposed Deeming Regulation places the burden on individual manufacturers to demonstrate that each of their products (SKUs) meets the “public health” requirement in the PMTA. It would be unnecessarily redundant, costly, and would serve to further complicate the daunting task which FDA faces in defining how e-vapor are regulated to require individual e-vapor companies address the potential population-level impact posed by *each* of their products. **Rather, the population-level impact of these products is a general regulatory policy issue for this category of product, not a product-specific issue.** We understand that Congress established the public health standard in the Tobacco Control Act, but believe that there is nothing preventing FDA from initiating a separate rulemaking requesting data and information from the public on whether or not the availability of e-vapor products as a category is “appropriate for the protection of the public health”. Indeed, FDA is already addressing this general regulatory issue via a variety of activities, including sponsored research (*e.g.*, the Population Assessment of Tobacco and Health (PATH) study, a national longitudinal study of tobacco use and how it affects the health of people in the United States), public workshops, consumer surveys, etc.

What if FDA required individual sponsors seeking licenses for new vaccines to prove in their applications that adaptive immunity can be elicited by vaccination, to address all of the concerns of the vaccine denier/autism advocacy community, or to demonstrate the benefit of vaccination to the entire population at large? That would be unduly burdensome, and contrary to public health interests. Rather, what is well established by regulatory precedent is that the specific risks and benefits of the product are what need to be addressed in any application to the Agency. Moreover, such assessment needs to occur at the level of representative samples of individual users, not at the general public level. Vaccines clearly work better when herd immunity is factored in, rather than efficacy and effectiveness at the level of the individual, but they are tested and licensed by demonstrating appropriate risk/benefit at the level of groups of tested individuals to whom the vaccine has been administered (relative to control groups). So too should the risks and benefits of a specific e-cigarette product be demonstrated at the level of adequately powered groups of tested individuals, rather than at the general population level. Population-level analyses concerning an entire product category or technology are subject to many confounding variables which can obscure and complicate risk/benefit assessments for individual products. **In the case of the potential population-level impact of e-vapor products in general, even though Congress required FDA consider the public impact of new tobacco products, it is critical for the Agency to recognize that this is a regulatory policy issue, separate from the risks and benefits of a *specific* product.**

FDA should also acknowledge the extensive and growing body of literature on the safety and public health benefit of e-vapor products (compared to conventional cigarettes). Based on



this, FDA should recognize in the final Deeming Regulation that a less rigorous implementation of premarket documentation is appropriate for non-combusted non-tobacco products such as e-cigarettes and e-liquid. We address the key public health factors supporting this argument below, namely the public health impact of e-liquid flavor variety and the lack of evidence demonstrating e-vapor products are a gateway to smoking.

2. Public Health Benefit of E-Liquid Flavors

Despite the negative connotations often associated with flavored e-liquid in the media, these products actually provide a public health benefit. Specifically, one of the primary reasons that consumers of open-system vaporizers are much less likely to engage in “dual use” with cigarettes, or revert to smoking compared to consumers of “cigalike” e-cigarettes is the fact that the open-system products may be used in conjunction with refillable e-liquids that come in a variety of flavors, allowing adult consumers to tailor their vaping experience to fit their tastes and needs. There are thousands of e-liquid manufacturers and vape shops across the country which, in turn, produce tens of thousands of individual e-liquid products. The fact that e-liquids come in such a wide variety of flavors other than tobacco and menthol is the primary reason why vapers continue to vape rather than smoke.

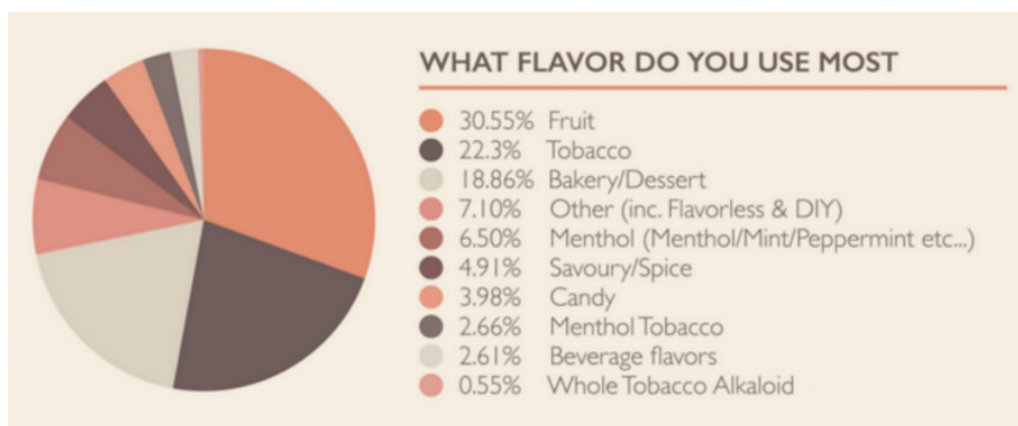
To better understand the impact that flavors have on e-cigarette users, a research team led by Dr. Farsalinos conducted a survey of 4,618 dedicated vapers.⁵⁶ Of the 4,515 participants that reported their current cigarette smoking status, the overwhelming majority (91.1%) were former smokers (*i.e.*, vapers who have transitioned completely to e-cigarettes from combustible cigarettes). Of the remaining current smokers (*i.e.*, vapers that continue to smoke cigarettes), they had, on average, reduced their cigarette consumption from 20 to 4 units per day. Both subgroups (former smokers and current smokers) had a median smoking history of 22 years and had been using e-cigarettes for 12 months. On average, the participants were using three different types of e-liquid flavors on a regular basis, with former smokers switching between flavors more frequently, compared to current smokers. Specifically, 69.2% of the former smokers reported using different e-liquid flavors on a daily basis or during the day. Fruit flavors were more popular at the time of participation, while tobacco flavors were more popular at initiation of e-cigarette use. In other words, smokers making the transition to vaping were like to initially make the switch using tobacco flavored e-liquids, but then began enjoying other flavors. On a scale from 1 (not at all important) to 5 (extremely important) participants answered that variability of flavors was “very important” (score = 4) in their effort to reduce or quit smoking. The majority reported that restricting flavor variability will make e-cigarettes less enjoyable and more boring, while 48.5% mentioned that it would increase craving for combustible cigarettes. Nearly 40%

⁵⁶ See Farsalinos, K., *et al. Impact of Flavour Variability on Electronic Cigarette Use Experience: An Internet Survey*, 10(12) Int. J. Environ. Res. Public Health 7272-7282 (2013), available at: <http://www.mdpi.com/1660-4601/10/12/7272>.



said that it would have been less likely for them to reduce or quit smoking if not for flavored e-liquids. The number of flavors used was independently associated with smoking cessation.⁵⁷

This public health benefit of e-liquid flavors was also reinforced by a survey of 10,000 vapers conducted by the Electronic Cigarette Forum (ECF).⁵⁸ When asked which e-liquid flavor they used most, only about 25% of the participants indicated tobacco or menthol tobacco. This means that three-quarters of the adult e-cigarette users surveyed actually prefer flavors *other* than tobacco, including fruit (31 percent), bakery/dessert (19 percent), and savory/spice (5 percent)⁵⁹:



Approximately 65.5% of the former smokers surveyed consider e-liquid flavors important in helping them transition completely to vaping and away from smoking.

⁵⁷ Of course, as noted above, none of the e-liquids produced by AEMSA Members are marketed for use in smoking cessation or as NRTs, but rather only for recreational use by adults. Any smoking cessation or reduced cigarette consumption resulting from the use of e-liquids or e-cigarettes generally is a corollary benefit of these products.

⁵⁸ See McLaren, Neil, *Vaping.com Big Survey 2014 - Initial Findings General*, (2014), available at: <http://vaping.com/data/vaping-survey-2014-initial-findings>. This survey was conducted in late June and early July 2014. Of the more than 10,000 members of E-Cigarette Forum, 78 percent of whom live in the United States. Their ages ranged from 18 to “65 and over,” with 74 percent between 22 and 54.

⁵⁹ See *Vaping.com Big survey 2014 - initial findings general*, available at: <http://vaping.com/data/vaping-survey-2014-initial-findings>. See also *Survey Shows Adults Who Use E-Cigarettes To Quit Smoking Prefer Supposedly Juvenile Flavors*, Forbes.com, (2014), available at: <http://www.forbes.com/sites/jacobsullum/2014/07/17/survey-shows-adults-who-use-e-cigarettes-to-quit-smoking-prefer-allegedly-juvenile-flavors/>.



FDA itself has recognized the importance of having palatable cigarette alternatives available in order to reduce harm. Specifically, in the case of the Nicorette® gum, FDA has determined that a variety of flavors such as White Ice Mint®, Cinnamon Surge™, Fruit Chill™, FreshMint™ and Mint provide a more palatable alternative for adult smokers and do not present a significant risk for abuse.⁶⁰ In the case of Nicorette, the Agency clearly determined that the benefit of having a variety of palatable/flavored options outweighed the risk that the flavors might attract adolescents or non-smokers to the over-the-counter product, or otherwise lead to the product being abused. There are, in fact, many consumable products on the market today that are intended for adults and are offered in fruity, candy and other flavors, such as flavored alcohol beverages.⁶¹

Although e-cigarettes and e-liquids are recreational use products and not intended to be smoking cessation devices, the same principle applies to these products. Non-tobacco e-liquid flavors assist e-cigarette users to associate their nicotine fix and/or smoking “habit” with a new taste, helping them transition away from smoking and creating an additional barrier to relapse, as returning to combustible cigarettes would mean getting used to the burning flavor of tobacco smoke again. Indeed, when switching to vaping, many smokers may initially try tobacco-flavored e-cigarettes because they are looking for a close replacement. Many of those newly switching often need to try 20+ tobacco flavored e-liquids to find just one or two products that are subjectively satisfactory to replace combustible tobacco use.⁶² But as their olfactory and sense of taste return, as their cigarette consumption decreases, new vapers often experiment with more pleasant and enjoyable e-liquid flavors which, in turn, keep them from reverting to cigarette use (here again, even with non-tobacco flavors, consumers consistently report trying 20 or 30 flavors to find two or three subjectively satisfactory). Unlike combustible tobacco use (wherein consumers generally find one brand/”flavor” and stick with it), as delineated hereinabove in the survey citations, vapers constantly change flavors even during a single day and much more over time. If *only* tobacco-flavored e-liquids were permitted, smokers would be

⁶⁰ See <http://www.nicorette.com/nicorette-gum> (“Quitters agree — Nicorette Gum tastes great. Choose from six sugar-free flavors: White Ice Mint®, Cinnamon Surge™, Fruit Chill™, FreshMint™, Mint and Original.”)

⁶¹ Many alcohol beverages, including vodka, are offered in a wide variety flavors such as fruit flavors, fluffed marshmallow, iced cake, kissed caramel, and root beer float, to name a few. See, for example, <http://www.smirnoff.com/en-us/vodkas/flavors/> and <http://www.biteclubbeats.com/flavored-vodkas-from-bacon-to-fruit-loops/>.

⁶² In addition, the device combinations available in open systems can and do vary the experience from one device to another, and these changes influence the “vapor character” and experiences for an individual user, as verified by consumer purchasing experiences. This reinforces the need for a variety of products to allow users to customize until they discover their desired vaping experience.



less likely to disassociate their habit from such flavor. In short, tobacco-flavored e-liquids could re-trigger an urge to smoke cigarettes.

Ultimately, as traditional cigarette use continues to decrease, without sufficient scientific data to support a product standard restricting or banning the use of characterizing flavors in e-cigarettes and e-liquids, the Agency must proceed with extreme caution before promulgating any such standard.⁶³ If FDA were to move too quickly in this regard, such a move could be detrimental to the public health, as smokers who prefer flavor variety while vaping would have no palatable recreational alternatives to turn to. Such smokers could switch back to harmful cigarettes.

The growing body of evidence supports that flavored e-liquids help adult smokers disassociate their nicotine addiction and smoking habit from the taste of tobacco, thereby providing a public health benefit. Moreover, AEMSA agrees that in order to minimize any potential harm, preventing adolescents from accessing these products is paramount, and supports banning sales of these products to minors. Specifically, manufacturers should market their flavored products in a responsible manner by, for example, (1) making clear that such products are not intended for use by anyone under the legal smoking age⁶⁴, (2) preventing the products and any marketing materials from being accessed by minors either online or in vape shops, and (3) using responsible product names that are not more likely to attract youth.

Finally, it should be clearly acknowledged that other consumer products that pose potential youth use and/or access are never regulated based on that risk as a primary consideration factor. Historic poison control call statistics (hereinabove) verify this reality (analgesics, cosmetics, toys, etc.). For all other such youth access potential risk products (e.g. alcohol(s), knives, over the counter drugs, liquid glues, bleach products, kerosene, even BB & Pellet guns, etc.), responsible parental oversight is the only consideration.

3. As Cigarette Smoking Rates Continue to Decline No Evidence that E-Vapor is a Gateway to Smoking

⁶³ Moreover, any ban on flavored e-liquids would likely result in an unintended ban of *all* electronic cigarette products. See Dr. Michael Siegel, “Glantz and Colleagues Essentially Call for a Ban on Electronic Cigarettes: Banning Flavors Would Ban All Existing E-Cigarettes,” available at: <http://tobaccoanalysis.blogspot.com/2014/06/glantz-and-colleagues-essentially-call.html>.

⁶⁴ Manufacturers should implement robust online age-verification systems that will verify the age of online purchasers using either official government identification or verification through a reputable credit agency. AEMSA also encourages brick-and-mortar e-liquid vendors to ensure that the age of any in-person purchasers under the age of 26 is properly verified.



The growing body of scientific data supports the fact that e-cigarettes and the e-liquids used in them:

- Do not have an adverse impact on smoking initiation and cessation rates (*i.e.*, the evidence indicates that the products have contributed to the continuing decline in the percentage of the population that smokes cigarettes); and
- Have not resulted in an increase in adolescent cigarette smoking rates (*i.e.*, no “gateway” to smoking exists).

Based on this data it is clear that not only are e-cigarettes and the e-liquids used in them less harmful for individual tobacco users compared to tobacco-leaf products, they also provide a net positive population level “public health” impact.

a) Declining Smoking Rates

The growing body of evidence indicates that e-cigarette use has no adverse impact on overall smoking initiation and cessation rates, and has actually contributed to the continually declining smoking rates, which is at an all-time low in the United States. A Gallup poll published in December 2015 reported a decline in smoking among adults aged 18-29 by a 12 percentage points to 22 percent over the past decade – a new low. Young people are now no more likely to smoke than those aged 30 to 64. These findings align with the Centers for Disease Control and Prevention’s own surveys, which found that cigarette smoking has dropped most sharply among 18- to 24-year-olds. Specifically, data released in April 2015 showed regular smoking continuing to fall among high school students while vaping was increasing, with 9.2 percent of students saying they smoked a cigarette in the last month – a fall of 3.5 percent from 2013. Over the same time period, students who reported using e-cigarettes increased from 4.5 percent to 13.4 percent.⁶⁵ This clear trend away from smoking was also documented in the 2014 National Youth Tobacco Survey (NYTS). However, rather than focusing on the very positive results demonstrating that while e-cigarette *experimentation*⁶⁶ has increased among adolescents,

⁶⁵ Guy Bentley, “Gallup Poll Shows Smoking Rate Collapsing As E-Cigarette Use Soars,” December 11, 2015, available at: <http://dailycaller.com/2015/12/11/gallup-poll-shows-smoking-rate-collapsing-as-e-cigarette-use-soars/#ixzz3uMAx98TD>.

⁶⁶ A recent study published in *Tobacco Control* evaluated patterns of e-cigarette use by investigating the number of days out of the past 30 days when adults had used e-cigarettes. The analysis found that use ≤ 5 days in the past 30 days demarcated a cluster of infrequent users at the low end of the distribution. Among those with use in the past 30 days, infrequent users were the majorities of current (59%) and never smokers (89.5%), but fewer than half of former smokers (43.2%). Infrequent users were more likely to cite curiosity and less likely to cite quitting/cutting down other tobacco use as reasons for use. The study concluded that defining adult prevalence as any use in the past 30 days may include experimenters unlikely to continue



the cigarette smoking rate among the same population has declined dramatically, to all-time low levels,⁶⁷ both FDA and CDC conflated e-cigarette use with all other tobacco use, and focused on the fact that “overall current use of tobacco products” has not changed. Considering that vaping is significantly less harmful than smoking, as documented above, conflating the use of the two products and implying they are equally harmful could itself have adverse public health consequences.

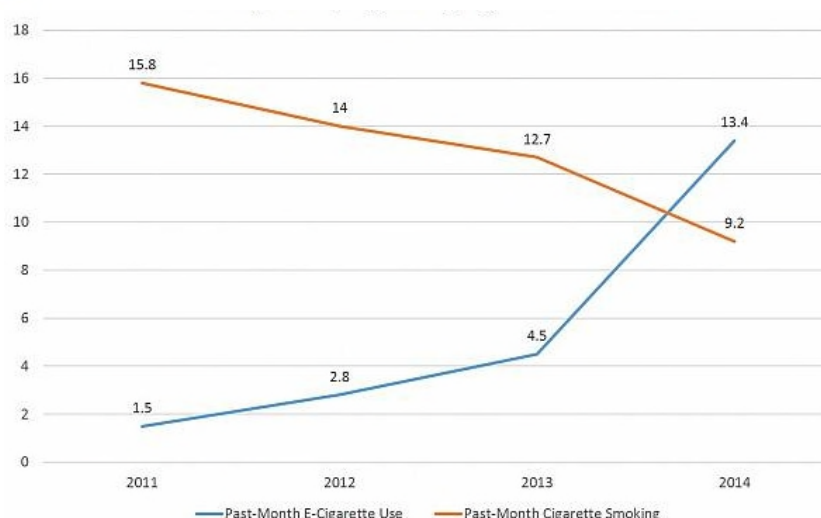
b) No Evidence of Gateway Effect

Finally, and perhaps most importantly, the recent CDC report further dispelled the unsubstantiated notion that e-cigarettes are a gateway that will result in non-smoking vapers taking up cigarettes. According to the study, only 0.4 percent of people who had never smoked tobacco were current vapers. Among the adults who had never smoked cigarettes, a meagre 3.4 percent had ever tried and e-cigarettes. While more studies are necessary, there is little doubt that as teenage smoking continues to fall so does the viability of the argument that these products are a gateway to smoking⁶⁸:

use, and is of questionable utility for population surveillance of public health trends over time. Defining prevalence as > 5 days excludes those infrequent users. *See* Amato, Michael S., Boyle, Rayond G., and Levy, David, *How to define e-cigarette prevalence? Finding clues in the use frequency distribution*, Tob Control doi:10.1136/tobaccocontrol-2015-052236, abstract available at: <http://tobaccocontrol.bmj.com/content/early/2015/05/15/tobaccocontrol-2015-052236.abstract>.

⁶⁷ Please note that neither AEMSA nor any of its Members support the sale of e-cigarettes or e-liquids to anyone under the legal age of purchase. As stated clearly on AEMSA’s website, we advocate e-cigarette products for adult-use only and support bans on sales to minors. We further agree that marketing imagery, nomenclature, and product naming must not target persons under the legal age of purchase. Currently 46 states prohibit e-vapor sales to minors.

⁶⁸ *See* Jacob Sullum, *E-Cigarettes Are Not Tobacco Products: The CDC Misleads the Public About the Hazards of Vaping*, REASONS.COM (Apr. 27, 2015), available at: <http://reason.com/archives/2015/04/27/e-cigarettes-are-not-tobacco-products#.zmf3lk:fcwT>.



Insofar as these results provide evidence about whether e-cigarette use is a gateway to smoking or a *replacement* for smoking, the NYTS data suggests that in adolescents, at least so far, the replacement hypothesis is the likelier of the two.

Placed in the proper context, the recent CDC and NYTS data actually demonstrate that e-cigarettes can be a tool for tobacco harm reduction. The dramatic decline in both overall and youth smoking rates corresponds directly with the increase in e-cigarette use over the last few years, demonstrating the public health benefit these products provide. Beyond the NYTS, there is a growing body of evidence in the public literature (detailed in the AEMSA FDA comment) that demonstrates that e-cigarettes and the e-liquid used in them are having a net positive population-level impact by providing a significantly less harmful source of nicotine for current tobacco users and cigarette smokers, and are not having the “gateway” effect to cigarettes feared by many.

4. Creation of an Unregulated and Untaxed Black Market and Other Unintended Consequences

Numerous consumer surveys indicate that they would turn to the black market if products they currently use are effectively banned. For example, a survey conducted by the E-Cigarette Forum (ECF) last year found that 79% of 10,000 vapers surveyed would look to purchase products illegally on the black market.⁶⁹ The only other viable option for many other than the black market or “DIY” liquids, would be to revert back to cigarette smoking. Either way, FDA

⁶⁹ See Steven Nelson, “E-cigarette Users Would Ignore Bans, Turn to Black Market, Study Finds,” July 17, 2014, US News and World Report, *available at*: <http://www.usnews.com/news/articles/2014/07/17/e-cigarette-users-would-ignore-bans-turn-to-black-market-survey-finds>.



must be cognizant, as required by EO 12866, of the potential unintended consequences of the Deeming Regulation such as the development of an unregulated, untaxed black market. This will have a serious adverse impact on the public health. While adverse public health impacts of a potential black market are the primary concern, obviously there would be substantial economic impacts to both federal and state government agencies to respond to and/or minimize the realities of a black market (while on a smaller scale, we hopefully learned something from prohibition).

VIII. Proposed Regulatory Solutions

A. Amend the Current Grandfather Date

The proposed Deeming Regulation imposes the existing February 15, 2007 Grandfather Date to newly deemed products, including all e-vapor products. FDA indicated in the preamble of the proposed rule that, because the date is set forth in the statute, it does not believe it has the legal authority to alter or amend it for the newly deemed products. Thus, if the proposal were to become effective as drafted, any deemed product would also be considered a “new tobacco product” subject to premarket review if it was not commercially marketed in the United States as of February 15, 2007, or modified in any way from a product that was commercially marketed on that date. Although FDA proposed a “compliance policy” in the Deeming Regulation that would delay enforcement of the premarket authorization requirements for two years (*i.e.*, the PMTA submission deadline for products on the market would be the second anniversary of the effective date of the regulation), that is simply not enough time for e-vapor manufacturers to generate the data needed to support such application, particularly considering that clinical studies can take years to complete.

We are not aware of any e-vapor products that were marketed on February 15, 2007, meaning practically all e-vapor products would be “new” and subject to the PMTA. But, even if an e-cigarette were available on that date, such product would be an early first-generation “cigalike” product. Compared to today’s products, first-generation cigalikes are rudimentary devices that were not designed with consumer safety in mind. As a result, grandfathering this type of device would have the unintended consequence of eliminating numerous innovative safety features developed over the last several years. Compared to the early cigalike models, today’s advanced vaporizers are better designed and incorporate numerous safety features including, but not limited to:

- Control circuits with temperature control/limiting capability;
- Microprocessors used to monitor and adjust the power and heat delivered, ensuring consistent aerosol delivery;
- Over/under-charge and short-circuit protections (internal on device circuit boards);



- “Smart charging” ability using cell phone technology which stops charging current flow to battery when fully charged;
- Newer refillable tanks/atomizers do not contain the cartomizer filler material found in cigalikes, which has the potential to melt/char if heated after the e-liquid is consumed;
- “Boost circuits” which help to ensure consistent aerosol output by maintaining the heat level, as well as offer adjustable airflow features allowing the user to customize their experience and prevent potential “dry puff”; and
- For cigalikes, airflow sensors that detect when the user is using the device, which turns the battery on to provide power to the vaporizer.

Applying the 2007 Grandfather Date to this industry would allow manufacturers to produce products identical to those rudimentary products, if any, that may have been on the market on that date, and to ignore and exclude technological advancements that benefit the public health. Utilizing the 2007 date would analogously equate to trying to regulate today’s cell phones and tablets based on rudimentary rotary phone technology. This would also completely disincentivize any and all current and future *safety features* innovations, as well as eliminate many that have already been adopted and that are in development. For these reasons, it makes little sense for FDA to strictly apply the original Grandfather Date to e-vapor products.

Requiring essentially all of the e-cigarette and e-liquid products available today to obtain premarket authorization by way of a PMTA will result in these products eventually being removed from the market and effectively banned, even though this was never intended by Congress. While such a result would undoubtedly be disastrous for the public health, as millions of former smokers would likely turn back to harmful tobacco-leaf and combusted products or an e-vapor black market, it may be prevented if the Agency utilizes a more appropriate grandfather date for e-vapor products. We first discuss the legal authority FDA has to create a new grandfather date for deemed products and then discuss several potential new dates.

1. FDA’s Enforcement Discretion and Rulemaking Authority

Amending the Grandfather Date for e-vapor products is necessary because Congress did not intend the Tobacco Control Act requirements, such as the statutory Grandfather Date, to be *strictly* applied to novel products that do not contain tobacco leaf and only deliver aerosolized nicotine. For this reason, FDA should use its rulemaking authority to promulgate a regulation establishing a new date for e-vapor products.

In this regard, it is important to realize that because the Tobacco Control Act amended the FDCA, it attached itself to lots of well-established jurisprudence and precedent. The FDCA has always been interpreted as providing FDA with much rulemaking and enforcement flexibility. For example, Section 701(a) of the FDCA gives the Agency the authority to



promulgate substantive rules that will provide for the “efficient enforcement” of the Act. Furthermore, the Tobacco Control Act itself states in Section 3 that the purpose of the law is to “provide new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry’s efforts to develop, introduce, and promote less harmful tobacco products.” The ability to exercise enforcement discretion also follows from the Obama administration’s mandate that FDA “identify and consider regulatory approaches that reduce burdens and maintain flexibility and freedom of choice for the public.” Agency decisions regarding whether or not to take enforcement action and the criteria for making such decisions has also been supported by the courts.

There are numerous examples of FDA using its rulemaking authority to implement appropriate regulatory solutions other than those anticipated by explicit language in the FDCA, a number of which are provided in AEMSA’s comment to the Deeming Regulation. This is true not only with respect to FDA regulation of foods, drugs and medical devices but also tobacco, where the Agency has made ample use of its enforcement discretion with respect to the currently regulated products. For example, although not specifically permitted by the statute, FDA has stated in its guidance documents that the premarket authorization requirements do not apply to components parts, but only finished tobacco products. FDA has also indicated that tobacco blending changes made to address the natural variation of tobacco in order to maintain a consistent product would not create a new tobacco product that must go through premarket review. Even in the proposed Deeming Regulation, the 24-month compliance policy described above is a clear example of FDA using its enforcement discretion.

In short, although FDA has stated that it does not believe it can alter or amend the Grandfather Date from the February 15, 2007 date set in the statute, there appears to be ample legal basis for FDA to use its rulemaking authority to establish a more appropriate grandfather date for deemed e-vapor products. Such action is also necessary to protect the public health.

2. Potential New Grandfather Dates

The underlying purpose for establishing the Grandfather Date was to create a rigorous premarket process to ensure that new, more harmful *tobacco leaf-containing* products did not enter the market. But as detailed above, e-cigarettes and their e-liquid components are drastically less harmful than tobacco leaf products and, in particular, combusted products. Rather, these provide a clear public health benefit and the rapidly evolving technology is only making these products safer and less risky. Indeed, innovation in the e-cigarette industry is very different from that of traditional tobacco. As companies have become more sophisticated, the use of higher quality ingredients and parts, as well as production quality standards (such as AEMSA’s) have become more common. There is a vibrant competition among e-cigarette and e-liquid



manufacturers to develop safer products for adult smokers looking to transition to less harmful forms of nicotine.⁷⁰

There are several potential dates that FDA could adopt as the new grandfather date for e-vapor products. To understand which dates might make the most sense, it is important to consider why February 15, 2007 was selected as the statutory Grandfather Date. That date is arbitrary and has no special meaning other than it was simply the date that the House and Senate bills that eventually became the Tobacco Control Act were reintroduced in Congress, after previous versions of the bill had failed to pass.⁷¹ In fact, even though it was H.R. 1256, introduced on March 3, 2009 in the 111th Congress,⁷² that was ultimately signed by the President, we suspect that the original February 15, 2007 grandfather date was kept in the legislation, at least in part, because that was the date that put the tobacco industry on official notice not only that it would be subject to FDA's authority, but *how* it would be regulated.

Using this same logic of “first notice,” FDA could use several dates as the new grandfather date for e-vapor products:

- **April 25, 2011** – this is the date that FDA published a letter to e-cigarettes stakeholders on its website that it would not appeal the *Sottera Inc. v. FDA*, 627 F.3d 891 (D.C. Cir. 2010) decision (which held that e-cigarettes that contain nicotine derived from tobacco and are sold for recreational fall under the meaning of “tobacco product” and are not drug delivery devices), and conceded that such e-cigarettes would be captured under its authority by the Deeming Regulation. That letter is available here: <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm252360.htm>.
- **April 25, 2014** – this is the date that the Notice of Proposed Rulemaking for the Deeming Regulation was published in the Federal Register and made available for

⁷⁰ A few examples of the types of safety and engineering advancements that have now become common in e-cigarettes include improved battery and charger technology, auto-shut off capabilities, short-circuit protections, temperature limitations, activation time limiters, and e-liquid wicking and quality improvements. E-liquids are also much safer (*i.e.*, contain fewer unintended impurities, etc.) as the quality of ingredients and manufacturing processes have improved.

⁷¹ See Library of Congress Summary of S. 625 (110th): Family Smoking Prevention and Tobacco Control Act, *available at*: <https://www.govtrack.us/congress/bills/110/s625#summary/libraryofcongress>.

⁷² See Library of Congress Summary of Text of the Family Smoking Prevention and Tobacco Control Act, *available at*: <https://www.govtrack.us/congress/bills/111/hr1256/text>.



public comment, putting the e-vapor industry on official notice that FDA intends to regulate it in the same manner as currently regulated tobacco products.

- **The Effective Date of the Deeming Regulation (To Be Determined)** – the Proposed Rule could go through significant changes before it is finalized, so using the effective date of the actual rule would make the most sense. In addition, the e-vapor product category is a rapidly evolving, and the technology used in products today is quite different (*e.g.*, variable wattage and/or temperature control) from products that were on the market in 2007, 2011 and even 2014. Use of the earlier dates would not grandfather the many now standard safety features in today’s advanced e-cigarettes. FDA may consider using the effective date of the Deeming Regulation as the new grandfather date for these products to ensure that it captures the latest engineering and safety advancements that benefit the public health.

3. Baseline Product Standards Needed

As noted above, the majority of product safety features typically found on today’s products, as well as e-liquid manufacturing standards, were developed after 2007. Accordingly, we appreciate that modifying the Grandfather Date will result in a large number of poorly manufactured or otherwise unsafe products that are currently on the market being “grandfathered” and exempt from the premarket authorization requirements. While, as noted above, the FDCA gives FDA the authority to remove adulterated and misbranded products from the market as soon as Deeming becomes effective, we think the most prudent approach to safeguard the public health while amending the Grandfather Date would be to simultaneously establish baseline e-vapor device and e-liquid standards. Under this monograph-like approach⁷³, manufacturers with products on the market as of the new Grandfather Date would also need to show that their products are meeting the baseline safety standards in order to remain on the market. Enacting baseline standards would embrace e-vapor products in a way that ensures responsible manufacturers thrive and irresponsible manufacturers are pushed out of the market, instead of the current approach pushing all manufacturers off the market.

For e-liquids, we offer AEMSA’s manufacturing standards, first published in 2012, as baseline Good Manufacturing Practices for which products on the market as of the new Grandfather Date must show compliance. As noted above, AEMSA is the first and only manufacturers’ trade association completely dedicated to creating responsible and sustainable standards for the manufacturing of e-liquids. One of AEMSA’s primary goals is to provide consumers with higher degrees of confidence that our members’ products are manufactured with

⁷³ See *Over-the-Counter (OTC) Drug Monograph Process*, available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ucm317137.htm>.



professionalism, accuracy and in a safe manner until such time as FDA promulgates GMPs for e-liquids. AEMSA believes that e-liquid manufacturers⁷⁴ have the responsibility to:

- Verify the accuracy of nicotine content in e-liquid products;
- Ensure the quality of all ingredients in e-liquid products;
- Prepare e-liquid products in a clean, sanitary and safe environment;
- Ensure e-liquid products are packaged and delivered in a safe manner; and
- Provide a level of transparency into the monitoring and verification process.

These are the core beliefs underlying AESMA's manufacturing standards. To ensure that the public health is protected and that e-liquids are manufactured in compliance with the Tobacco Control Act, FDA should propose for public comment GMPs based on these standards, which will ensure that e-liquids are not contaminated or manufactured in such a way that will result in the products being adulterated. To be clear, we are suggesting that AEMSA's standards themselves could be used as an e-liquid GMP baseline, not AEMSA Membership or certification status. Many e-liquid manufacturers in the United States and around the world, not only official AEMSA Members, have made use of our publicly available standards and either meet or exceed the standards. Such non-AEMSA Member manufacturers likely have sufficient evidentiary documentation to verify compliance.

For devices, FDA should consider requiring all products on the market as of the new Grandfather Date be able to demonstrate that they have minimal safety features, such as those first incorporated into advanced vaporizers. Specifically, the first e-cigarette control circuit (the "Darwin") was launched by Evolv, Inc. in 2010. The Darwin was the first product to market that utilized variable wattage control (U.S. Patent No. 8820330), which provided consistent vapor in spite of the variability of cartomizers of the day. The Darwin also had an LCD screen displaying wattage, battery state, voltage, amperage and coil resistance in real time. Its output was adjustable and it featured USB "smart" charging and a larger high capacity battery. The features introduced in the Darwin revolutionized e-cigarette technology and has set the standard for all of the devices which have come after it. More specifically, the Darwin directly controlled output wattage, rather than voltage or duty cycle, as all previous e-cigarettes had done, allowing the user to receive a consistent mass flow rate of vapor regardless of the heating coil attached or degradation of that heating coil over time. In the intervening five years virtually the entire e-cigarette industry transitioned over to this method of output control. Accordingly, FDA might

⁷⁴ Further, there could be specific credentialing requirements for manufacturers with safe handling logistics, such as dedicated handling space with appropriate PPE and ventilation, clean-up and disposal specifications, for handling pure or 1000 mg nicotine reductions and dilutions to working levels. There could also be maximum limits for commercially available or wholesale nicotine content to registered or licensed e-liquid manufacturers (such as 250 mg), a maximum refillable e-liquid content (such as 36 mg for open systems, perhaps up to 45mg for closed systems) and a maximum nicotine level for consumer self-use (such as 100 mg).



consider requiring any newly grandfathered devices to have some or all of the safety features first brought to market with the Darwin.

B. Create a Streamlined/Expedited PMTA Process

FDA should create a streamlined PMTA process for new e-cigarette and e-liquid products that focuses on product-specific risks and benefits. Based on the extensive existing literature on the safety and public health benefit of e-cigarettes (compared to conventional cigarettes) the Agency should acknowledge that a less rigorous implementation of premarket documentation is appropriate for non-combusted non-tobacco products such as e-cigarettes. Specifically, FDA should find that, as a class of products, the availability of e-cigarettes and their e-liquid components provides an overall positive impact on the health of the population. Accordingly, e-cigarette and e-liquid manufacturers should not have to consider the potential population-level impact of their individual products, but should instead only be required to demonstrate that their products are not unnecessarily harmful to the health of individual consumers by, for example, complying with the baseline device and e-liquid product standards described above.⁷⁵

We understand that more studies are needed before FDA can make a regulatory determination about whether e-vapor products as a category are appropriate for the protection of the public health. For this reason, we suggest that the Agency initiate a separate rulemaking procedure (perhaps an *Advanced* Notice of Proposed Rulemaking) seeking data and information precisely on this question. Advanced Notices of Proposed Rulemaking (ANPRMs) are promulgated when the Agency needs early public input on key issues before proposing a new rule.

⁷⁵ For example, FDA could require a PMTA process that establishes a baseline product as a “maximum specification” for approvals. In other words, have a molecular analysis of a product that has high quality nicotine, accuracy of content, USP certified diluents, flavorings that meet a maximum allowable diacetyl/acetyl propionyl content (combining “non-detected” flavors may still result in detectable trace levels of these substances in the final e-liquids), specified guidelines that allow for additional molecular limitations if/when other substances of proven risk may be found, specific clean manufacturing standards, tamper evidence, child-resistant caps, appropriate labeling, and traceability. Such a “comparison/baseline” product could establish an *objective* standard for evaluating products (as opposed to the completely subjective current standard for a PMTA) while providing an incentive to meet or exceed the baseline standard. Such application requirements could include batch-level evidentiary documentation and a quantitative GCMS (or other reasonably identified and SME supported analysis) per SKU to meet the *objectively measured* baseline. This approach would avoid pushing manufacturers out of the industry due to impossibly high application costs with no indication of ongoing business viability.

We have already highlighted the dramatic decline in both adult and teen cigarette smoking rates since e-vapor products became more prevalent. In addition, a number of studies have been performed and are currently underway directly assessing how e-vapor products can help smokers transition away from combustible tobacco products. Here are just a few examples:

- A study in England published in the journal *Addiction* found that smokers trying to quit were substantially more likely to succeed if they used e-cigarettes than over-the-counter therapies such as nicotine patches or gum.⁷⁶ Two randomized controlled trials were conducted and suggested that while many factors could influence real-world effectiveness, e-cigarettes can aid smoking cessation. The study included 5,863 adults who had smoked within the previous 12 months and made at least one quit attempt during that period with either an e-cigarette only (n=464), NRT bought over-the-counter only (n=1922) or no aid in their most recent quit attempt (n=3477). About a fifth of those who said they were using e-cigarettes had stopped smoking at the time of the survey, compared with about a tenth of people who had used patches and gum. More specifically, e-cigarette users were more likely to report abstinence than either those who used NRT bought over-the-counter (odds ratio 2.23, 95% confidence interval 1.70 to 2.93, 20.0% vs. 10.1%) or no aid (odds ratio 1.38, 95% confidence interval 1.08 to 1.76, 20.0% vs. 15.4%). The adjusted odds of non-smoking in users of e-cigarettes were 1.63 (95% confidence interval 1.17 to 2.27) times higher compared with users of NRT bought over-the-counter and 1.61 (95% confidence interval 1.19 to 2.18) times higher compared with those using no aid. The study authors concluded that among smokers who have attempted to stop without professional support, those who use e-cigarettes are more likely to report continued abstinence than those who used a licensed NRT product bought over-the-counter or no aid to cessation. This difference persists after adjusting for a range of smoker characteristics such as nicotine dependence.
- Another recent study from England also suggests that e-cigarettes are helping to accelerate smoking cessation, rather than hinder it.⁷⁷ According to this study, the prevalence of e-cigarette use began to rapidly increase in 2012 and has continued to climb steadily through the first quarter of 2014. The key finding from the study is that the annual rate of smoking cessation (that is, the percentage of current smokers who quit smoking during the past year), which had reached a low of 4.6% in 2011, increased markedly to 6.2% in 2012, 6.1% in 2013, and 8.7% for the first quarter of 2014, concomitant with the dramatic rise in e-cigarette use among these smokers. The

⁷⁶ See Jamie Brown et al., *Real-World Effectiveness of E-Cigarettes When Used to Aid Smoking Cessation: A Cross-Sectional Population Study*, 109 ADDICTION 1531-1540 (2014), available at: <http://onlinelibrary.wiley.com/doi/10.1111/add.12623/abstract>.

⁷⁷ See R. West, J. Brown & E. Beard, *Trends in Electronic Cigarette Use in England, Smoking Toolkit Study*, London: University College London, (April 4, 2014), available at: <http://www.smokinginengland.info/latest-statistics/>.

proliferation of electronic cigarettes in England has also been associated with a dramatic increase in the proportion of smokers who tried to stop in the past year (from 33.5% in 2011 to 40.3% in 2014) and an increase in the success rate for smokers who tried to quit (from 13.7% in 2011 to 21.4% in 2014). The proliferation of e-cigarettes was also associated with an acceleration in the decline in smoking prevalence. Taken together, these data suggest that the widespread use of e-cigarettes among smokers in England has advanced the degree of smoking cessation.⁷⁸

- A survey of more than 19,000 vapers from around the world reported in the *International Journal of Environmental Research and Public Health* found that almost all of the participants (99.5%) were smokers when they started vaping. Four-fifths of them had stopped smoking completely, while the rest had reduced their cigarette consumption, on average, from 20 to four per day.⁷⁹ This survey clearly demonstrates that e-cigarettes are reducing harm from tobacco/cigarette use and not acting as a gateway to initiation.
- Respondents from three surveys were recruited from a panel of adults in Britain to estimate prevalence and attitudes of e-cigarettes in England.⁸⁰ Preliminary online and face-to-face qualitative research informed the development of a smokers' survey (486 smokers who had used e-cigarettes and 894 smokers who had not). Representative samples of adults in Britain were then constructed from the panel for population surveys in 2010 (12,597 adults, including 2,297 smokers) and 2012 (12,432 adults, including 2,093 smokers), generating estimates of the prevalence of e-cigarette use and trial in Great Britain. Awareness, trial, and current use increased between 2010 and 2012; for example, current use more than doubled from 2.7% of smokers in 2010 to 6.7% in 2012. The proportion of ever-users currently using e-cigarettes was around one-third in both years. In 2012, 1.1% of ex-smokers reported current e-cigarette use, and a further 2.7% reported past use. Approximately 0.5% of never-smokers reported having tried e-cigarettes. The authors concluded that there was evidence supporting the view that e-

⁷⁸ See Michael Siegel, *New Data from England Suggest that Electronic Cigarettes are Helping to Accelerate Smoking Cessation, Not Hinder It* (Apr. 10, 2014), available at: <http://tobaccoanalysis.blogspot.com/2014/04/new-data-from-england-suggest-that.html> (providing analysis on *Trends in Electronic Cigarette Use in England*).

⁷⁹ See Konstantinos E. Farsalinos et al., *Characteristics, Perceived Side Effects and Benefits of Electronic Cigarette Use: A Worldwide Survey of More than 19,000 Consumers*, 11(4) INT. J. ENVIRON. RES. PUB. HEALTH 4356-4373 (2014), available at: <http://www.ncbi.nlm.nih.gov/pubmed/24758891>.

⁸⁰ See Martin Dockrell et al., *E-Cigarettes: Prevalence and Attitudes in Great Britain*, 15(10) NICOTINE TOB. RES. 1737-1744 (2013), available at: <http://www.ncbi.nlm.nih.gov/pubmed/23703732>.

cigarette use may be a bridge to quitting and that there was little evidence of e-cigarette use among adults who had never smoked.

- In one of the first studies to examine the hypothesis that e-cigarettes are a gateway for youth to become addicted to cigarettes, Dr. Theodore Wagener from the University of Oklahoma Health Sciences Center reports being able to find only one young person who initiated nicotine use with e-cigarettes and then went on to smoke cigarettes, out of a sample of 1,300 college students.⁸¹ Overall, 43 students said their first nicotine product was an e-cigarette. Of that group, only one person said they went on to smoke regular cigarettes. And the vast majority who started with e-cigarettes said they weren't currently using any nicotine or tobacco. This study provides preliminary evidence that electronic cigarettes are not currently serving as a major gateway to cigarette smoking.⁸² Similarly, in national survey of 3,240 adults to determine use and awareness of emerging tobacco products (e.g., snus, waterpipe, dissolvable tobacco, and e-cigarettes), only 6 (six) non-smokers, out of a total of 2,000 non-smokers in the sample, had *ever* used e-cigarettes.⁸³
- Self-administered written surveys assessing tobacco use behaviors were conducted in two large U.S. suburban high schools. The surveys demonstrated that, while the use of e-cigarettes increased among the students, such increase was primarily observed in students who were already smoking cigarettes.⁸⁴ Specifically, the prevalence of e-

⁸¹ See Brenda Goodman, *E-Cigarettes May Not Be Gateway to Smoking: Study*, HEALTHDAY.COM (Oct. 29, 2013), available at: <http://consumer.healthday.com/cancer-information-5/tobacco-and-kids-health-news-662/e-cigarettes-may-not-be-gateway-to-smoking-study-681597.html>.

⁸² For more analysis of this study, See Michael Siegel, *First Study to Examine E-Cigarette Gateway Hypothesis Can Find Only One Nonsmoker Who Initiated with E-Cigs and Went on to Smoke* (Oct. 31, 2013), available at: <http://tobaccoanalysis.blogspot.com.au/2013/10/first-study-to-examine-e-cigarette.html>.

⁸³ See Robert McMillen, Jeomi Maduka & Jonathan Winickoff, *Use of Emerging Tobacco Products in the United States*, 2012 J. ENVIRON. & PUB. HEALTH (2012), available at: <http://www.hindawi.com/journals/jeph/2012/989474/>; Michael Siegel, *National Study of Adults Can Find Only Six Nonsmokers Who Have Ever Tried Electronic Cigarettes*, (May 8, 2013), <http://tobaccoanalysis.blogspot.com/2013/05/national-study-of-adults-can-find-only.html> (providing analysis of study referenced in *Use of Emerging Tobacco Products in the United States*).

⁸⁴ See Deepa R. Camenga et al., *Trends in Use of Electronic Nicotine Delivery Systems by Adolescents*, 39 ADDICTIVE BEHAVIORS 338-340 (2014), available at: <http://www.sciencedirect.com/science/article/pii/S0306460313002736>.

cigarette use during the previous 30 days increased from 0.9% in February 2010 to 2.3% in June 2011 ($p = 0.009$). This is an indication of harm reduction, however, as current cigarette smokers had increased odds of e-cigarette use. When adjusted for school, grade, sex, race and smoking status, students in October 2010 and June 2011 had increased odds of past-30 day use of e-cigarettes compared to February 2010. The prevalence of e-cigarette use doubled in the sample of high school students, but current cigarette smoking was the strongest predictor of current use.

- A prospective 6-month pilot study conducted in Catania, Italy examined the effect of e-cigarettes on smoking reduction and cessation and demonstrated that the use of e-cigarettes helps smokers, not intending to quit, to remain abstinent or reduce their cigarette consumption.⁸⁵ The execution of this study involved monitoring possible modifications in the smoking habits of 40 regular smokers (unwilling to quit) by experimenting the 'Categoria' e-cigarette with a focus on smoking reduction and smoking abstinence. Study participants were invited to attend a total of five study visits: at baseline, week-4, week-8, week-12 and week-24. At each visit, product use, number of cigarettes smoked, and exhaled carbon monoxide (eCO) levels were all measured. In addition, smoking reduction and abstinence rates were calculated and adverse events and product preferences were also reviewed. The researchers found a sustained 50% reduction and smoking abstinence in 22/40 (55%) participants, with an overall 88% reduction in cigarettes/day. Although mouth (20.6%) and throat (32.4%) irritation, and dry cough (32.4%) were common, these side effects diminished substantially by week-24. Overall, two to three cartridges/day were used throughout the study and participants' perception and acceptance of the product was good. The researchers concluded that the use of e-cigarettes substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit.
- A 2011 study conducted in Philadelphia, Pennsylvania surveyed experienced e-cigarette users in the interest of identifying the e-cigarette products used by experienced e-cigarette users, their pattern of e-cigarette use and the impact on tobacco use. Specifically, the study involved face-to-face surveys of 104 experienced e-cigarette users. Researchers found that 78% of participants had not used any tobacco in the prior 30 days. Researchers noted that these e-cigarette users had previously smoked an average of 25 cigarettes per day and had tried to quit smoking an average of nine times before they started using e-cigarettes. Researchers also observed that two-thirds of e-cigarette users had previously tried to quit smoking using an FDA-approved smoking cessation NRT products. The majority of the sample in this study had used e-cigarettes daily for at least a

⁸⁵ See Riccardo Polosa et al., *Effect of an Electronic Nicotine Delivery Device (E-Cigarette) on Smoking Reduction and Cessation: A Prospective 6-Month Pilot Study*, 11 BMC PUB. HEALTH 786 (2011), available at: <http://www.biomedcentral.com/content/pdf/1471-2458-11-786.pdf>.

year and three quarters started using e-cigarettes with the intention of quitting smoking. Notably, almost all participants who identified as e-cigarette users felt that the e-cigarette had helped them to succeed in quitting smoking. Researchers further noted that most participants used advanced vaporizers which are designed to enable the atomizer to more consistently achieve a more satisfying vapor. Researchers concluded that further evidence should be collected regarding the safety and efficacy of e-cigarettes for smoking cessation and that until then, smokers should use proven treatments such as counseling and FDA-approved medicines. Nevertheless, the researchers also concluded that smokers who successfully switch to e-cigarettes, should continue vaping e-cigarettes and not revert to smoking cigarettes.⁸⁶

- A 2011 internet survey in English and French examined 3,587 participants (70% former tobacco smokers, 61% men, mean age 41 years) to assess the profile, utilization patterns, satisfaction and perceived effects among users of e-cigarettes.⁸⁷ The researchers observed that the median duration of e-cigarette use was 3 months, users drew 120 puffs/day and used five refills/day. Most participants (96%) said the e-cigarette helped them to quit smoking or reduce their smoking (92%). Reasons for using the e-cigarette included the perception that it was less toxic than tobacco (84%), to deal with craving for tobacco (79%) and withdrawal symptoms (67%), to quit smoking or avoid relapsing (77%), because it was cheaper than smoking (57%) and to deal with situations where smoking was prohibited (39%). Most ex-smokers (79%) feared they might relapse to smoking if they stopped using the e-cigarette. Users of nicotine-containing e-cigarettes reported better relief of withdrawal and a greater effect on smoking cessation than those using non-nicotine e-cigarettes. The researchers concluded that participants used e-cigarettes similar to people who take nicotine replacement medications – by former smokers to avoid relapse or as an aid to cut down or quit smoking.
- A 2012 study examined the effects of the White Super e-cigarette on desire to smoke, nicotine withdrawal symptoms, attention and working memory.⁸⁸ Researchers selected eighty-six smokers, and randomly allocated them to either: 18 mg nicotine e-cigarette

⁸⁶ See J. Foulds, S. Veldheer & A. Berg, *Electronic Cigarettes (E-Cigs): Views of Aficionados and Clinical/Public Health Perspectives*, 65(10) INT'L J. CLIN. PRACT. 1037-1042 (2011), available at: <http://www.ncbi.nlm.nih.gov/pubmed/21801287>.

⁸⁷ See Jean-François Etter & Chris Bullen, *Electronic Cigarette: Users Profile, Utilization, Satisfaction and Perceived Efficacy*, 106(11) ADDICTION 2017-2028 (2011), available at: <http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.2011.03505.x/abstract>.

⁸⁸ See Dawkins, L., et al., *The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition*, 37(8) ADDICT BEHAV. 970-973 (2012), abstract available at: <http://www.ncbi.nlm.nih.gov/pubmed/22503574>.

(nicotine), 0 mg e-cigarette (placebo), or just hold the e-cigarette (just hold) conditions. Participants rated their desire to smoke and withdrawal symptoms at baseline (T1), and five (T2) and twenty (T3) minutes after using the e-cigarette ad libitum for 5 min. A subset of participants completed the Letter Cancellation and Brown-Peterson Working Memory Tasks. Researchers found that after 20 minutes, compared with the just hold group, desire to smoke and some aspects of nicotine withdrawal were significantly reduced in the nicotine and placebo group; the nicotine e-cigarette was superior to placebo in males but not in females. Researchers also determined that the nicotine e-cigarette also improved working memory performance compared with placebo at the longer interference intervals. There was no effect of nicotine on Letter Cancellation performance. Researchers concluded that the White Super e-cigarette alleviated desire to smoke and withdrawal symptoms 20 min after use although the nicotine content was more important for males.

- Based on data gathered from a national online study of 2,649 adults and the Legacy Longitudinal Smoker Cohort study of 3,658 adults, researchers used multivariable models to examine e-cigarette awareness, use, and harm perceptions.⁸⁹ In the online survey, 40.2% (95% confidence interval [CI] = 37.3, 43.1) had heard of e-cigarettes, with awareness highest among current smokers. Utilization was higher among current smokers (11.4%; 95% CI = 9.3, 14.0) than in the total population (3.4%; 95% CI = 2.6, 4.2), with 2.0% (95% CI = 1.0, 3.8) of former smokers and 0.8% (95% CI = 0.35, 1.7) of never-smokers ever using e-cigarettes. The study authors concluded that awareness of e-cigarettes is high, and use among current and former smokers is evident.
- A study published in 2012 examined e-cigarette use among teenagers and young adults in Poland, and concluded that most youth that tried e-cigarettes and previously smoked.⁹⁰ The researchers conducted a survey with a cluster sample of 20,240 students enrolled at 176 nationally representative Polish high schools and universities between September 2010 and June 2011. To estimate national e-cigarette prevalence among various demographic groups, researchers used population weights. In addition, researchers used multiple logistic regression to evaluate which demographic factors were independent predictors of two outcomes: ever use of e-cigarettes and use in the previous 30 days. The researchers found that among high school students, aged 15 to 19 years, 23.5% had ever used e-cigarettes and 8.2% had done so within the previous 30 days. Among those in

⁸⁹ See Jennifer L. Pearson et al., *E-Cigarette Awareness, Use, and Harm Perceptions in U.S. Adults*, 102(9) AM. J. PUB. HEALTH 1758-1766 (2012), available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474361/>.

⁹⁰ See M.L. Goniewicz & W. Zielinska-Danch, *Electronic Cigarette Use among Teenagers and Young Adults in Poland*, 130(4) PEDIATRICS e879-885 (2012), available at: <http://www.ncbi.nlm.nih.gov/pubmed/22987874>.

universities, aged 20 to 24 years, 19.0% had ever used an e-cigarette and 5.9% had done so in the previous 30 days. In multivariate analyses that controlled for covariates, smoking cigarettes, male gender, living in an urban area, and having parents who smoke were associated with ever using e-cigarettes. Overall, 3.2% of students who had never smoked reported ever using e-cigarettes. The researchers concluded that about one-fifth of Polish youth have tried e-cigarettes; most of whom previously smoked cigarettes. This study shows the potential for harm reduction that e-cigarettes provide.

- In another study in Poland conducted in 2013, the patterns and effects of e-cigarette use and user beliefs about safety and benefits were examined.⁹¹ Researchers recruited 179 e-cigarette users in Poland online and asked about their smoking history, patterns of e-cigarette use, beliefs and attitudes regarding the product and information on concurrent use of conventional cigarettes. Sixty-six percent (66%) were no longer smoking conventional cigarettes and twenty-five (25%) had reduced their consumption to less than five cigarettes a day. Most participants (82%) did not think that e-cigarettes were completely safe, but correctly understood that they are less dangerous than conventional cigarettes. The study found that the participants primarily used e-cigarettes to assist their efforts to stop smoking or as an alternative to conventional cigarettes; the majority of participants reported that they successfully stopped smoking.
- A 2011 study conducted in Italy examined the association between nicotine dependence and depression in two subjects.⁹² Specifically, researchers conducted a case study of two heavy smokers with an established history of depression. Both subjects had previously attempted intensive smoking cessation programs with no success. Researchers found, however, that e-cigarette use led each to successfully quit smoking. Although the researchers acknowledge that the findings cannot be generalized, they note that high quit rates would be desirable among smokers suffering from depression (who generally respond poorly to smoking cessation efforts) and that, therefore, additional studies should be conducted to explore whether e-cigarette use should be considered as a potential tool to aid in smoking cessation.

⁹¹ See M.L. Goniewicz et al., *Patterns of Electronic Cigarette Use and User Beliefs About Their Safety and Benefits: An Internet Survey*, 32(2) DRUG ALCOHOL REV. 133-140 (2013), available at: <http://www.ncbi.nlm.nih.gov/pubmed/22994631>.

⁹² See Pasquale Caponnetto et al., *Smoking Cessation with E-Cigarettes in Smokers with a Documented History of Depression and Recurring Relapses*, 2(3) INT'L. J. CLINICAL MEDICINE 281-284 (2011), available at: <http://www.scirp.org/journal/PaperInformation.aspx?PaperID=6134#.U9kbLxCORWw>.

- A 2013 U.S. population survey revealed that current smokers were more likely than never-smokers to report use of e-cigarettes.⁹³ Survey respondents were asked if they had heard of e-cigarettes, where they heard of e-cigarettes, whether and how often they used e-cigarettes, and why. Responses were weighted to represent the entire U.S. population. A high proportion, 75.4%, reported having heard about e-cigarettes. About 8.1% had tried e-cigarettes, and 1.4% were current users. These rates were twice those of snus (4.3% and 0.8%, respectively). Among current smokers, 32.2% had tried e-cigarettes, and 6.3% were current users. Over 80% of current e-cigarette users were non-daily users. Women were significantly more likely to have tried e-cigarettes than men. Those who had tried e-cigarettes were more likely than those who tried snus to report their products being safer than regular cigarettes (49.9% vs. 10.8%). Almost half (49.5%) of current smokers were susceptible to using e-cigarettes in the future. The study authors concluded that e-cigarettes have surpassed snus in adoption rate, even before any promotion by major tobacco companies, suggesting that the former have tapped into smokers' intuitive preference for potentially harm-reducing products, probably due to the product design.
- Researchers from the University of Geneva and the University of Auckland, New Zealand, recruited 477 volunteers from websites devoted to e-cigarettes and/or smoking cessation, and followed their smoking and vaping habits over one-month (477 subjects) and one-year (367 subjects) periods.⁹⁴ At the one-month mark, among the former smokers who were regular e-cigarette users, only 6% had taken up smoking again. Of those who both smoked and used e-cigarettes, 46% had quit smoking by the one-year mark. The study shows that dual use may ultimately lead to smoking cessation.
- A prospective 12-month double-blind, controlled, randomized clinical study with two different nicotine strengths of a very popular e-cigarette brand was conducted to evaluate smoking reduction, smoking abstinence and adverse events in smokers who were not otherwise intending to quit.⁹⁵ The authors concluded that the use of e-cigarettes, with or

⁹³ See Shu-Hong Zhu et al., *The Use and Perception of Electronic Cigarettes and Snus among the U.S. Population*, 8(10) PLoS ONE e79332 (2013), available at: <http://www.plosone.org/article/abstract?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0079332&representation=PDF>.

⁹⁴ See Jean-François Etter & Chris Bullen, *A Longitudinal Study of Electronic Cigarette Users*, 39(20) ADDICT. BEHAV. 491-494 (2014), available at: <http://www.sciencedirect.com/science/article/pii/S0306460313003304>.

⁹⁵ See Pasquale Caponnetto et al., *Impact of an Electronic Cigarette on Smoking Reduction and Cessation in Schizophrenic Smokers: A Prospective 12-Month Pilot Study*, 10(2) INT'L J. ENVIRON. RES. PUB. HEALTH 446-461 (2013), available at: <http://www.mdpi.com/1660-4601/10/2/446/htm>.

without nicotine, decreased cigarette consumption and elicited enduring tobacco abstinence without causing significant side effects. Three hundred smokers were recruited and placed into three equal study groups: Group A received 7.2 mg nicotine cartridges for 12 weeks; Group B received 6-weeks of 7.2 mg nicotine cartridges followed by a further 6-weeks of 5.4 mg nicotine cartridges; and Group C received no-nicotine cartridges for 12 weeks. The study consisted of nine visits during which cigarette day use and exhaled carbon monoxide (eCO) levels were measured. Declines in cigarette per day use and eCO levels were observed at each study visits in all three study groups, with no consistent differences among study groups. Smoking reduction was documented in 22.3% and 10.3% at week 12 and week 52 respectively. Complete abstinence from tobacco smoking was documented in 10.7% and 8.7% at week 12 and week 52 respectively, leading to the conclusion that the use of e-cigarettes helped to reduce cigarette consumption and in some cases resulted in tobacco abstinence.

- A year-long study of 14 smokers (not intending to quit) with schizophrenia was conducted to determine impact of e-cigarettes on their smoking behavior and condition.⁹⁶ The study authors concluded that the use of e-cigarettes substantially decreased cigarette consumption without causing significant side effects in chronic schizophrenic patients. Product use, number of cigarettes smoked, carbon monoxide in exhaled breath (eCO) and positive and negative symptoms of schizophrenia levels were measured. Sustained 50% reduction in the number of cigarettes per day at week 52 was shown in 50% of participants, with their median of 30 cigarettes per day decreasing significantly to 15 cigarettes per day. Sustained smoking abstinence at week 52 was observed in 2 participants with combined sustained 50% reduction and smoking abstinence in 9 participants. Overall, one to two e-cigarette cartridges per day were used throughout the study. The authors concluded that positive and negative symptoms of schizophrenia are not increased after smoking reduction/cessation in patients using e-cigarettes.
- In a study that sought to characterize e-cigarette use, users, and effects in a sample of Electronic Cigarette Company (TECC) and Totally Wicked E-Liquid (TWEL) users, the authors concluded that e-cigarettes are used primarily for smoking cessation, but for a longer duration than nicotine replacement therapy, and users believe them to be safer than smoking.⁹⁷ Respondents (1347) completed a questionnaire regarding their e-cigarette use,

⁹⁶ See Caponnetto P, et al, *Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study*, 10(2) Int J Environ Res Public Health 446-461 (2013), available at: <http://www.mdpi.com/1660-4601/10/2/446/htm>.

⁹⁷ See Lynne Dawkins et al., *Vaping' Profiles and Preferences: An Online Survey of Electronic Cigarette Users*, 108(6) ADDICTION 1115-1125 (2013), available at: <http://onlinelibrary.wiley.com/doi/10.1111/add.12150/abstract>.

and 74% reported not smoking for at least a few weeks since using the e-cigarette and 70% reported a reduced urge to smoke. E-cigarettes were generally considered to be satisfying to use, elicit few side effects, be healthier than smoking, improve cough/breathing, and resulted in low levels of craving. Among ex-smokers, ‘time to first vape’ was significantly longer than “time to first cigarette,” suggesting a lower level of dependence to e-cigarettes. Ex-smokers reported significantly greater reduction in craving than current smokers although few other differences emerged between these groups. Compared with males, females opted more for chocolate/sweet flavors and liked the e-cigarette because it resembles a cigarette.

- A qualitative study was conducted to determine how e-cigarettes compare to NRTs in maintaining cigarette abstinence.⁹⁸ Using focus groups, e-cigarette users discussed their perceptions of e-cigarette efficacy for smoking cessation compared to NRTs. The study sought to explain the popularity of these devices and to shed light on the factors which influence the efficacy of different smoking cessation products. Five themes emerged that describe users’ perceptions of why e-cigarettes are efficacious in quitting smoking: 1) bio-behavioral feedback, 2) social benefits, 3) hobby elements, 4) personal identity, and 5) distinction between smoking cessation and nicotine cessation. The authors concluded that tobacco control practitioners must pay increased attention to the importance of the behavioral and social components of smoking addiction. By addressing these components, in addition to nicotine dependence, e-cigarettes appear to help some cigarette smokers transition to a less harmful replacement tool, thereby maintaining cigarette abstinence.
- In a survey study conducted across four countries (Canada, U.S., U.K. and Australia), the authors examined patterns of e-cigarette awareness, use, and product-associated beliefs among current and former smokers, concluding that e-cigarettes may have the potential to serve as a smoking cessation aid.⁹⁹ The study showed that 79.8% reported using e-cigarettes because they were considered less harmful than traditional cigarettes, 75.4% stated that they used e-cigarettes to help them reduce their smoking, and 85.1% reported using e-cigarettes to help them quit smoking.

⁹⁸ See Amanda M. Barbeau et al., *Perceived Efficacy of E-Cigarettes Versus Nicotine Replacement Therapy among Successful E-Cigarette Users: A Qualitative Approach*, 8(1) ADDICT. SCI. CLIN. PRACT. 5 (2013), available at: <http://www.biomedcentral.com/content/pdf/1940-0640-8-5.pdf>.

⁹⁹ See S.E. Adkison et al., *Electronic Nicotine Delivery Systems: International Tobacco Control Four-Country Survey*, 44(3) AM. J. PREV. MED. 207-215 (2013), available at: <http://www.ncbi.nlm.nih.gov/pubmed/23415116>.

- A study conducted in 2009 by the Northern Sweden cohort of the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) concluded that the use of e-cigarettes was a significant factor in the low prevalence of smoking, especially among younger men and women in Northern Sweden.¹⁰⁰
- A 2014 study documented the prevalence of e-cigarette ever use, current use, and established use in a nationally representative survey of 2,236 current and former cigarette smokers in the U.S.¹⁰¹ Participants completed a web-based survey in June 2013. The data from that survey was analyzed using multivariate logistic regression, which identified demographic and smoking-related factors associated with each use category. Researchers observed that almost half of the study participants had tried e-cigarettes (46.8%), but prevalence of established use remained low (3.8%). Researchers further observed that although trial of e-cigarettes was highest among daily smokers, it was much more likely for former smokers to identify as an established e-cigarette user. Importantly, the results demonstrated that most/all of the survey's established e-cigarette users who were also former smokers became former smokers by switching to e-cigarettes.
- A single-blind randomized trial measured the short-term effects of an e-cigarette on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects.¹⁰² Study participants included 40 adult dependent smokers of 10 or more cigarettes per day. Researchers randomized study participants to use e-cigarettes containing 16 mg nicotine or 0 mg capsules, Nicorette nicotine inhalator or their usual cigarette on each of four study days 3 days apart, with overnight smoking abstinence before use of each product. Researchers found that over 60 minutes, participants using 16 mg an e-cigarette recorded 0.82 units less desire to smoke than the placebo e-cigarette (p=0.006). Researchers did not observe a difference in desire to smoke between the 16 mg e-cigarette and the Nicorette nicotine inhalator. Study participants found e-cigarettes

¹⁰⁰ See B. Rodu, J.H. Jansson & M. Eliasson, *The Low Prevalence of Smoking in the Northern Sweden MONICA Study*, 41(8) SCAND. J. PUB. HEALTH. 808-811 (2013), available at: <http://www.ncbi.nlm.nih.gov/pubmed/24052339>.

¹⁰¹ See Daniel P. Giovenco et al., *Factors Associated with E-cigarette Use, a National Population Survey of Current and Former Smokers*, AM. J. PREV. MED. (2014), available at: <http://www.ncbi.nlm.nih.gov/pubmed/24880986>.

¹⁰² See C. Bullen et al., *Effect of an Electronic Nicotine Delivery Device (E Cigarette) on Desire to Smoke and Withdrawal, User Preferences and Nicotine Delivery: Randomised Cross-Over Trial*, 19 TOB. CONTROL 98-103 (2010), available at: <http://tobaccocontrol.bmj.com/content/19/2/98.abstract>.

to be more pleasant to use than the inhalator ($p=0.016$) and produced less irritation of mouth and throat ($p<0.001$). Researchers observed that, on average, the e-cigarette increased serum nicotine to a peak of 1.3 ng/mL in 19.6 min, the Nicorette nicotine inhalator to 2.1 ng/ml in 32 min and cigarettes to 13.4 ng/ml in 14.3 min. Researchers concluded that the 16 mg Ruyan V8 e-cigarette alleviated desire to smoke after overnight abstinence, was well tolerated among study participants, and had a pharmacokinetic profile more like the Nicorette nicotine inhalator than a tobacco cigarette.

- Three quarters of e-cigarette users surveyed in a 2012 study reported that using e-cigarettes helped them quit smoking.¹⁰³ The study participants smoked an average of 25 cigarettes per day prior to the study and tried to quit smoking an average of nine times before using e-cigarettes (two-thirds of the participants had previously tried to quit smoking using an FDA-approved smoking cessation product). The majority of the e-cigarette users involved in the study had used e-cigarettes daily for at least a year. Most of the study participants did not use the type of e-cigarette that are commonly sold, i.e., those powered by a single 3.7 volt battery; these users represented only 8% of the study participants. Two-thirds of the participants used e-cigarettes designed to enable the atomizer to achieve hotter, more intense vapor with e-liquids containing medium to high concentrations of nicotine (13 mg +). Due to the results of the survey the study authors have concluded that those who already have switched to e-cigarettes should focus on staying off cigarettes, rather than quitting e-cigarettes.
- Over two hundred smokers who had tried e-cigarettes were surveyed online to examine the effectiveness of e-cigarettes as a smoking cessation tool.¹⁰⁴ The primary outcome of interest in the study was the point prevalence of smoking abstinence at 6 months after initial e-cigarette purchase. In summary, the point prevalence of smoking abstinence at 6 months after initial e-cigarette purchase was 31.0% (95% CI=24.8%, 37.2%). A large percentage of respondents reported a reduction in the number of cigarettes they smoked (66.8%), and almost half reported abstinence from smoking for a period of time (48.8%). The participants that reported using e-cigarettes more than 20 times per day had a quit rate of 70.0%. Of respondents who were not smoking at 6 months, 34.3% were not using e-cigarettes or any nicotine-containing products at the time. The researchers concluded that e-cigarettes are a promising smoking-cessation tool worthy of further study using more rigorous research designs.

¹⁰³ See M. Leelavathi & S. Das, *Electronic Cigarettes: New Kit on the Rack*, 66(4) INT'L. J. CLIN. PRACT. 417 (2012), available at: <http://www.ncbi.nlm.nih.gov/pubmed/22420500>.

¹⁰⁴ See Michael B. Siegel et al., *Electronic Cigarettes as a Smoking-Cessation: Tool Results from an Online Survey*, 40(4) AM. J. PREV. MED. 472-475 (2011), available at: <http://www.ajpmonline.org/article/S0749-3797%2810%2900792-0/abstract>.



- In an Internet study of 81 e-cigarette users in France, Canada, Belgium, and Switzerland, participants answered open-ended questions regarding their use of e-cigarettes, and opinions regarding these products.¹⁰⁵ Over half of participants (63%) were former smokers; 37% of participants were current smokers. Participants reported using e-cigarettes either to quit smoking, to reduce cigarette consumption, to avoid disturbing other people with secondhand smoke, or to be able to smoke in smoke-free places. There were numerous positive effects associated with e-cigarettes. These included reports that the products are useful in quitting cigarette smoking, and confer the benefits of abstinence from cigarette smoking (less coughing, improved breathing, better physical fitness).

IX. Conclusion

In summary, OMB/OIRA must compel FDA to rethink the manner in which it has proposed to regulate e-vapor products. Application of the requirements of the Tobacco Control Act, as proposed, to the e-vapor industry would effectively ban these products and decimate the entire industry and tens of thousands of jobs. There is no viable pathway for e-vapor products under the Tobacco Control Act framework and no comparable products that were on the market as of the Grandfather Date to file a Substantial Equivalence Report. The PMTA process, as discussed above, would be economically and logistically impossible, not to mention subjectively evaluated. Moreover, although e-vapor products are clearly reduced risk compared to combustible tobacco, the Modified Risk Tobacco Product Application is also untenable. Therefore, the entire approach of the FDA in the proposed Deeming Regulation would make it impossible for any e-vapor manufacturer to comply. Additionally, because the PMTA process is entirely subjective, with massive costs, there is virtually no incentive for an e-vapor manufacturer to even apply for a PMTA, as they would have no baseline, objective standard to work towards and zero confidence in having their application approved.

Our concern is that current regulatory approaches being proposed are doomed to fail. It is evident that the relevant government authorities do not presently have a desire and/or motivation to see/create a “window of potential” for the e-vapor products to remain on the market. The authorities do not yet understand the products, how they work, why they work, the options needed for them to work, the dynamics of how and why the entrepreneurial based consumer incentivized industry (with all innovations and safety features resulting from consumer input) allowed them to work in the first place providing the necessary dynamics for the industry’s growth and for so many cigarette smokers to switch (9 million here in US according to CDC and exponentially more globally, and more). As a result: even those looking for that

¹⁰⁵ See Jean-François Etter, *Electronic Cigarettes: A Survey of Users*, 10 BMC PUB. HEALTH 231 (2010), available at: <http://www.biomedcentral.com/content/pdf/1471-2458-10-231.pdf> (advocating that further research on e-cigarettes is urgently required, particularly with respect to the efficacy and toxicity of these devices).



“window of potential” are taking the same approach used for other large commercially introduced products (narrow the subjective down to minutely measurable objectivity to “measure”, contain and possibly incrementally advance). However, this approach has no way to succeed – it can only fail because it completely ignores all of the very factors that are 100% necessary to create that “window of potential”, as noted above. Ultimately, e-vapor products need to have that “window of potential” to remain on the market for vapers/smokers, regulated in such a way so as to continue to provide subjectively effective substitutions for tobacco, *e.g.*, various tanks and atomizers, various devices with safety features and a structure that provides incentives for innovations, research and product advancements.

Enclosures:

Appendix – AEMSA Standards

Appendix - AEMSA Standards



E-LIQUID MANUFACTURING STANDARDS

AEMSA advocates electronic cigarette products for **ADULT USE ONLY**.
AEMSA supports ban on sales to minors.



PURPOSE

The purpose of these Standards is to create a responsible and sustainable practices and process for the safe manufacturing of “e-liquids” used in electronic cigarettes. Our members believe we have a responsibility to self-regulate the e-liquid manufacturing process based on professional criteria. AEMSA aims to accomplish this by creating, implementing and upholding standards for the manufacture of e-liquids. One of AEMSA’s primary goals is to provide consumers with higher degrees of confidence our members’ products are manufactured with professionalism, accuracy and safety **AEMSA standards are established based on the following Core Beliefs:**

- We have a responsibility to verify the accuracy of any nicotine content in the products we distribute.
- We have a responsibility to ensure the quality of all ingredients in our e-liquids.
- We have a responsibility to prepare our products in a clean, sanitary and safe environment.
- We have a responsibility to ensure our products are packaged and delivered in a safe manner.
- We have a responsibility to provide a level of transparency into the monitoring and verification process.

The 2012 AEMSA Standards are living documents and subject to changes according to the AEMSA corporate structure and procedures.

SCOPE

These standards apply to all AEMSA general members that engage in the manufacturing or processing of Eliquids. 2015 E-Liquid Manufacturing Standard will be used as a basis for:

- Evaluating compliance for membership acceptance
- Confirming compliance of existing membership



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Article I. Verifying the accuracy of the nicotine content in products

Section 1.01 Accuracy of nicotine

- (a) All manufactures must confirm the accuracy of nicotine content upon delivery from supplier

Section 1.02 Titrated/verified after dilution

- (a) All nicotine must be titrated/verified for content accuracy after dilution to working level

Section 1.03 Measuring Nicotine

- (a) All equipment used in measuring nicotine from working level to final product must be either
 - (i) NIST (calibrated)
 - (ii) ASTM compliant (calibrated)

Section 1.04 Tolerance level

- (a) All products produced will be within the tolerance level of +/-10% nicotine content in final product

Section 1.05 Maximum allowable nicotine content

- (a) The maximum allowable nicotine content in final flavored product will be no greater than 36 mg / ml

Section 1.06 Retail nicotine sold for unflavored/DIY nicotine

- (a) Will follow the same criteria for verifying the nicotine content and quality on all batches when received and titrated after dilution at various sales levels
- (b) Is not subject to maximum allowable nicotine content in final flavored product

Article II. Ensure the quality of the all ingredients of in e-liquid

Section 2.01 Nicotine Sources

- (a) All manufacturers must purchase and comply with at least one of the following:
 - (i) USP CERTIFIED nicotine (with evidentiary documentation from a certified lab)
 - (ii) Free-base nicotine from suppliers who can provide source evidentiary documentation from a certified lab confirming (batched) nicotine conforms to the Nicotine Quality Standard (see Section 2.02)
 - (iii) Purchase from nicotine suppliers who can provide evidentiary documentation from a certified lab confirming the incoming (batched) free-base nicotine conforms to the Nicotine Quality Standard (see Section 2.02)



Section 2.02 Nicotine Quality Standard

- (a) All nicotine used in manufacturing must meet the following nicotine quality standards:
 - (i) Nicotine purity greater than or equal to 99%*
 - (ii) Total combined of all other possible contaminants less than or equal to 1.0%
 - (iii) Per existence of any solvent must not exceed 0.06%
 - (iv) Per existence nicotine oxide less than or equal to 1%
 - (v) Per existence nicotine-N-oxides less than or equal to 1%
 - (vi) Cumulative heavy metals *content* cannot exceed 10ppm
 - (vii) Cumulative Arsenic *content* cannot exceed 1ppm
 - (viii) All diluents after source pure must be USP certified thru chain of custody

Section 2.03 Base liquid ingredients

- (a) Base liquid diluent ingredients such as Propylene Glycol, Vegetable Glycerin, Glycerol, or any other e-liquid bases (either regularly or exclusively) will be at a minimum level of USP (US Pharmacopoeia) grade certified
 - (i) Material must maintain full certification throughout chain of custody on raw materials used in manufacturing process
 - (ii) Manufacturer must exclusively use certified base products throughout the manufacturing process

Section 2.04 Ingredients/ Components other than base liquids

- (a) Ingredients/ Components other than base liquids will contain only the highest grade base materials
 - (i) Flavorings (including menthol) used will be at a minimum of food grade and/or Generally Recognized as Safe (GRAS) standard certifications whenever the ingredient is produced at those standards
 - (ii) Flavorings containing artificial food coloring will identify food coloring information to include coloring number in advertising and product descriptions
 - (iii) Flavorings containing Custard Notes will identify advertising and product descriptions
 - (iv) Water used (if any) will be either deionized or distilled
 - (v) Alcohol and additional additives (if any) will be:
 - 1) Used in the purest form commercially available and safe for human consumption
 - 2) Minimum of US Food grade standards



Section 2.05 The following will not be added or used in the creation of eliquids

- (a) Including but not limited to:
 - (i) WTA (whole tobacco alkaloids)
 - (ii) Medicinal - or prescription medicinal
 - (iii) Illegal or controlled substances
 - (iv) Caffeine
 - (v) Vitamins or Dietary supplements (other than for preservative purposes)
 - (vi) Artificial Food Coloring
 - 1) AEMSA members will not add any artificial coloring or dyes during the e-liquid manufacturing process. Non vendor manufactured flavorings containing artificial food coloring will identify food coloring information to include coloring number in advertising and product descriptions
 - (vii) AEMSA reserves the right to review, evaluate and deny/approve any potential substance used in the creation of e- liquids at any given time
- ***Note: Diacetyl and Acetyl Propionyl (2,3 -- Pentanedione) standards are undergoing active re-evaluations. All standards amendments are posted immediately after ratifications.**

Section 2.06 Process / Records / Traceability

- (a) Manufactures will maintain sufficient process and records to enable the manufacturer to trace any individual product distributed to the test results for nicotine content to include source nicotine (see section 2.02)

Article III. Clean, Sanitary and Safe Preparation of Products

Section 3.01 General

- (a) All Lab/Mixing employees are required to be fully familiar with all AEMSA standards
 - (i) There will be a special emphasis placed on nicotine handling, storage and clean-up
- (b) Each member will create and maintain written lab/mixing protocol and make accessible to all lab/mixing employees
- (c) All Persons allowed in process area must comply with applicable protection/ safety and standards
- (d) All products will be created and/or bottled in dedicated manufacturing space reserved exclusively for e-liquid



Section 3.02 Manufacturing Environment

- (a) Manufacturing processes will meet food preparation standards to include (i) Non-porous sanitized preparation work surface
- (b) All surfaces in lab/mixing area (floors, counters, etc.) shall be cleaned with anti-bacterial agents at least once each day and after any spill of any mixing ingredient or any possible-contaminants
- (c) Equipment will be cleaned by FDA Approved Chemical Sanitation or autoclave
- (d) All supplies and material will be disposed of in a manner that is appropriate to component disposal -- proper disposal of production material
- (e) There shall be no open fans, dusty boxes and/or other potential sources of airborne contaminants etc. in dedicated space
- (f) All bottles and materials unpacked outside of dedicated lab/mixing space

Section 3.03 Hand washing / sanitation

- (a) Not in sink used for cleaning mixing utensils, and/or other e-liquid materials
- (b) Minimum 20 seconds with commercial (food handler's grade) antibacterial hand washing agent and warm water
- (c) Hands washed each and every time entering mixing room
- (d) After bathroom use, coughing, sneezing, eating and/or drinking, engaging in any other activities which potentially expose hands to any form of potential contaminants
- (e) During mixing as often as necessary to remove any mixing products on hands
- (f) Before proceeding to a subsequent mixing session -> to prevent any cross contamination from one batch to the next

Section 3.04 Health / Illness

- (a) All open wounds or abrasion will be properly covered
- (b) Any/All mixing employees report any illness/abrasion(s)/lesions to person in charge before entering the process
- (c) Employees must report to person in charge if exposed to any contagion or infection - viral or bacterial - from anywhere (including others in their homes, other work environments, other domiciles, etc.) before entering lab/mixing area
 - (i) Such exposure/conditions excludes said individual from entering mixing room for a period of three (3) asymptomatic days have passed and/or cleared with medical documentation (equivalent to commercial food handling)
 - (ii) Discharge from eyes, nose and/or mouth:
 - (iii) Report to business any persistent discharge from eyes, nose, and/or mouth. Any employee exhibiting such symptoms shall not enter the mixing room until such symptoms cease

Section 3.05 Eating / Drinking

- (a) No eating, drinking, vaping and/or smoking in the lab/mixing area at any time



Section 3.06 Hair Restraints

- (a) Each member must establish written hair and beard standards

Section 3.07 Animals

- (a) No animals shall be permitted in the mixing room at any time for any reason

Section 3.08 POISONOUS OR TOXIC MATERIALS

- (a) POISONOUS OR TOXIC MATERIALS shall be stored so they cannot contaminate PRODUCT COMPONENT, FOOD, EQUIPMENT, UTENSILS, and SINGLE-USE ARTICLES by:
 - (i) Separating the POISONOUS OR TOXIC MATERIALS by spacing or partitioning
 - (ii) Locating the POISONOUS OR TOXIC MATERIALS in an area that is not above PRODUCT COMPONENTS, FOOD, EQUIPMENT, UTENSILS, or SINGLE-USE ARTICLES
 - (iii) This does not apply to EQUIPMENT and UTENSIL cleaners and SANITIZERS that are stored in WAREWASHING areas for availability and convenience if the materials are stored to prevent contamination of PRODUCT COMPONENT, FOOD, EQUIPMENT, UTENSILS, LINENS, and SINGLE--SERVICE and SINGLE-USE ARTICLES
 - (iv) All POISONOUS OR TOXIC MATERIALS will be disposed of in a safe manner
 - (v) Only those POISONOUS OR TOXIC MATERIALS that are required for the operation and maintenance of a lab/mixing area, such as for the cleaning and SANITIZING of EQUIPMENT and UTENSILS and the control of insects and rodents, shall be allowed in a lab/mixing area (kept sealed and separate - never above - from any/all mixing supplies)
 - (vi) A container previously used to store POISONOUS OR TOXIC MATERIALS may not be used to store, transport, or dispense any other substance

Section 3.09 Employee Safety

- (a) Employers MUST provide their employees with a workplace that does not have serious hazards and follow all relevant OSHA safety and health standards including - but not limited to - the following mandatory personal protective equipment (P.P.E.):
 - (i) Eye protection
 - (ii) Lab Coat / Apron
 - (iii) Fully covered footwear
 - (iv) All manufacturing spaces must have easily accessible
 - 1) First aid kit
 - 2) Emergency eye wash kit



Article IV. Safe Packaging and delivery of products

Section 4.01 Child proof caps

- (a) Child proof caps required for all consumer level e-liquid products
- (b) Zero Nicotine Products do not require child proof caps

Section 4.02 Tamper Evident packaging

- (a) All Products require tamper evident packaging once leaving vendor chain of custody

Section 4.03 Labeling

- (a) Smear Resistant Labeling is required on all e-liquid products
 - (i) Must pass “30 second submerged” test for all required elements
- (b) Nicotine content must be clearly displayed
- (c) Safety and health Warning must be clearly displayed
 - (i) Contains Nicotine
 - (ii) Keep away from Children and Pets
- (d) Nicotine Traceability elements (i.e. Batch ID or nicotine batch ID or production date)

Section 4.04 Delivery

- (a) All shipped liquid must be bagged or wrapped to provide waterproof barrier between packaging and product for spill protection
- (b) Safe handling information must be included in all packaging

Section 4.05 Active Age Verification

- (a) All Vendors must use Active age verification for all sales (retail and/or online)
- (b) AMESA Members will not knowingly sell products to any persons under the legal smoking age



Article IV. Transparency into the monitoring and verification process

Section 5.01 Within the organization

- (a) Members must provide information to applications and compliance committees required to establish compliance including:
 - (i) Documented evidence of compliance
 - 1) Photographic and Video evidence
 - 2) Unfettered access to facilities for inspection (scheduled and/or unscheduled)
 - 3) Process and records
- (b) Member to member profiles will contain only minimal information for the identification and communication amongst and between members
 - (i) Current status of compliance - by facility
 - (ii) Contact Information
 - 1) Name
 - 2) DBA
 - 3) Email
 - 4) Phone
 - 5) Location(s)/ Facilities of production

Section 5.02 To the consumer

- **Note: Subsections (a) and (b) are already posted on AEMSA website. Subsections (c) and (d) are intended for specific information warranted situations ONLY; these may include - but not limited to - allergy sensitivities, other specific medical conditions/sensitivities, etc. Subsection (e) shall be available on member's web site**
 - (a) A substantive version of the AEMSA Standards be published on Website
 - (b) AEMSA Membership Status
 - (c) **Members will provide consumers tracking nicotine test results as far back as the source nicotine**
 - (i) **Information on the supplier may be redacted to protect intellectual property and trade secrets**
 - (ii) **The member may charge a reasonable and fair fee for said tracing requests**
 - (d) Members will provide answers to consumers on ingredients of products
 - (i) Yes/No answers to specific questions as pertains to specific customer sensitivity questions



- (ii) No intellectual property or trade secrets of the e-liquid ingredient has to be revealed
 - 1) This includes revealing the source supplier and trademarked/brand name ingredient
- (e) Clearly identified products that are not manufactured by AEMSA Members
 - 1) If the member sells liquid that is manufactured in a non AEMSA compliant facility it must:
 - 2) Clearly identify/ differentiate products that are AEMSA compliant and those that are not AEMSA compliant on a product by product basis

Section 5.03 To potential regulators

- (a) To be decided on case by case basis



APPENDIX A: TERMS AND DEFINITIONS

Active Age Verification: Taking active measures to ensure that all customers are of legal age. Can be accomplished in many ways including Photo Identification and 3rd party verification systems. Note: Having pop up box asking the person to indicate they are over a specified age is not Active Age Verification

ASTM - American Society for Testing and Materials: An international standards organization that develops and publishes voluntary consensus technical standards for a wide range of materials, products, systems, and services

Chain of custody: The chronological documentation or, showing the custody, control, transfer, analysis, and disposition of physical component; tracking a product along the supply chain to the point of sale

Components: A part or element of a larger whole; a substance that forms part of a mixture. Any substance, material or the tangible substance that goes into the manufacturing of e- liquid

Contaminants: An impurity or foreign substance present in a material or environment that affects one or more properties of the material

Custard Notes: Flavor compounds that impart a buttery, creamy, or custard taste or sensation. Most commonly used are acetoin, acetyl propionate and diacetyl

Dedicated Manufacturing Space: A clean safe environment that is used exclusively for the manufacturing of e-liquid

Diacetyl: A natural byproduct of fermentation. It is a vicinal diketone (two C=O groups, side-by-side) with the molecular formula C₄H₆O₂. Diacetyl occurs naturally in alcoholic beverages, other natural sources and is added to some foods to impart a buttery flavor. Diacetyl, while not problematic for ingestion via digestion, has been identified as a potential inhalation risk and has been reported in some flavorings. As a preventative and good product stewardship measure, many e-liquid manufacturers are now testing, reformulating and/or removing identified flavors from inventory to avoid potential inhalation risks.

Direct Operation: A facility or process where Full time employees for an organization directly supervise and oversee production and process

DIY: Do it Yourself

Electronic cigarette: Also known as an e-cigarette (e-cig) is an electrical inhaler that vaporizes a propylene glycol and/or glycerin-based liquid solution into an aerosol mist simulating the act of tobacco smoking

E-liquid: Liquid for producing vapor in electronic cigarettes, known as e-juice or e-liquid

E-liquid manufacturing: Fabrication: the act of making something (a product) from raw materials; to include all processes from supply acceptance to the point of customer delivery

Free-base: An amine or nitrogen-containing organic compound, such as nicotine, in its basic (high pH) form, in contrast to its acidic (low pH) form, which is often called the "salt" form. Unless an acid has been added to nicotine, or it is purchased as the salt, it is in the freebase form. Free-base describes the form of the compound, not its purity



Generally Recognized as Safe (GRAS): Generally recognized as safe (GRAS) is an American Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts, and so is exempted from the usual Federal Food, Drug, and Cosmetic Act (FFDCA) food additive tolerance requirements

Indirect Operation: A facility or process where supervision and/or oversight of production and/or process for an organization is conducted by a 3rd party or contractor (subcontractor)

Mg / ml: Milligrams per Milliliter – a scale (or ratio) for measuring an ingredient component, in liquid form, where accuracy is measured in mg per ml - or a percentage equivalent

Nicotine: Nicotine is an alkaloid found in the nightshade family of plants (Solanaceae) that acts as a nicotinic acetylcholine agonist. The biosynthesis takes place in the roots and accumulation occurs in the leaves of the Solanaceae. It constitutes approximately 0.6–3.0% of the dry weight of tobacco and is present in the range of 2–7 µg/kg of various edible plants

NIST -The National Institute of Standards and Technology: A non-regulatory agency of the United States Department of Commerce. The institute's official mission is to: Promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life

OSHA: The United States Occupational Safety and Health Administration (OSHA) is an agency of the United States Department of Labor. Congress established the agency under the Occupational Safety and Health Act, was signed into law on December 29, 1970. OSHA's mission is to "assure safe and healthful working conditions for working men and women by setting and enforcing standards and by providing training, outreach, education and assistance". The agency is also charged with enforcing a variety of whistleblower statutes and regulations

PPM: Parts Per Million

SINGLE-USE ARTICLES: Utensils, containers and tools designed and constructed to be used once and discarded

Tamper Evident: Tamper-evident describes a device or process that makes unauthorized access to the protected object easily detected. Seals, markings or other techniques may be tamper indicating

Titration: Also known as titrimetry, is a common laboratory method of quantitative chemical analysis that is used to determine the concentration of an identified component; the determination of rank or concentration of a solution with respect to water with a pH of 7 (the pH of pure H₂O under standard conditions)

USP (US Pharmacopoeia): The United States Pharmacopeia (USP) is the official pharmacopeia of the United States, published dually with the National Formulary as the USP-NF. The United States Pharmacopeial Convention (usually also called the USP) is the nonprofit organization that owns the trademark and copyright to the USP-NF and publishes it every year. Prescription and over-the-counter medicines and other health care products sold in the United States are required to follow the standards in the USP- NF. USP also sets standards for food ingredients and dietary supplements

WTA (whole tobacco alkaloids): A full-spectrum mixture of all alkaloids extracted from whole tobacco. WTA can contain, in addition to nicotine, anabasine, cotinine, myosmine, anatabine, and/or nornicotine, in varying compositions, largely dependent on the tobacco species



STANDARDS

VERSION 2.3

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For more information or to become a member, please visit:

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