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

Re: Electronic Cigarettes and the Public Health: A Public Workshop; Docket No. FDA-2014-N-1936

The American E-Liquid Manufacturing Standards Association (AEMSA) appreciates this opportunity to respond to the request by the Food and Drug Administration (FDA or Agency) for comments in conjunction with its public workshops to gather scientific information about electronic cigarettes (e-cigarettes) as announced in Docket No. FDA-2014-N-1936.[1] The purpose of this letter is to provide AEMSA's responses to a subset of FDA's product science questions related to e-liquid and aerosol constituents and e-cigarette device designs and characteristics.[2]

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-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 safe manner until such time as FDA promulgates Good Manufacturing Practices (GMPs) for e-liquids. In this regard, AEMSA has developed manufacturing standards for of e-liquids, which are included in **Appendix I** hereto, and may be downloaded from our website at:

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[1] *See* 79 Fed. Reg. 71437 (December 2, 2014), available online at: https://www.federalregister.gov/articles/2014/12/02/2014-28261/establishment-of-a-public-docket-electronic-cigarettes-and-the-public-health-workshop.

[2] *See* http://www.fda.gov/TobaccoProducts/NewsEvents/ucm414814.htm.

http://www.aemsa.org/standards/. AEMSA supports reasonable, responsible and science-based regulation of e-cigarettes, including open-system refillable personal vaporizers and the e-liquids used in those products.

We note that although e-liquid and e-cigarette 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), but rather are recreational use products. See *Sottera Inc. v. FDA*, 627 F.3d 891 (D.C. Cir. 2010). Although the available evidence demonstrates that most current e-cigarette 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 these comments to FDA on behalf of its e-liquid manufacturing Members.

II. FDA's Request for Public Comment on Electronic Cigarette Product Science

The electronic cigarette 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. Assuming solely for the purposes of these comments that e-cigarettes and their e-liquid components (that contain tobacco-derived nicotine) are deemed to be *regulated* tobacco products,[3] we understand that FDA must weigh the pros and cons of these new products to determine the most effective regulatory scheme. One of the primary areas of concern for FDA in this regard is the safety profile of the aerosol inhaled by the consumer, *i.e.*, its chemical composition and toxicity. Indeed, in its request for public comment, FDA has asked a number of questions about the (1) composition of e-liquid, (2) constituents and impurities in the aerosol, (3) quantitative and qualitative relationships between the chemical contents in e-liquids and chemical constituents in the inhaled aerosols, as well as (4) how device design features could minimize or mitigate risk to users and non-users from, among other things, increased toxicant

[3] First and foremost, AEMSA's position is that e-cigarettes are technology products, not tobacco products, and that Congress should consider separate legislation specifically giving FDA authority over e-vapor products separate from the Agency's tobacco and drug authorities. We believe that attempting to force the Tobacco Control Act requirements onto these tobacco-free products is not an effective regulatory strategy. Nevertheless, for purposes of these comments, we assume, *arguendo*, that e-cigarettes and their e-liquid components will be "covered tobacco products" subject to the Tobacco Control Act requirements, assuming they are used with or contain nicotine derived from tobacco.

exposure. While each of these areas is important, the most critical element to being able to predict the safety profile of these products is the composition of the e-liquid. We discuss this in more detail below. We also discuss the importance of e-cigarette device design features that are capable of monitoring and limiting the temperature of the heating coil, as studies have shown that potentially harmful impurities can form when the devices are heated to unrealistic temperatures, as well as the need for the Agency to work with industry to develop GMPs and product standards, to minimize the potential for manufacturing byproducts in the e-liquid.

III. E-Liquid Composition

Although e-cigarettes may not be completely "harmless" products 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 cigarette smokers.[4] We understand, however, that in order to be able to predict the safety profile of these new products, FDA must understand the chemical composition of the e-liquid, as well as how they are produced.

Standard e-liquid ingredients include excipients (carriers) such as propylene glycol or vegetable glycerin (glycerol), nicotine, and flavorings. We examine each of these ingredients below. We further discuss the importance of ensuring that the ingredients used in e-liquids are suitably pure for their intended use. In particular, the flavorings are formulated compounds that may contain a number of substances and unintended impurities (*e.g.*, diacetyl and acetyl propionyl). Impurities such as heavy metals can also result from the e-liquid manufacturing process, as well as from materials used in the device.

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[4] As set forth in AEMSA's comments to the Notice of Proposed Rulemaking (NPRM) for the Deeming Regulation (FDA Docket No. FDA-2014-N-0189), tobacco leaf-containing products, especially those that are combusted, are the most harmful and dangerous products on the "continuum of risk" of nicotine products and should be treated as such. It is well established, for example, that the more pyrolyzed tobacco constituents a user inhales from a combustible tobacco product, such as a cigarette, the greater the risk of tobacco-related disease that product poses. See R.R. Baker, *et al.*, *The pyrolysis of tobacco ingredients*, 71 J. Anal. Appl. Pyrolysis 223-311 (2004). Of the approximately 5,300 chemicals identified in tobacco smoke, at least 60 are known human carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs). See Rodgman, A. and Perfetti, T.A., *The Chemical Components of Tobacco and Tobacco Smoke*, Boca Raton, FL: CRC Press (2009). Electronic cigarettes (including personal vaporizers) are far less risky to individual users than combustible cigarettes because they do not result in the inhalation of pyrolyzed chemicals.

a. Safety of Nicotine

It is critically important for FDA to acknowledge that it is not starting from a *tabula rasa* when it comes to understanding the safety of nicotine aerosols for inhalation using e-cigarettes. Nicotine, of course, is the component of most concern in e-liquids. It is well established, however, that while nicotine is not, *per se*, harmless, it is *not* the substance that kills smokers. As Mitch Zeller, the Director of FDA's Center for Tobacco Products has stated on several occasions, people may smoke cigarettes for the nicotine, but die from inhaling the smoke and tar from combusting tobacco. 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).[5] 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.[6] 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 published in 2013 for "Modifications To Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use".[7] 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

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

[6] 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 online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725009/.

[7] *See* 78 Fed. Reg. 19718 (April 2, 2013).

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).[8] 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-proof 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.[9] 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).[10] Other common household goods result in far more reported poisoning cases. 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

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

[9] *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), https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2012_NPDS_Annual_Report.pdf.

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

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%).[11]

b. Safety of 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.[12] 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.[13] 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.[14] 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

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[11] *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.

[12] *See* 21 C.F.R. §§ 182.1320 ("Glycerin") and 184.1666 ("Propylene glycol").

[13] Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) program: http://www.chem.unep.ch/irptc/sids/OECDSIDS/57-55-6.pdf and http://www.chemicals.moew.government.bg/chemical/site/File/registers/profile/56815p.pdf.

[14] *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.[15]

c. Safety of Flavor Compounds

i. Flavored E-Liquids Provide a Public Health Benefit

E-liquids come in a variety of 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. Konstantinos Farsalinos of the Onassis Cardiac Surgery Center in Athens, Greece, conducted a survey of 4,618 dedicated vapers.[16] 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

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[15] *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.

[16] *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 online at: http://www.mdpi.com/1660-4601/10/12/7272.

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% 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.[17]

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).[18] 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)[19]:

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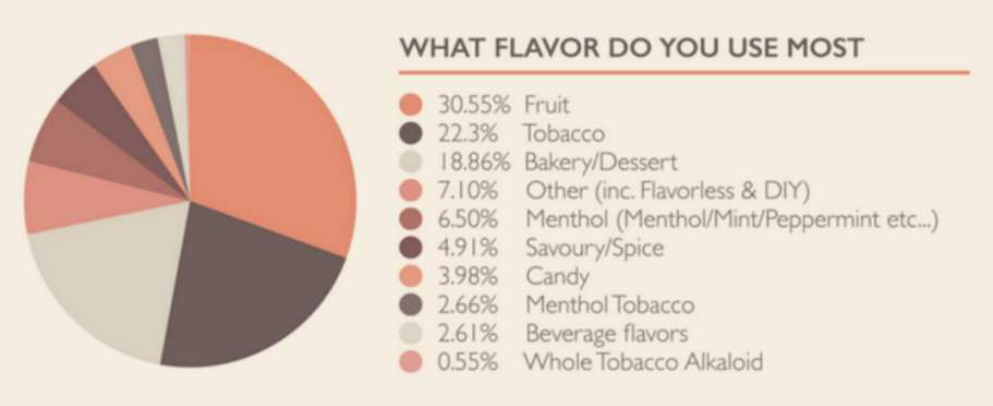
[17] Of course, as noted above, none of the e-liquids produced by AEMSA Members are marketed for use in smoking cessation or as NRTs, but rather only for recreational use by adults. Any smoking cessation or reduced cigarette consumption resulting from the use of e-liquids or e-cigarettes generally is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

[18] *See* Mclaren, Neil, *Vaping.com Big Survey 2014 - Initial Findings General*, (2014), available 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.

[19] *See Vaping.com Big survey 2014 - initial findings general*, available online 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 online at: http://www.forbes.com/sites/jacobsullum/2014/07/17/survey-shows-adults-who-use-e-cigarettes-to-quit-smoking-prefer-allegedly-juvenile-flavors/.



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

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.[20] 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.[21]

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

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[20] *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.")

[21] 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 **Appendix II** hereto for sample images of such products.

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. 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. If *only* tobacco-flavored e-liquids were permitted, smokers would be 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.[22] 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 age[23], (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.

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

[23] 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.

ii. AEMSA Recommends Testing Flavor Compounds for Potential Impurities

As noted above, to ensure the safety of these products, it is critical that the ingredients used in e-liquids be suitably pure for their intended use.[24] This is particularly important for flavorings used in e-liquids, which are formulated compounds that may contain a number of substances as well as unintended impurities. Ingredients and impurities of concern should be identified and, if possible, minimized and removed. While many of these flavor ingredients have been determined to be safe for use in food, research is actively being done on the risks posed when these substances are inhaled. 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.[25] A study published in the journal *Nicotine and Tobacco Research* evaluated the presence of diacetyl and acetyl propionyl in e-liquids.[26] Researchers led by Dr. Farsalinos tested 159 e-liquid samples (all sweet-flavored) for the presence of diacetyl and acetyl propionyl. The study found that 74.2% of the samples contained either diacetyl or acetyl propionyl, with more samples containing diacetyl. The levels were on average slightly lower than currently-established safety limits (set by the National Institute of Occupational Safety and Health (NIOSH)). It is also important to note that tobacco cigarette smoke contains both compounds, at levels 100 times higher for diacetyl and 10 times higher for acetyl propionyl compared to the average daily exposure from e-cigarette vapor..

As detailed below, although no specific health risks have been established from the use of these substances at the levels typically present in some e-liquids, AEMSA has been working with

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[24] See, for example, 21 C.F.R. Section 174.5 of FDA's food additive regulations.

[25] In the U.S. most e-liquid manufactures buy flavors components from the same approximately 10 companies ("End Flavor Suppliers"). But there are various companies within the supply chain moving flavor products between the source manufacturer and the End Flavor Supplier (e.g., wholesaler to wholesaler). Some of these companies may be "compounders" who combine flavors purchased from the source manufacture, to create new or combined/compounded "flavors". When an End Flavor Supplier claims (in product descriptions) that its products are diacetyl- and/or acetyl propionyl-"free," they may be relying on claims from the source manufacturer, and may not be aware of possible mid-supply-chain "compounding". They also may not be performing independent testing of their own.

[26] See Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins, Nicotine Tob Res (2015) 17 (2): 168-174, available online at http://ntr.oxfordjournals.org/content/17/2/168.

its Members to ensure that their products are tested, and has encouraged its Members work to eliminate diacetyl and acetyl propionyl from their products.[27]

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.[28] 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 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.[29] 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.

Nevertheless, because the nature and magnitude of the possible effects resulting from high levels of inhalation exposures to diacetyl suggests, AEMSA agrees that strong 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.

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[27] See http://www.aemsa.org/aemsa-recommends-flavor-testing/.

[28] See FDA's food additive regulations, 21 CFR § 184.1228 (2014) ("Diacetyl"); available online at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1278&SearchTerm=diacetyl. That 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.

[29] 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 online at: http://www.cdc.gov/niosh/docket/archive/pdfs/NIOSH-245/0245-081211-draftdocument.pdf.

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 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.

IV. Device Design Features

a. Excessive Heat Results in "Dry Puff" Conditions and Release of Aldehydes

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 such as formaldehyde and acetaldehyde. It is important to understand, however, that during actual e-cigarette use, the potential for human exposure to these substances is quite low because consumers are unlikely to allow their devices to reach such high temperatures. More specifically, the excessive heat required to generate these harmful compounds results in what is known as the "dry puff" phenomenon – the unpleasant, burning taste experienced by the user when the heater coil overheats – which makes the vapor uninhalable. 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. In short, users are able to avoid the dry puff scenario that results in exposure to harmful chemicals, as described in further detail below. While regulatory standards and temperature limits are needed, it is important for FDA to understand the difference between laboratory measurements and true consumer exposure.

In a letter recently published in the New England Journal of Medicine,[30] 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

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

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 Dr. Farsalinos[31]:

> 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

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[31] *See* http://www.ecigarette-research.com/web/index.php/2013-04-07-09-50-07/2015/191-form-nejm.

> 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 has been submitted 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

	Formaldehyde (ug/10 puffs)	Acetaldehyde (ug/10 puffs)	Acetone (ug/10 puffs)	Acrolein (ug/10 puffs)
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
10 watts				
A1	11.3	4.5	ND	1.0
A2 [dry puff]	344.6	206.3	22.5	210.4
Tobacco cigarettes[32] (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.[33] 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.

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[32] *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.

[33] *Id.*

These results confirm that while it is possible for e-cigarettes 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 electronic cigarette 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-cigarette use, even when they used advanced open-system e-cigarette devices.

b. Need for Product Standards and Temperature Limits

The potential toxicity of the inhaled e-cigarette aerosol depends on a number factors, including the ingredients and impurity profile of the e-liquid, the materials and manufacturing methods used, and, as demonstrated by the aldehyde study above, the maximum temperature the device and its component parts (*e.g.*, heater coil) can reach during use. Identifying and determining how to control each of these factors is a feasible regulatory objective and the only way FDA will be able to predict the safety profile of these products.[34] Electronic cigarette technology is rapidly evolving, and it is important for FDA to work with the industry to establish appropriate manufacturing practices and product standards to ensure consumer safety without stifling innovation. Considering that excessive heat causes the release of harmful compounds, FDA should consider working with the e-cigarette industry to establish commercially and technically feasible temperature limits for the heater coil during operation. This is critically important because we know that the breakdown of the consumable e-liquid fluid into potentially harmful substances is primarily a function of temperature. In other words, the chemical composition of the inhaled aerosol will largely depend on the temperature to which the e-liquid and internal vaporizer components (coil) are heated. Excessive heat may result in the formation of unintended impurities/degradation compounds, such as formaldehyde. Of course, any product

[34] Tobacco leaf products, on the other hand, can vary greatly simply because they are *agricultural* products, dependent on factors such as growing conditions and other uncontrollable natural variations. Because e-cigarettes are *technology* products, however, the various processes and chemical reactions that occur during use can be identified and, ultimately, controlled.

standard such as a temperature limit will need to go through FDA's notice and comment rulemaking procedures before becoming effective.

In addition to regulatory temperature limits, e-cigarette product standards (promulgated though FDA's notice and comment rulemaking procedures) should focus on the following core principles:

- Products should incorporate standard safety features including, but not limited to, auto-shut off capabilities, short-circuit protections, and "smart charging" ability,[35] over/under-charge protections, and consumer safety features to prevent abuse/misuse (*i.e.*, child-proof packaging).

- All e-cigarette devices and components shall incorporate electronic protections designed and constructed so that a short-circuit in the atomizer, improperly installed battery, incorrect battery or any reasonably foreseeable error by the consumer (*i.e.*, using unauthorized car charger) will not cause unacceptably elevated temperatures, charring, smoke or fire.

- Batteries and chargers should be designed to ensure they will not over-heat or cause electrical damage to the device.

- Electronic cigarette devices and components should be required to meet standards similar to the European Union's Restriction of Hazardous Substances Directive 2002/95/EC (RoHS or RoHS2), which restricts the use of certain hazardous substances (*e.g.*, lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyls, polybrominiated diphenyl ether) in electrical and electronic equipment.

- Standards for the manufacture and use of the various e-cigarette component parts (*e.g.*, 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.) should be developed.

- Standards should be developed to ensure consistent aerosol delivery. Boost circuits may be required to ensure consistent aerosol output by maintaining the heat level, or adjustable airflow features (*e.g.*, airflow sensors).

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[35] Smart charging ability refers to technology typically found in smart phones that stops charging current flow to the battery when fully charged.

Of course, in addition to product standards, industry-specific GMPs should be developed to ensure that the devices and components are safely manufactured. We discuss the need for e-liquid manufacturing practices in Section V below.

FDA should work with industry to establish a standards-setting body whose mission will be to develop science-based[36] product standards and specifications for e-cigarettes, e-cigarette component parts and e-liquids. Many other industries have benefitted from this approach, and FDA has worked with standards setting bodies in the past in this very way. For example, in 2006 FDA issued an updated list of consensus standards recognized by the Agency for use in evaluating medical devices prior to receiving premarket approval for entry. The Food and Drug Administration Modernization Act (FDAMA) of 1997 authorized the Agency to recognize standards developed in an open and transparent process, such as those developed by American National Standards Institute (ANSI)-accredited standards developing organizations, as well as the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC).[37]

Ultimately, with respect to e-liquids, product standards should be designed to ensure that the ingredients used are suitably pure for their intended use (where applicable, ingredients should meet U.S. Pharmacopeia (USP) requirements for purity), that the presence of ingredients of concern such as diacetyl and related compounds are minimized, and that the concentrations of nicotine and other baseline ingredients are verifiable and accurate. Child-resistant and tamper evident packaging for any e-liquid containing nicotine sold to consumers should also be

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[36] According to FDA's own *Strategic Plan for Regulatory Science*, the Agency's "core responsibility is to protect consumers by applying the best possible science to its regulatory activities." In this regard, "FDA is also responsible for advancing the public health by helping to speed innovations that provide our nation with safe and effective medicines and devices and keep our food supply safe, while helping Americans get the accurate, science-based information they need to use medical products and consume foods to improve and maintain their health." We recommend FDA heed its own advice, and base any decisions with respect to the regulation of e-cigarettes and e-liquids on sound, peer-reviewed science. See *Introduction: Strategic Plan for Regulatory Science*, available online at: http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268098.htm.

[37] *See* ANSI, *FDA Issues List of Recognized Consensus Standards for Medical Devices*, available online at: http://www.ansi.org/news_publications/news_story.aspx?menuid=7&articleid=1190.

mandated. Furthermore, as detailed below, GMPs for e-liquids should be established based on AEMSA's manufacturing standards to ensure these products are manufactured in a safe manner.

V. E-Liquid Manufacturing Standards

As noted above, unintended impurities in the e-liquid can also result from the e-liquid manufacturing process. Good Manufacturing Practices or "GMPs" are systems and procedures that are designed to ensure the quality and safe manufacturing of a product. FDA has established GMPs codified in its regulations for food, dietary supplements, drugs and medical devices. With respect to tobacco products, the Tobacco Control Act gives FDA the authority to issue regulations related to tobacco product manufacturing practice in order to protect the public health and to assure that tobacco products are in compliance with the law. Specifically, Section 906(e) of the Act requires that FDA prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, preproduction design validation (including a process to assess the performance of a tobacco product), packing, and storage of tobacco products conform to (i) current GMPs or (ii) hazard analysis and critical control point methodology. Of importance, Section 906(e) also states that the GMP regulations "may differ based on the type of tobacco product involved."

Assuming solely for the purposes of these comments that e-cigarettes and their e-liquid components (that contain tobacco-derived nicotine) are deemed to be *regulated* tobacco products, FDA should establish GMPs for the manufacture of e-liquids based on AEMSA's well-established e-liquid manufacturing standards, which are available online (at http://www.aemsa.org/standards/) and included in **Appendix I** hereto. This is especially critical because many e-liquids used in cigalike devices are produced in China, where there is little regulatory oversight over their manufacture. AEMSA Members have been able to demonstrate for several years now that content and quality in e-liquids (including nicotine content) is verifiable and sustainable.

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 professionalism, accuracy and in a safe manner until such time as FDA promulgates GMPs for e-liquids. AEMSA believes that e-liquid manufacturers 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 assure that 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 or misbranded.

* * *

AEMSA appreciates the opportunity to submit these comments to FDA, and would be glad to discuss these comments at its earliest convenience.

Respectfully submitted,

Jeff Hammel
President
American E-Liquid Manufacturing Standards Association

On behalf of:

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2. Azure Vaping – Robert Jack
3. Ecigcharleston – Joe Atwell
4. EC Blend – Carol Williams
5. Firebrand – Brian Gage
6. Hot Vapes – Tim Roche
7. iVape/JP Ventures LLC – Joe Battista
8. J Vapes – Jourdan Wheeler
9. Juicy Vapor – Anthony Brancato
10. Madvapes – Scott Church
11. Mister E-Liquid – Dan Lawitzke
12. Molecule Labs – Michael Guasch
13. Mountain Oak Vapors – Steve Nair
14. NicVape – Richard Henning
15. NicQuid – Adam Knudsen
16. Puffing Monkey – Joe Wofford
17. Purebacco – Kevin Beilman
18. Purilum – Bianca Iodice
19. Tampa Vapor – John Synychak
20. Texas Select Vapor – Brett Coppolo
21. The Vapor Bar – Schell Hammel
22. The Vaper's Knoll – Richard Gue
23. Two Peas in a Pod – Orlan Johnson
24. VaporHQ – Adam Black
25. VaporShark – Brandon Leidel
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Consumer Advocates:

1. Lou Ritter (President Emeritus)
2. Linc Williams (Compliance Chairman)
3. Jesse Ray

Enclosures:
Appendix I – AEMSA E- Liquid Manufacturing Standards
Appendix II –Examples of Flavored Alcohol Beverages

This document was delivered electronically.

Appendix I – AEMSA Standards

Creating responsible and sustainable practices and process for the safe manufacturing of "e-liquids" used in electronic cigarettes.

Version 2.1 | 2.14.2015

E-LIQUID MANUFACTURING STANDARDS

RESPONSIBILITY • STANDARDS • TRANSPARENCY

877.68.AEMSA (23672) INFO@AEMSA.org www.AEMSA.org

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 and safety 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 E-liquids. 2012 E-Liquid Manufacturing Standard will be used as a basis for:

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

Definitions

Term	Definition
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, sideby-side) with the molecular formula C4H6O2. Diacetyl occurs naturally in alcoholic beverages and is added to some foods to impart a buttery flavor. It has been eliminated from many commercial flavorings due to risk of lung damage
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"[2]. 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

E-Liquid Manufacturing Standard

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 equipment

(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 and safety 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 99.0% *

(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 safe or 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 e-liquids

(a) Including but not limited to:

(i) Diacetyl

(ii) WTA (whole tobacco alkaloids)

(iii) Medicinal - or prescription medicinal

(iv) Illegal or controlled substances

(v) Caffeine

(vi) Vitamins or Dietary supplements (other than for preservative purposes)

(vii) Acetyl Propionyl (2,3- -Pentanedione)

(viii) Artifical 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

(iv) AEMSA reserves the right to review, evaluate and deny/approve any potential substance used in the creation of e-liquids at any given time

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 V. 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 II – Flavored Alcohol Beverages

SMIRNOFF® RUBY RED GRAPEFRUIT

SMIRNOFF® BLUEBERRY

SMIRNOFF® CHERRY

SMIRNOFF® CINNAMON CHURROS

SMIRNOFF® CITRUS

SMIRNOFF® COCONUT

SMIRNOFF® CRANBERRY

SMIRNOFF® FLUFFED MARSHMALLOW

SMIRNOFF® GRAPE

SMIRNOFF® GREEN APPLE

SMIRNOFF® ICED CAKE

SMIRNOFF® KISSED CARAMEL®

SMIRNOFF® LIME

SMIRNOFF® MANGO

SMIRNOFF® ORANGE

SMIRNOFF® PASSIONFRUIT

SMIRNOFF® PEACH

SMIRNOFF® PINEAPPLE

SMIRNOFF® POMEGRANATE

SMIRNOFF® RASPBERRY

SMIRNOFF® ROOT BEER FLOAT

SMIRNOFF® STRAWBERRY

SMIRNOFF® VANILLA

SMIRNOFF® WATERMELON

SMIRNOFF® PEACH

SMIRNOFF® PINEAPPLE

SMIRNOFF® POMEGRANATE

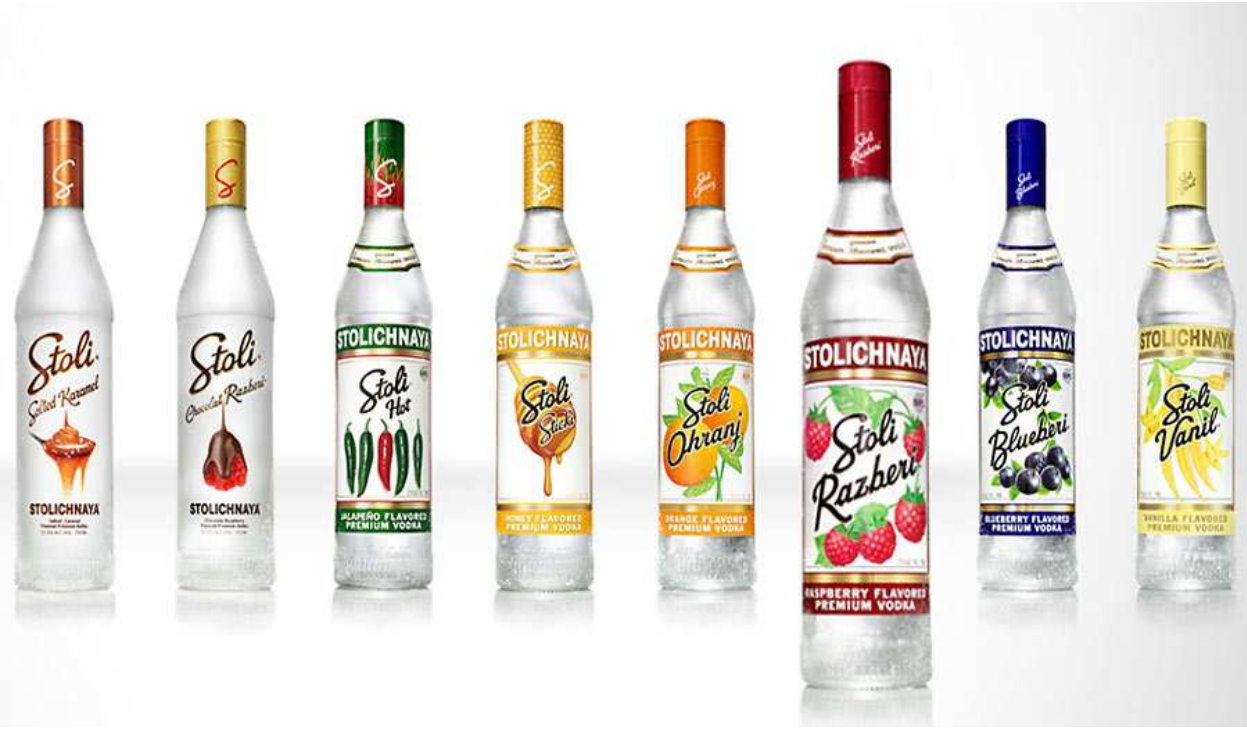
SMIRNOFF® RASPBERRY

SMIRNOFF® ROOT BEER FLOAT

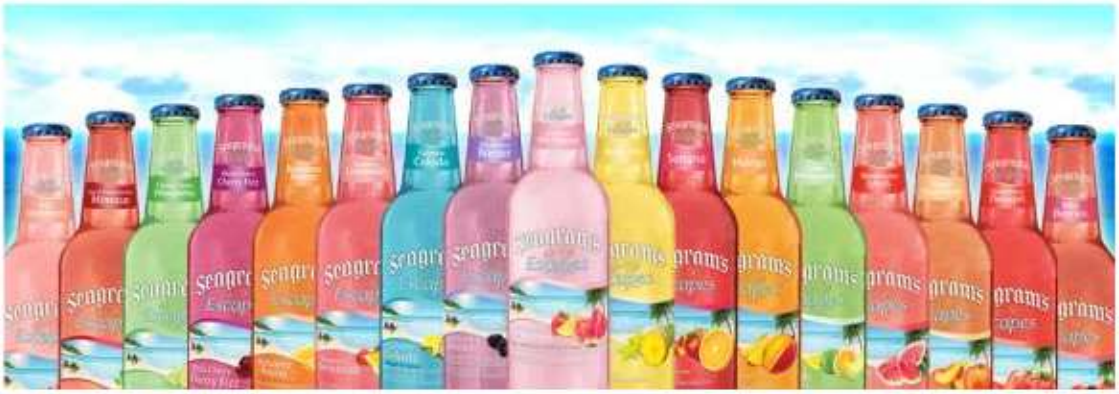
SMIRNOFF® STRAWBERRY

SMIRNOFF® VANILLA

SMIRNOFF® WATERMELON



We live on a court and one thing we love to do is hang out in the driveway with drinks and snacks. The parents all talk and laugh while the kids are off in one of the yards playing 'Ghost in the Graveyard' (remember that game from childhood??)! I was very excited at our last get together to be able to share some of the new flavors from Seagram's Escapes. Now, I want to be clear, we are not a bunch of drunkards hanging out on the driveaway. We all have one or two drinks! Honest! And I love Seagram's Escapes because they are alcoholic big in flavor. Speaking of flavors, there are so many choices and varieties!



Source: http://www.shugarysweets.com/2013/06/seagrams-escapes-cocktails