August 7, 2014

SUBMITTED BY HAND AND VIA REGULATIONS.GOV

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

Re: *Docket No. FDA-2014-N-0189, RIN 0910-AG38: Deeming Products To Be Subject to the Federal Food, Drug and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations on the Sale and Distribution of Tobacco Products and Warning Statements for Tobacco Products; Proposed Rule*

These comments are submitted by Lorillard Inc. (Lorillard). Lorillard is the parent company of LOEC, Inc. d/b/a blu (blu) a Delaware corporation that manufactures and markets the bluCigs® (blu™ electronic cigarettes). blu™ is the leading brand of electronic cigarettes in the United States, accounting for approximately 40.9% of the electronic cigarettes sold today.

Since the enactment of the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which amended the Federal Food, Drug and Cosmetic Act (FDCA), Lorillard has shared its perspectives and provided appropriate information on a continuous basis to the Food and Drug Administration (FDA or the Agency) as the Agency has sought to implement its new tobacco product authorities. Lorillard's record of compliance with FDA requirements has been demonstrated by (among other things) successful FDA inspections and the fact that Lorillard was the first company to obtain orders of substantial equivalence for two of its conventional cigarette products. Lorillard is proud of this record of compliance and looks forward to continuing to work cooperatively with the Center for Tobacco Products (CTP).

Lorillard appreciates the opportunity to comment on the above-referenced proposal, hereafter referred to as the "Proposed Deeming Regulation." As discussed in depth below, Lorillard welcomes FDA regulation of electronic cigarettes and other tobacco products,[1] but believes that

[1] Lorillard's comments address only the regulation of electronic cigarettes. The company takes no express position on the regulation of other tobacco products, including cigars. For purposes of these comments, Lorillard uses the term "electronic cigarette" to refer to products that utilize a heating element such as a battery-activated coil to heat a solution that contains nicotine and (continued…)

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the promise and opportunity presented by electronic cigarettes demands a unique and thoughtful regulatory approach. Electronic cigarettes hold the potential to advance the public health dramatically by moving existing users of conventional tobacco products to lower risk options. In fact, an international expert panel recently estimated that electronic cigarettes have only four percent of the maximum relative harm of conventional cigarettes, suggesting that substitution of electronic cigarettes for conventional cigarettes is likely to provide a significant public health benefit. Given the compelling public health benefit offered by electronic cigarettes, FDA must ensure that the application of its tobacco authorities to electronic cigarettes permits the continued development of this product category and does not unnecessarily inhibit innovation.

Below Lorillard offers a number of proposals on how FDA should implement its tobacco authorities in a manner that will advance the public health and align the interests of industry and the public health community.

Lorillard's comments proceed in two parts: Part 1 provides Lorillard's comments on FDA's proposed regulatory approach for electronic cigarettes; Part 2 provides Lorillard's comments on the scientific issues associated with electronic cigarettes and responds to the Agency's requests for available scientific data on these products.

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flavors to produce a vapor that is inhaled. Electronic cigarettes are only one type of product in the marketplace that utilizes a heating element to produce a vapor.

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PART 1: COMMENTS ON FDA'S PROPOSED REGULATORY APPROACH FOR ELECTRONIC CIGARETTES

INTRODUCTION AND EXECUTIVE SUMMARY

Electronic cigarettes represent a unique and compelling opportunity for FDA, the tobacco industry and the public health community to potentially reduce the harms associated with conventional cigarettes. As described in detail below, electronic cigarettes present the potential to move existing users of conventional cigarettes to products that present far fewer health risks.[2] Electronic cigarettes offer an unprecedented opportunity to align the interests of the tobacco industry, public health advocates and regulatory agencies such as FDA.

Tobacco products span a broad continuum of risk. On one end of that spectrum are combustible tobacco products, including conventional cigarettes. While the scientific understanding of electronic cigarettes is still developing, the existing body of literature makes one thing clear -- electronic cigarettes present a fundamentally different risk profile as compared to conventional tobacco products. The emerging body of literature suggests the following:

- Chemical/toxicological lab analyses show that electronic cigarette users are exposed to fewer and much lower levels of harmful constituents than with conventional cigarettes;
- Research on health effects is in early stages but the acute effects of electronic cigarettes are minimal and significantly less than with conventional cigarettes;
- Nicotine-containing electronic cigarettes are addictive, but users may be less dependent on them than smokers are on conventional cigarettes;
- Electronic cigarettes are associated with a significant reduction in number of conventional cigarettes smoked per day and may help some smokers quit;
- Users are almost exclusively current/former smokers; dual use is common but often temporary as smokers transition away from smoking conventional cigarettes; and
- Use by adolescents is low; there is no evidence that electronic cigarettes are a gateway to smoking.

While Lorillard acknowledges that substantial additional scientific evaluation of electronic cigarettes is needed, the science developed to date shows that electronic cigarettes have the

[2] Lorillard's comments on the disease and health risks of electronic cigarettes are intended to be considered by FDA as a regulatory Agency. blu has not claimed in promotional materials for blu™ electronic cigarettes or any other product that its electronic cigarettes present reduced risk or lower risk. blu responsibly promotes its products as alternative tobacco products, not as modified risk tobacco products (MRTPs) or as drugs. Unless blu obtains a product approval as an MRTP, it will not promote its products with any reduced-exposure or reduced-risk claims.

potential to play a critical role in smoking risk reduction and to significantly advance the public health. Available scientific information indicates that electronic cigarettes do not encourage smoking initiation; that they could help some smokers quit smoking; and that electronic cigarettes expose users to far lower levels of harmful or potentially harmful constituents (HPHCs) than conventional cigarettes. All of these data suggest that electronic cigarettes can offer long-term population-level health benefits.

Given this potential, Lorillard urges FDA to implement its tobacco product authorities for electronic cigarettes in a thoughtful and prudent manner, proportional to the harm-reduction potential that these products present. Aspects of the existing regulatory system for conventional tobacco products are not well-suited for electronic cigarettes. FDA should reconsider the current regulatory system and the manner in which the Agency should apply certain elements of that system to electronic cigarettes specifically. Moreover, before certain aspects of the FDCA can be implemented, there needs to be further development of key scientific and regulatory tools.

Lorillard is not taking the position that FDA should not regulate electronic cigarettes. To the contrary, Lorillard recognizes that reasonable regulation can help foster product quality and consistency, as well as responsible marketing to ensure that the public health benefits of this product category are fulfilled. In light of the foregoing considerations, Lorillard supports many aspects of the Proposed Deeming Regulation, including the following:

- Registration of electronic cigarette manufacturers;
- Listing of electronic cigarette products;
- Submission of electronic cigarette ingredients;
- Restrictions on youth access;
- Reasonable warnings for electronic cigarettes, including nicotine warnings;
- Limitations on vending machine sales;
- Limitations on sampling;
- Initiation of inspections;
- Prohibitions against misbranding; and
- Prohibitions against adulteration.

These aspects of the FDCA can and should be implemented within a reasonable time period -- such as 6 months -- after the effective date of the final deeming regulation. Implementing these aspects of the FDCA will permit FDA to begin understanding the range of electronic cigarette products that are on the market, bring consistency to the marketplace, further reduce the potential for youth access to electronic cigarettes and allow the Agency to remove products that present

public health concerns -- including products that are adulterated or that are marketed with improper promotional practices. In addition to implementing these measures, FDA could:

- Develop and implement regulations for good manufacturing practices (GMPs) for electronic cigarettes.[3] The development and implementation of GMPs will help to ensure product consistency and quality and reduce the possibility of contamination;

- Develop a list of "banned" substances (*e.g.*, diethylene glycol (DEG), heavy metals) by defining exposure limits for certain substances;

- Issue recommendations or regulations regarding child-proof/tamper-resistant standards for nicotine solution that is sold separately or intended to be used to refill electronic cigarettes; and

- Develop an ingredients reporting format specific to electronic cigarettes that takes into consideration the product structure and elements unique to this product category.

At the same time, however, Lorillard believes that regulation that fails to account for the unique properties and promise of electronic cigarettes threatens to undermine the product category and the substantial progress that has been made in this area. Given limitations in the current state of science surrounding electronic cigarettes, some aspects of the FDCA cannot be implemented at present. Specifically, there is a complete absence of standardized and validated testing methodologies to compare one electronic cigarette to another, or to compare an electronic cigarette to a conventional cigarette. While such methodologies have existed for many years for conventional cigarettes (*e.g.*, the International Organization for Standardization (ISO) method), there are no such methodologies that have been validated for electronic cigarettes. FDA has acknowledged this significant gap.

Moreover, unlike conventional cigarettes, there are no longitudinal surveys or other reliable sources of data that assess population-level usage patterns or the health effects of electronic cigarettes. Lorillard anticipates that the development of such methodologies and sources of data will require a concerted effort over several years and will require an open and transparent process involving many stakeholders. Lorillard urges FDA to begin an open dialogue to develop these methodologies, which are a prerequisite to implementing HPHC reporting or premarket review for electronic cigarettes. Absent the ability to compare products to evaluate their constituent deliveries, or to reach conclusions about population-level effects, FDA cannot implement a meaningful and consistent premarket review process for electronic cigarettes.

Accordingly, as part of the final deeming regulation, FDA should announce that it will exercise enforcement discretion over (1) the requirement in Section 904 regarding HPHC reporting for electronic cigarettes and (2) the requirement in Section 910 for premarket review. That

[3] Given the dramatic differences between conventional cigarettes and electronic cigarettes, Lorillard believes that GMPs must be product-specific. General GMPs for all tobacco products are unlikely to provide sufficient controls for electronic cigarettes.

enforcement discretion policy should continue while FDA (together with industry, academia and the public health community) develops appropriate standardized and validated methodologies for evaluating electronic cigarettes. Lorillard recommends that FDA begin this process by scheduling a series of public workshops, as it has done with other important public policy issues. FDA should also consider empaneling the Tobacco Products Scientific Advisory Committee (TPSAC) as part of this scientific process and consider identifying electronic cigarette ad-hoc TPSAC experts. Additionally, Lorillard proposes that FDA condition the exercise of enforcement discretion on a requirement that the manufacturer of an electronic cigarette submit (again, within a reasonable time period after the final deeming regulation) a product report that contains key information about that product, such as information about ingredients, labeling and technology used in the electronic cigarette. Once FDA has developed the appropriate scientific tools, FDA could withdraw its enforcement discretion over these aspects of the FDCA after a sufficient compliance period to permit manufacturers to prepare their premarket submissions.

Implementing most aspects of the FDCA immediately while exercising enforcement discretion for HPHC reporting and premarket review (coupled with the submission of a product report) will allow FDA to begin regulating electronic cigarettes while simultaneously increasing the Agency's understanding of these products. This increased scientific understanding will in turn inform how FDA applies premarket pathways once appropriate scientific/regulatory tools are developed.

In addition, to the extent that premarket review is required, FDA should implement a system that accounts for the potential benefits of electronic cigarettes and allows electronic cigarette manufacturers to utilize all aspects of the FDCA, consistent with congressional intent. Lorillard suggests that FDA do at least the following:

- FDA should exercise enforcement discretion not to require premarket review of electronic cigarettes introduced into United States commerce on or before the effective date of the final deeming regulation. This would create a situation that reflects the initial implementation of the FSPTCA: electronic cigarettes on the market prior to the effective date of the final deeming regulation would not be subject to premarket review and those electronic cigarettes introduced after that date but before FDA withdraws its enforcement discretion policy would be regarded as "provisional" electronic cigarettes for which either a substantial equivalence (SE) report or premarket tobacco application (PMTA) would be required after a reasonable compliance period. Electronic cigarettes introduced into commerce after the effective date of the final deeming regulation would have to undergo premarket review before being marketed. FDA has ample authority -- as illustrated by numerous precedents -- to take this logical step.

- FDA should take steps to ensure that the FDCA and all of its premarket pathways are available to electronic cigarettes. In particular, FDA should permit all products that were introduced before the date of the final deeming regulation to serve as predicates upon which an SE report under Section 905(j) for a later-introduced product may be based. Only products that are not substantially equivalent to a product on the market before the effective date of the final deeming regulation should be required to submit a PMTA.

Again, this logical step will ensure that all of the premarket pathways in the FDCA are available to electronic cigarettes.

- If FDA does not permit products introduced to the market after February 15, 2007 to serve as predicates, FDA should use other approaches to permit the SE process to be used for electronic cigarettes. For example, FDA could utilize its authorities in Section 907 to define a product standard for electronic cigarettes. Through a product standard, it could establish a monograph for an electronic cigarette, describing the features and HPHC deliveries of an electronic cigarette. For products that meet the product standard, as demonstrated through an SE report, FDA could exercise enforcement discretion for these products by waiving the requirement for a PMTA.

Regardless of how FDA implements the requirements for premarket review for electronic cigarettes (*e.g.*, through Section 905(j) or 910), FDA should ensure that the data requirements for electronic cigarettes are clear, tailored to the specific product category and not unduly burdensome. For example:

- FDA should publish guidance documents on the required data elements for electronic cigarette substantial equivalence reports and PMTAs, which should be specific to electronic cigarettes.

- For both substantial equivalence reports and PMTAs, FDA's review should be focused on the e-vapor[4] and constituent deliveries. Once FDA develops methodologies and validated approaches to measuring HPHCs in electronic cigarettes, the key issue focus of premarket review should be on the e-vapor deliveries to the user -- regardless of the underlying technology.

- For PMTAs, FDA should do the following:

    - FDA should ensure that the requirement for premarket review is balanced against the ability of a company to develop and submit post-market data to the Agency. FDA should permit companies to obtain approvals based on a robust set of data on the toxicological properties of electronic cigarettes and a more limited amount of data and information demonstrating the longitudinal/population effects of electronic cigarettes, so long as the company agrees to develop these data post issuance of a PMTA order.

    - FDA should develop guidance and models for how manufacturers assess the population-based impacts of electronic cigarettes.

    - FDA should create a PMTA supplement process consistent with the streamlined supplemental application process for drugs and medical devices approved under a

[4] Lorillard uses the terms e-vapor and aerosol interchangeably to describe the deliveries to an electronic cigarette user as a result of vaping an electronic cigarette.

premarket approval (PMA). For example, FDA should develop an approach that mirrors 21 C.F.R. § 814.39 by defining major, moderate and minor changes to a PMTA-approved electronic product and the corresponding type of supplemental application required for each change. For moderate and minor changes, the level of data required should be significantly less burdensome than a full PMTA and the Agency's review should be quicker.

In short, FDA has substantial discretion and authority to develop a regulatory approach that is consistent with the statutory requirements of the FDCA and that accounts for the unique public health promise of electronic cigarettes. Lorillard stands ready to assist FDA as it develops appropriate and reasonable regulatory solutions for this product category.

DISCUSSION

I. Background on Electronic Cigarettes

A. Overview of Electronic Cigarettes

Electronic cigarettes represent a new and growing United States market that has increased significantly in recent years.[5] The modern electronic cigarette was pioneered and launched initially in China in the early 2000s.[6] Based on the information available to Lorillard, electronic cigarettes were not introduced in the United States until approximately mid-2007 and did not experience significant market growth until early 2008.

As discussed further below, electronic cigarettes have mainly been adopted by adult smokers who use the device as an alternative source of nicotine. This trend is supported by the responsible marketing and promotional policies adopted by many electronic cigarette manufacturers, including age verification at point of sale, marketing (including TV, radio, print and internet) primarily to adult audiences and limiting promotional events, such as sponsorships or sampling events, to primarily adult events or adult-only spaces within those events.

Although there is significant variability among electronic cigarettes currently on the United States market, these products can be defined functionally as novel electronic devices designed to provide nicotine through inhalation of a vaporized solution. Because nicotine from an electronic cigarette is delivered through vaporization instead of combustion, an electronic cigarette does not expose its user to smoke, ash, or other byproducts of combustion typical of conventional cigarettes.

Electronic cigarettes are generally comprised of two primary components:

- a cartridge that contains a liquid solution (referred to as "e-liquid") and
- a heating element, or atomizer.

The cartridge and atomizer can also be combined in one element called a "cartomizer."[7] Most electronic cigarettes have small cartridges or cartomizers and may be used with small batteries (which may be sold with the electronic cigarette or purchased separately). A typical electronic cigarette design, together with a battery, is pictured below:

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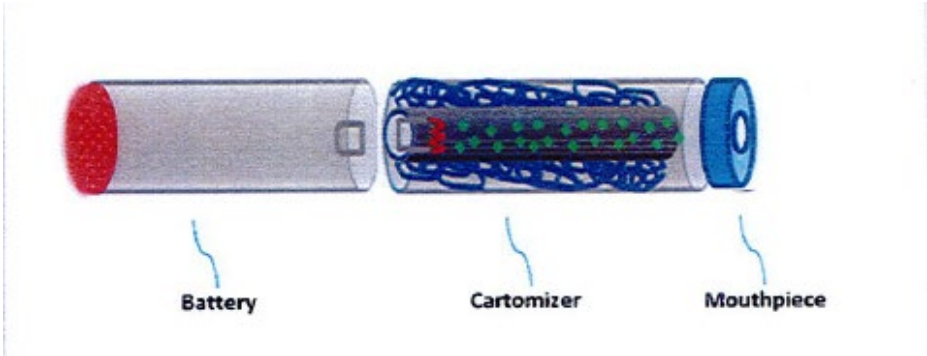
[5] Gora, T., *Are E-Cigarettes Losing Ground in the Vapor Market?*, Wall Street Journal (Apr. 14, 2014) (citing figures from tobacco industry analyst Bonnie Herzog at Wells Fargo).

[6] Dockrell, M., *E-cigarettes: Prevalence and Attitude in Great Britain*, 15 Nicotine & Tobacco Research 1737 (Oct. 2013).

[7] Brown, C. et al., *Disposable Electronic Cigarettes Do Not Have Rechargeable Batteries and are Generally Not Refillable., E-cigarettes: Product Characterisation and Design Considerations*, 23 Tob Control ii4, ii5 (2014).



By "puffing" on the mouthpiece of the device, a user triggers an electronic airflow or pressure sensor and automatically activates the atomizer, which then heats the e-liquid in the device and generates aerosol that can be inhaled by the user through the mouthpiece.[8] Some electronic cigarettes are also designed with a light-emitting diode (LED) indicator at the tip of the device that signals each activation (*e.g.*, each inhalation) of the device; some are also equipped with an off-on button.

In traditional electronic cigarette designs, a cartridge generally contains an absorbent material saturated with the e-liquid solution. The e-liquid generally contains a carrier, nicotine, water and any added flavorings. Commonly used carrier liquids include propylene glycol (PG) and glycerin, substances generally recognized by FDA as safe.[9]

The atomizer generally consists of a metal or ceramic heating element that is coiled around a wick bundle.[10] The e-liquid is generally delivered from the cartridge to the atomizer via capillary action through the wick.[11] The heating element then heats the e-liquid so that it condenses and produces aerosol that can be inhaled by the user. The heating element's resistance, material and voltage may influence aerosol properties.[12]

In addition, the devices are typically powered by a battery, which may be supplied with the electronic cigarette or may be sold separately. The battery component powers the atomizer and is generally housed in the body of the device. Electronic cigarettes are generally powered by a permanent rechargeable battery, a non-rechargeable battery or a user-replaceable battery.[13]

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[8] *Id.*

[9] 21 C.F.R. § 182.1320; 21 C.F.R. § 184.1666.

[10] Brown, *supra* note 7, at ii5.

[11] There are other known methods of delivery, including use of pumps or by a user directly dripping e-liquid onto a heating element before puffing. *Id.* at ii6.

[12] Increasing the heating element temperature produces warmer air, which can hold more e-liquid and may affect aerosol particle size, which might impact absorption and toxicity levels. *Id.*

[13] Brown, *supra* note 7, at ii6.

Moreover, some electronic cigarettes utilize ordinary, off-the-shelf batteries. Because the battery may be sold separately from the electronic cigarette, Lorillard believes that the battery should be regarded as an accessory to the electronic cigarette, together with other accessories such as carrying cases and chargers.

The market for "vaping" devices has evolved in recent years and many alternative vaping devices have been introduced to the market. Most of these products have higher-capacity batteries and atomizers that can be rebuilt and/or refilled with liquid. These products include "tank" or "mods" designs. Under the "mods" design, a user can configure and customize his or her own vaping device out of separately purchased components (*e.g.*, battery, atomizer and cartridge). The "mods" design can, but does not have to, include a "tank" design for the e-liquid, which uses a storage reservoir for e-liquid that is in direct contact with the heating coil and that can be filled by user-customized e-liquid.[14]

B. blu™ Electronic Cigarettes

1. Background on blu™ electronic cigarettes

In 2009, blu launched its electronic cigarettes in the United States. Lorillard acquired blu in April 2012 as a wholly-owned subsidiary. As of April 12, 2014, blu had net retail sales in the past year of approximately $321 million and held approximately 40.9% of the retail market share in the United States.

The blu™ electronic cigarette is currently available in a disposable model, which is approximately 118 mm in length and approximately 9 in mm diameter, and two rechargeable models, available in two lengths, one that is approximately 89 mm in length and approximately 8 in diameter when assembled and a Premium 100 model that is approximately 99 mm in length and approximately 10 mm in diameter when assembled. blu™ electronic cigarettes are black with a blu™ LED tip. Unlike many of other electronic cigarettes, blu™ electronic cigarettes are not sold in colors associated with conventional combustible cigarettes (*e.g.*, white and cork colors), which visibly distinguishes blu™ electronic cigarettes from conventional cigarettes. The rechargeable blu™ electronic cigarette contains a blu™ cartridge, with a built-in atomizer, which can be screwed into the rechargeable battery. The disposable blu™ electronic cigarette is constructed with the cartomizer and battery in one piece.

blu™ electronic cigarettes are also sold as kits, which include chargers, a select number of cartridges and batteries, and each element of a kit is also available for sale individually. blu™ electronic cigarettes are available for sale behind the counter in retail stores, from blu's online store and in limited cases, for sale by personnel in beauty shops, cruise ships and casinos.

[14] *See* Dawkins, L., *'Vaping' Profiles and Preferences: An Online Survey of E-cigarette Users*, 108 Addiction 1115 (2013). The efficiency of nicotine delivery and amount of nicotine in the device can vary significantly depending on the design of the electronic cigarette. *See, e.g.*, Schivo, M., *Non-Cigarette Tobacco and the Lung*, 46 Clinical Rev. Allerg. Immunol. 36, 47 (2014).

The blu™ cartridges used in the rechargeable model are sold at various levels of nicotine, ranging in strength from no nicotine, to low (approximately 6 to 8 mg), medium (approximately 9 to 12 mg) and high (approximately 13 to 16 mg). blu markets seven different cartomizer flavors for the rechargeable model: tobacco, menthol, vanilla, cherry, coffee, peach schnapps and Pina Colada. The disposable model is available in only three flavors: tobacco (containing approximately 20 to 24 mg nicotine), menthol (containing approximately 17 to 24 mg nicotine) and cherry (containing 17-24 mg nicotine). Current blu™ electronic cigarette sales data show that adult consumers prefer the tobacco, menthol and cherry crush flavors.

2. blu is committed to ensuring the quality and integrity of its products and to responsible marketing

blu is committed to developing and manufacturing a consistent product, including the development of responsible quality control and product stewardship policies. Lorillard has also committed to advancing scientific research into the safety and efficacy profile of electronic cigarettes, including their potential to be safer than combustible cigarettes or as effective as nicotine replacement therapy. Regardless of the harm reduction potential for blu™ products or electronic cigarettes more generally, blu is scrupulous about marketing its products only as alternative tobacco products, not as reduced harm or reduced risk products. Moreover, blu responsibly markets its products only to adult smokers and takes significant steps to limit youth exposure to its marketing or promotional activities. The company's commitment to quality and integrity manifests itself through a number of key activities:

- ***blu's commitment to quality manufacturing and stewardship.*** blu has voluntarily implemented a product stewardship program that focuses on (among other things):
    - integrity of product design;
    - product performance testing;
    - working with responsible audited or certified suppliers;
    - obtaining quality ingredients from suppliers; and
    - manufacturing under strict corporate quality standards.

  As part of its stewardship and quality programs, blu invests significant resources in quality control testing of its ingredients. For example, Lorillard requires approved formulas and ingredient suppliers for blu™ e-liquids and will require a qualification process that includes sample and batch testing against blu-established specifications (including nicotine, PG, glycerin and water content, certain detectable metals, viscosity, flashpoint, pH and specific gravity). The company requires further validation testing prior to manufacturing of the finished product. Manufacturers will be required to provide Certificates of Analysis (COAs) with each lot of production and blu plans to perform verification testing of the COAs. In addition, blu has contracted with an independent laboratory for testing verification upon receipt.

For manufacturing of the finished product, blu has implemented robust quality controls for the manufacturing process. As an initial matter, blu selects contract manufacturers based on their eventual ability to comply with pharmaceutical and medical device GMPs or quality system regulations (QSRs) and requires its manufacturers generally to follow FDA's requirements set forth in 21 C.F.R. § 820.[15] For example, blu requires traceability by lot number, incoming quality testing on key components, sample testing of each shipment of products that leaves the contract manufacturer and performs additional production monitoring on finished products. The company also conducts scheduled quarterly audits and unscheduled audits of the factories, reviews any corrective actions and maintains weekly manufacturing oversight through a third-party management company.

blu also has a complaint process wherein safety-related complaints regarding blu™ products are referred to appropriate personnel for investigation and resolution, as necessary.

- ***blu is committed to research regarding the safety of its products.*** Lorillard, on behalf of blu, has conducted various toxicological, environmental and clinical testing of blu™ products to assess product safety. The results of these studies suggest that the safety profile of blu™ electronic cigarettes is more favorable than that of combustible cigarettes and comparable to smokeless tobacco products, which is consistent with the larger body of literature described in Part 2 of these comments. Lorillard has conducted research in the following areas:

    - Lorillard has conducted a toxicology assessment of the e-liquid and aerosol of certain blu™ electronic cigarettes. The assessment included 4 *in vitro* assays to test for genotoxicy, cytotoxicity, mutagenicity and inflammatory response and was based on traditional combustible cigarette analyses modified for electronic cigarette use. The results showed that the electronic cigarettes tested did not produce any meaningful toxic effects under the experimental conditions.

    - Lorillard has conducted aerosol testing using a modified smoking machine to measure the level of certain smoke constituents in the aerosol of certain blu™ electronic cigarettes.

    - Lorillard has conducted an exhaled aerosol study with human subjects to test the level of HPHCs in exhaled aerosol of certain blu™ electronic cigarettes as compared to the level of HPHCs in the smoke of a combustible cigarette.

    - Lorillard has conducted a puffing topography study with human subjects to assess the puffing profile (puff volume, duration and number of puffs) of certain blu™ electronic cigarettes.

[15] blu also maintains a mandatory list of secondary suppliers for key components (*e.g.*, batteries), which are selected after substantial due diligence by blu.

- Lorillard has partnered with external parties to conduct a real-world vaping/environmental study to compare second-hand exposure from environmental tobacco smoke constituents from combustible cigarettes to environmental aerosol constituents from certain blu™ electronic cigarettes.

- Lorillard has partnered with an external party to conduct a randomized, partially single-blinded, six-period crossover clinical pharmacokinetics study to characterize nicotine exposure and urge-to-smoke following controlled administration and short-term use of certain blu™ electronic cigarettes as compared to combustible cigarettes.

Lorillard intends to publish the results of its electronic cigarette research.

- ***blu is committed to continued innovation.*** blu is committed to future development and innovation of its electronic cigarettes to improve further the safety profile of its products.

- ***blu is committed to responsible marketing practices.*** blu believes that electronic cigarettes are not a product for youth and that any youth usage is unacceptable. Furthermore, although electronic cigarettes show promise as a safer alternative to combustible cigarettes, the company has taken significant steps to avoid claims that its products are safer than traditional combustible products. Therefore, blu has adopted internal guidelines that require its advertising and promotion to be directed to adults, by the means of various age-related restrictions, and to avoid any claims, implied or express, that electronic cigarettes are healthy or safer than combustible cigarettes, or that they may help consumers quit smoking.

  For each of these advertising and promotional tools, blu has implemented the following age-related restrictions to limit youth exposure:

  - Television Advertisements: Stations and air times for television advertisements are selected based on demographic data that confirm at least 85% of the intended audience is adults. The television show content must also be directed to adult viewers.

  - Radio Advertisements: Stations and air times for radio advertisements are selected based on demographic data that confirm at least 85% of the intended audience is adults. The radio show content must also be directed to adult listeners. For its radio advertisements, blu has relied on demographic data obtained directly from Clear Channel Media and Entertainment that confirmed at least 85% of the audience was 21 years of age or older.

  - Print Advertisements: Print advertising is limited to publications with at least 85% adult readership and/or a circulation of no more than two million or more readers under 18 years of age. blu relies on demographic data obtained from readership surveys, such as Mediamark Research, Inc. and/or Simmons, where available, or demographic information from the magazine.

- Internet Advertisements: Internet ads (including web and mobile banners) must be placed only on websites in which the target audience is adults. As described more particularly below, for blu's website, blu has implemented an age verification process to ensure only visitors who have been verified as adults can purchase products from the site. Visitors to the site are also required to certify that they are 18 years of age or older prior to accessing the site.

- Product Placement: Product placement is limited to movies with at least an R-rating and television programs where the program content is directed to adults and demographic information confirms 85% of the intended audience is 18 years of age or older.

- Outdoor Advertising: Billboard advertisements will not be placed within 500 feet of playgrounds or schools.

- Social Media: Social media use is limited to an adult audience through the use of age verification/restriction software, where available. For example, blu uses such age restriction software for its Facebook page and Twitter account to prevent access by minors. For other sites, blu confirms with demographic data that the site's target audience consists primarily of adults and adds a disclaimer on posted material that its products are not for sale to minors.

- Sponsorships: Sponsorship is limited to events where the event organizer confirms that at least 85% of the intended audience is adults.

- Product Sampling: Sampling at events is limited to adult-only events or age-restricted venues at open events. blu brand ambassadors are trained in blu's policy against distribution of samples or promotional items to minors and use age verification devices to certify age before sampling.

- Point-of-Sale Advertisements: Advertisements must include a warning that electronic cigarettes are not to be sold to minors.

- Packaging: Packaging on electronic cigarettes includes a warning that electronic cigarettes are not to be sold to minors.

- ***blu is committed to responsible sales practices.*** blu sells its products primarily to consumers through retail and online sales. blu does not use vending machines to sell its products. For retail sales, its primary distribution channel, blu has merchandising agreements with retailers that require retailers to maintain "We Card" or similar signage that restrict sales of blu™ products to persons of legal age to purchase tobacco products and to comply with local or state laws that restrict the sale and merchandising of electronic cigarettes. With limited exceptions, the merchandising agreements further require that blu™ products be displayed behind the counter or be sold only through direct contact with a sales clerk. blu periodically monitors retail locations to ensure compliance with the merchandising agreement.

For online sales, blu sells its products only through its website, www.blucigs.com, and employs a two-stage age-screening process to screen out minors. A consumer seeking to access the site must certify that he or she is 18 years of age or older. Then, prior to the purchase of any product, the consumer must provide personal information, including name, address and date of birth, which is verified against third-party systems (Experian and Aristotle) for identity and age. Only age-verified adult consumers are permitted to complete the sales transaction.

II. Overview of the Emerging Scientific Understanding of Electronic Cigarettes

In Part 2, Lorillard provides a comprehensive assessment of the available scientific literature on the potential effects of electronic cigarettes on the public health in response to FDA's information requests in the preamble. The available information can be categorized into the following general issues: (1) chemical and toxicological laboratory analyses; (2) health effects; (3) addiction and dependence; (4) smoking reduction and cessation; (5) patterns of use, especially dual use; (6) youth issues; and (7) marketing and consumer perceptions of risk. While the scientific understanding of electronic cigarettes is still emerging, the available data suggest that the products do have significant potential to reduce harm at both the individual and population levels. The information available to date suggests that electronic cigarettes have minimal health impact on individuals, especially when compared to conventional tobacco products, do not promote initiation of smoking and may help some people reduce or quit smoking. We briefly summarize these overall conclusions of the assessment below, which is provided in greater detail in Part 2:

- ***Scientific Evidence Suggests that the Level of Toxicants in Electronic Cigarette E-Vapor and E-Liquid Is Generally Less Than in Conventional Cigarette Smoke***. FDA expresses concerns that "[s]ome studies have revealed the existence of toxicants in both the e-cigarette liquid and the exhaled aerosol of some e-cigarettes."[16] Multiple studies have compared the level of toxicants, including harmful or potentially harmful constituents, in electronic cigarette e-liquid, e-vapor and indoor air after vaping, to the levels in cigarette smoke, as well as the *in vitro* effects, including inflammatory response, mutagenicity, genotoxicity and cytotoxicity. Generalization of the chemistry and toxicology testing of electronic cigarette e-liquids and e-vapor is difficult because of the number of brands on the market, the rapidly evolving electronic cigarette designs, and the lack of standard testing protocols. Despite these limitations, the analyses available today generally suggest that the level of toxicants in electronic cigarettes is significantly lower than those found in conventional cigarette smoke and that electronic cigarette e-liquid and vapor are substantially less cytotoxic than conventional cigarette smoke. While there is limited *in vitro* information available on inflammatory, mutagenic and genotoxic properties of electronic cigarettes, the information available suggests few effects. The few studies on "passive vaping" also suggest that the amount of harmful constituents is generally similar to that in indoor air and does not present additional risks to human health.

[16] 79 Fed. Reg. 23142, 23157 (April 25, 2014).

- ***Scientific Evidence Does Not Suggest that Electronic Cigarettes Pose a Risk of Acute Health Effects.*** FDA asks for "any health and behavioral data about the effects of using e-cigarettes."[17] The available clinical studies, as well as adverse event data from smoking cessation studies, surveys, case reports, and poison centers, do not raise significant health or safety issues. The clinical studies examined respiratory, cardiovascular and inflammatory endpoints and clinical symptoms in mainly smokers or former smokers. Although the studies were relatively small and short-term, the results suggest that the acute physiological effects of electronic cigarettes are minor and generally less severe than those associated with conventional cigarettes. The available data from smoking cessation studies, surveys, and case reports, some of which involved use of electronic cigarettes for longer periods of time than in the clinical studies, do not generally reveal any serious side effects or adverse events that could be attributed to electronic cigarettes. Although accidental or intentional poisoning with e-liquid is possible, the data suggest that exposure via common routes of administration (*e.g.*, ingestion or inhalation) does not generally result in serious adverse events. The available data on health effects do not permit any firm conclusions about long-term safety or overall population effects.

- ***Scientific Evidence Does Not Suggest that Electronic Cigarettes Are Likely To Be A Pathway to Nicotine Addiction and Dependence***. FDA raises the question of whether electronic cigarettes could serve as a path to nicotine addiction for non-tobacco users, stating "experts have expressed concern that e-cigarettes may draw more consumers to nicotine-containing products."[18] This concern is speculative and not supported by the available literature. A number of large surveys have consistently reported that very few never-smokers have tried, or use, electronic cigarettes. No studies have evaluated whether electronic cigarettes contribute to smoking relapse and existing data on this issue are too limited to draw any conclusions.

- ***Scientific Evidence Suggests that the Nicotine Addiction Potential Could Be Less for Electronic Cigarettes than for Conventional Cigarettes***. FDA asks for "supporting research, facts and other evidence, as to whether all tobacco products should be required to carry an addiction warning."[19] While nicotine, whether delivered by electronic or conventional cigarettes or any other product that contains nicotine, is addictive, the available surveys and studies on the nicotine addiction potential of electronic cigarettes suggest that users may be less dependent on electronic cigarettes than on conventional cigarettes. The surveys of electronic cigarette users suggest that users tend to decrease the levels of nicotine they use over time. The studies have also evaluated various aspects of dependence on electronic cigarettes as compared to conventional cigarettes and found lower levels of dependence for electronic cigarettes on the measured criteria for dependence.

[17] *Id*. at 23143.

[18] *Id.* at 23159.

[19] *Id.* at 23144.

- ***Scientific Evidence Suggests that Electronic Cigarettes Can Deliver Adequate Nicotine to Suppress Abstinence Symptoms and Help Smokers Reduce Smoking, but Is Inconclusive on Cessation***. FDA requests information on the "potential [of electronic cigarettes] to help cessation by delivering a sufficient nicotine dose, particularly for experienced e-cigarette users,"[20] and their potential efficacy to help smokers reduce smoking. The available clinical studies examining nicotine delivery of electronic cigarettes have consistently noted that experienced electronic cigarette users are able to obtain adequate nicotine levels to relieve withdrawal symptoms and craving. The controlled trials and intervention studies that have been conducted to date on smoking reduction and cessation have observed that electronic cigarette use results in statistically significant reductions in smoking for both smokers who wanted to quit and those who did not intend to quit. The clinical data regarding smoking cessation have been less consistent. Observational epidemiology studies assessing various cessation measures generally have found some evidence that electronic cigarette users were more likely to have attempted to quit smoking, but were not more likely to have been successful at doing so.

- ***Scientific Evidence Does Not Suggest Negative Effects from Dual Use of Conventional and Electronic Cigarettes***. FDA raises a concern about "effects e-cigarettes have in users who might have otherwise quit, but instead engage in dual use."[21] This concern is speculative as there are no data that suggest that the availability of electronic cigarettes keeps smokers from quitting. Dual use of conventional and electronic cigarettes has not been studied specifically, although it is our understanding that there are studies planned that intend to evaluate the health effects of dual use. The prevalence of dual use is currently not well understood. Smoking cessation studies, as stated above, however, have reported statistically significant reductions in conventional cigarette use among dual users. The reduction in cigarette consumption may lead to health benefits as experts have estimated that the potential harm of electronic cigarettes to be a small percentage of the maximum relative harm of conventional cigarettes. Furthermore, surveys of smokers who have reduced smoking with electronic cigarette use have generally reported improvements in health after initiating electronic cigarette use.

- ***Scientific Evidence Suggests that Flavors in Electronic Cigarettes Do Not Influence Initiation of Electronic Cigarette Use and May Aid in Smoking Cessation***. FDA raises a concern that the "use of fruit and candy-flavored nicotine liquids impact the likelihood that [an] individual will initiate use of combustible tobacco products and/or become a dual user with combustible tobacco products."[22] This concern is speculative as there are no studies that have addressed the role of flavored electronic cigarettes on later initiation of conventional cigarettes. There are data, however, that suggest that flavors reflect personal preferences and may aid in smoking cessation. Surveys of adult electronic

[20] *Id.* at 23152.

[21] *Id.* at 23152.

[22] *Id.* at 23157.

cigarette users suggest that flavors do not appear to be a strong factor in self-reported reasons for initiating electronic cigarette use. A limited number of studies have also suggested that some users perceive flavored electronic cigarettes to be helpful in smoking cessation. It is possible that some users choose other flavors because they do not want to be reminded of the tobacco flavor of a conventional cigarette. While Congress banned cigarettes with a characterizing flavor other than tobacco or menthol under the FSPTCA, it did not ban characterizing flavors for other tobacco products such as snuff or chewing tobacco. Depriving adults the right to use flavored e-cigarettes may have unintended effects, such as discouraging smokers from switching away from combustible cigarettes. If smokers do not like the taste of electronic cigarettes, they may not try or continue to use electronic cigarettes. A recent study published by Farsalinos et al. examined the impact of flavor variability on the electronic cigarette use experience. The researchers concluded flavor variability should be maintained because, among other factors, "[flavors] play a major role in the overall experience of dedicated users and support the hypothesis that they are important contributors in reducing or eliminating smoking consumption."[23] The study also reported that tobacco is the preferred flavor when starting to use electronic cigarettes but users later switch to other flavors, noting that a significant population of electronic cigarette users would be dissatisfied and/or less likely to quit smoking if flavored options were limited.[24]

- ***Scientific Evidence Does Not Suggest That Electronic Cigarettes Are A Path to Youth Nicotine Addiction or Initiation of Smoking***. FDA raises several concerns about adolescent use of electronic cigarettes, including the effect of flavors, whether electronic cigarettes are a gateway to smoking or nicotine addiction and whether adolescents are uniquely susceptible to nicotine addiction.[25] There are no studies that have examined the effect of flavors in electronic cigarettes on subsequent tobacco use and any suggestion that flavored electronic cigarettes might facilitate youth initiation is speculative. Furthermore, the available literature on adolescent use of electronic cigarettes does not suggest that electronic cigarettes are a gateway to later tobacco use. The single longitudinal study that provides data on the temporal relationship between electronic cigarette use and later smoking did not find a significant relationship. While there are analyses of cross-sectional surveys that have concluded that electronic cigarettes may encourage use of conventional cigarettes or inhibit cessation, their conclusions are flawed because cross-sectional data do not address order of use and have been criticized for inferring a result that is not supported by data. Finally, the available literature does not suggest that electronic cigarettes are a path to nicotine addiction for young people, but instead suggests that the prevalence of electronic cigarette use among adolescents who have never smoked is very low.

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[23] Farsalinos K.E., et al., *Impact of Flavour Variability on Electronic Cigarette Use Experience: An Internet Survey*, 10 Int'l J. Environ. Res. Public Health. 7272 (2013).

[24] For example, nicotine replacement therapy products are sold in a variety of flavors. Flavors of Nicorette gums and lozenges include White Ice Mint, Fruit Chill, Cinnamon Surge and Cherry.

[25] 79 Fed. Reg. at 23144, 23146, 23147.

- ***Evidence of Consumer Perceptions Indicates Beliefs that Electronic Cigarettes Are Safer than Conventional Cigarettes and Effective to Reduce or Stop Smoking***. There are multiple studies, including a systematic review of 49 studies, which have reported that adult consumers believe that electronic cigarettes are safer than conventional cigarettes. Many adult consumers also believe that electronic cigarettes helped them quit or reduce smoking.

III. FDA's Regulatory System Should Account for the Potential Public Health Benefit of Electronic Cigarettes

Electronic cigarettes are unlike other tobacco products. As demonstrated in Part 2, the studies of electronic cigarettes to date support the potential for these products to help reduce the negative public health effects of tobacco use. According to the recent Nutt et al. (2014) study, electronic cigarettes fall significantly lower on the harm continuum for nicotine-containing products than other tobacco products, including conventional cigarettes and cigars.[26] FDA acknowledges the potential public health benefit of these products numerous times in its preamble to the Proposed Deeming Rule: "Emerging technologies such as the e-cigarette may have the potential to reduce the death and disease toll from overall tobacco product use depending on who uses the products and how they are used."[27]

FDA's decisions regarding how to regulate electronic cigarettes must account for this important potential public health benefit. FDA recognizes this in the preamble to the Proposed Deeming Rule when it states that the Agency is "seeking comments, including supporting research, facts and other evidence, as to how e-cigarettes should be regulated based on the continuum of nicotine-delivering products . . . and the potential benefits associated with e-cigarettes."[28] The Agency should therefore adopt a careful approach to regulating electronic cigarettes that takes into consideration the uniqueness of the product category and encourages innovation in this area. The differences among tobacco products are substantial and policy actions that "help to switch use away from cigarettes and other smoked products" could have "massive public health gains."[29] A "one size fits all" approach to regulating electronic cigarettes in the same way as other tobacco products would have the detrimental effect of stifling electronic cigarette innovation, to the detriment of the public health.

Consistent with these principles, Lorillard supports FDA's decision to deem electronic cigarettes subject to the FDCA and to begin regulating these products.[30] Lorillard generally supports

[26] Nutt, D.J, et al., *Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach*, European Addiction Research, Research Report (Apr. 3, 2014).

[27] 79 Fed. Reg. at 23147.

[28] *Id.* at. 23152.

[29] Nutt, et al., *supra* note 26, at 224.

[30] In the Proposed Deeming Regulation, FDA requests comments on its proposed definitions of "components," "parts," and "accessories" of deemed tobacco products. 79 Fed. Reg. at 23152-23153. FDA proposes to regulate electronic cigarette components and parts under its proposed (continued…)

FDA's implementation of many provisions of the FDCA applicable to tobacco products in the near term, including, among others, the requirements for registration and listing, youth-access restrictions and a warning regarding nicotine addiction.

Lorillard, however, believes that at this juncture there are key scientific prerequisites that have not yet been established and that are necessary to implement the premarket review and HPHC reporting requirements of the FDCA. Substantial additional research is needed to ensure that the Agency's regulatory decisions with respect to these requirements are "based on good solid scientific data"[31] and foster innovation. The Agency should therefore exercise enforcement discretion with respect to premarket review and HPHC reporting until the Agency has a more complete understanding of electronic cigarettes and the most effective ways to implement these statutory requirements for this unique product category. Lorillard's proposed approach is explained in detail below.

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rule, although the Agency does not propose to apply the FDCA to electronic cigarette accessories. Lorillard agrees with FDA's proposal to limit its regulatory authorities to components and parts of deemed tobacco products only and not to accessories. Lorillard disagrees, however, with aspects of FDA's description of "components," "parts," and "accessories." FDA defines components and parts of tobacco products as follows:

> components and parts of tobacco products are those items that are included as part of a finished tobacco product or intended or expected to be used by consumers in the consumption of a tobacco product. Components and parts that would be covered under this proposal include those items sold separately or as part of kits sold or distributed for consumer use or further manufacturing or included as part of a finished tobacco product.

Id at 23153. In contrast, "FDA considers accessories to be those items that are not included as part of a finished tobacco product or intended or expected to be used by consumers in the consumption of a tobacco product, but may be used, for example, in the storage or personal possession of a proposed deemed product." *Id.* FDA's proposed definition of accessory is unduly narrow. In particular, the battery used for an electronic cigarette should be regarded as an accessory, not a component or part, even though it would be used in the consumption of the electronic cigarette. Many electronic cigarettes utilize off-the-shelf batteries. Moreover, many batteries are distributed separately from the electronic cigarette cartridges.

[31] *Proposed Fiscal 2015 Budget Request for the Food and Drug Administration: Hearing Before the Subcomm. on Agriculture, Rural Development, Food and Drug Administration and Related Agencies of the H. Comm. on Appropriations*, 113th Cong. (Unofficial Transcript from Congressional Quarterly, Mar. 27, 2014) (statement of Dr. Margaret A. Hamburg, Comm'r, FDA).

A. Provisions of the FDCA that FDA Should Apply to Electronic Cigarettes in the Final Deeming Regulation

When issuing the final deeming regulation, FDA's first steps in regulating electronic cigarettes should focus on two main goals: (1) implementation of the statutory provisions of the FDCA that FDA can apply to electronic cigarettes without the need for additional scientific understanding of electronic cigarettes and (2) development of the necessary scientific understanding and standards for electronic cigarettes required to implement the premarket review and HPHC reporting requirements of the FDCA.

With regard to the first goal, Lorillard fully supports FDA's decision to enforce, subject to a six-month compliance period following the final deeming regulation, the following requirements with respect to electronic cigarettes, some of which Lorillard implemented voluntarily before FDA's Proposed Deeming Regulation:

- **Youth-access restrictions**: FDA proposes to extend the age-restriction and identification requirements applicable to conventional cigarettes and smokeless tobacco to electronic cigarettes.[32] Lorillard fully supports the immediate implementation of these restrictions and as described above, has already implemented measures to limit youth access to its electronic cigarettes.

- **Vending machine sales limitations**: FDA is proposing to limit electronic cigarette vending machine sales to only those retail establishments in which the retailer ensures that individuals under 18 are prohibited from entering at any time.[33] Lorillard fully supports this proposed restriction.

- **Sampling limitations:** Lorillard supports FDA's decision to impose electronic cigarette sampling restrictions. FDA should, however, reconsider its decision to ban all electronic cigarette samples. FDA's regulatory decisions regarding electronic cigarettes should encourage tobacco users to choose tobacco products lower on the risk continuum of nicotine-containing products. A decision to ban all electronic cigarette sampling is inconsistent with this overarching goal. Lorillard therefore proposes that the Agency implement sampling restrictions for electronic cigarettes that are commensurate with the sampling limitations for smokeless tobacco, which permit smokeless tobacco samples to be distributed in qualified adult-only facilities.[34] Adopting this approach makes sense given that the risk profile of electronic cigarettes is closer to (and perhaps better than) the risk profile of smokeless tobacco than it is to the risk profile of conventional cigarettes. Further, permitting sampling in qualified adult-only facilities could encourage users of more harmful tobacco products such as conventional cigarettes to choose products, like

[32] *See* 79 Fed. Reg. at 23160.

[33] *See* Proposed 21 C.F.R. § 1140.14(b)(3); 79 Fed. Reg. at 23204.

[34] *See* 21 C.F.R. § 1140.16(d)(2).

electronic cigarettes, lower down on the risk continuum, which is in the best interest of the public health.

- **Application of the adulteration and misbranding provisions**: Lorillard fully supports FDA's enforcement of the adulteration and misbranding provisions of the FDCA against electronic cigarettes.[35] For example, Lorillard fully supports enforcement of the FDCA against unlawful labeling and promotion claims regarding cessation and health claims, including against claims that include modified-use descriptors without appropriate regulatory clearance.

- **Registration and listing**: FDA is proposing to require that electronic cigarette manufacturers register and list their products, consistent with Section 905 of the FDCA.[36] Lorillard supports implementation of this requirement and agrees with FDA that it will enable the Agency to gain critical information about electronic cigarettes. Specifically, the Agency will be able to better understand the range and diversity of electronic cigarette manufacturers and products on the United States market.

- **Ingredient listing:** FDA is proposing to require electronic cigarette manufacturers to list their product ingredients, consistent with Section 904(a)(1) of the FDCA.[37] Lorillard supports FDA's application of these ingredient-listing requirements to electronic cigarettes. Requiring all manufacturers of electronic cigarettes to submit ingredient lists to FDA will permit the Agency to obtain valuable information about the types of ingredients used in e-liquids.

  To permit these requirements to be meaningfully implemented, FDA will need to clarify how the term "ingredient" as used in Section 904(a)(1) applies to metal, plastic and other aspects of electronic cigarettes (*e.g.*, electronic cigarette hardware). Moreover, FDA will need to clarify which aspects of electronic cigarettes require ingredient reporting. For example, Lorillard believes that FDA's regulatory jurisdiction should extend only to the e-liquid and components of the electronic cigarette, such as the cartridge, that directly affect the e-vapor delivered to the user. Accessories of the electronic cigarette, such as the battery or charger, which can be sold separately and used interchangeably, should not be subject to the ingredient-listing requirements of Section 904(a)(1).[38]

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[35] 79 Fed. Reg. at 23148.

[36] *Id.* at 23148.

[37] *Id.*

[38] As discussed in Part 1.III.C, although Lorillard supports FDA's decision to require ingredient listing in the near term, FDA should not implement the requirements of Section 904(a)(3) related to HPHCs until testing methods needed for evaluating electronic cigarette HPHCs have been standardized and validated. Lorillard has supported this scientific effort by testing HPHCs using the best methods available and sharing the results with FDA. Once FDA has established standardized and validated test methods and a list of electronic cigarette HPHCs, Lorillard (continued…)

- **Inspections**: Lorillard fully supports FDA beginning to inspect electronic cigarette manufacturing facilities within a reasonable time after the final deeming rule is finalized.

- **Nicotine warnings**: FDA proposes to require the following warning on electronic cigarette packages and in electronic cigarette advertisements: "WARNING This product contains nicotine derived from tobacco. Nicotine is an addictive chemical."[39] FDA proposes that this warning comprise thirty percent of the area of the two principal display panels of the electronic cigarette package, similar to Congress's requirements for text-only warnings for smokeless tobacco. The proposed warning must also appear on at least twenty percent of the area of an electronic cigarette advertisement, again, consistent with similar requirements for smokeless tobacco products. Lorillard supports FDA's decision to require this warning. In fact, packaging for blu™ electronic cigarettes already includes the following warning: "Warning: This product contains nicotine, a chemical known to the state of California to cause birth defects or other reproductive harm." FDA should, however, clarify where the proposed warning must appear with respect to electronic cigarettes. Given the potential public health benefit of electronic cigarettes and their relative position on the continuum of risk versus smokeless tobacco, FDA should require that this warning be smaller than for smokeless tobacco product (*i.e.*, 20% of the principal display panel) and appear only on one of the principal display panels of the package as sold to consumers. Further, FDA should establish alternative methods for providing this warning statement on small electronic cigarette packages. FDA has created special rules for small food packages and small over-the-counter drug packages where the size of the package prevents the manufacturer from satisfying certain mandatory labeling requirements.[40] FDA should implement similar alternatives for displaying electronic cigarette warnings for small electronic cigarette packages. The warning on advertising materials should not exceed 10%.

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supports application of this requirement to electronic cigarettes, consistent with the comments in Part 1.III.C below. Proceeding to require general ingredient listing first, followed later by HPHC reporting, is supported by the Agency's implementation of these requirements for conventional cigarettes, wherein the Agency issued a final guidance on ingredient listing long before the Agency issued its draft guidance implementing the HPHC reporting requirements. *See* CTP, Guidance for Industry: Listing of Ingredients in Tobacco Products (Nov. 2009); CTP, Draft Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug and Cosmetic Act (Mar. 2012) (Draft HPHC Reporting Guidance).

[39] 79 Fed. Reg. at 23179.

[40] *See, e.g.*, 21 C.F.R. § 101.9(j)(13) (permitting required nutrition facts information to appear in a tabular or linear fashion rather than vertical fashion where, for example, the total surface area to bear labeling is less than twelve square inches); 21 C.F.R. § 201.66(d)(10) (establishing that if the mandatory over-the-counter drug labeling requires more than sixty percent of the total surface area available to bear labeling, then the manufacturer may comply with alternate size requirements for certain mandatory labeling).

B. Other Actions that FDA Could Take as Part of Its Initial Regulation of Electronic Cigarettes

In addition to implementing the requirements described above, FDA should undertake several further measures to regulate electronic cigarettes in the short term while the Agency develops the scientific understanding of this product category necessary to implement the premarket review and HPHC reporting requirements:

- **Require submission of a confidential product report.** To further the Agency's stated goal of collecting information about electronic cigarettes,[41] FDA could require that electronic cigarette manufacturers submit a confidential product report to the Agency to qualify for the Agency's enforcement discretion policy in the short term with respect to the premarket review provisions of the FDCA, which is described in Part 1.III.D.[42] Lorillard recognizes that electronic cigarette manufacturers possess information that will be vital to FDA's understanding of these products. To that end, Lorillard suggests that manufacturers submit in their electronic cigarette reports the following product information:

    - a list of ingredients (including additives);
    - literature review of the safety of the product's ingredients as well as other assessments of health risk conducted to date, if available;
    - a list of electronic cigarette components;
    - information on the level of nicotine in the product;
    - a list of properties and principles of the electronic cigarette's operation;
    - a description of manufacturing and processing methods; and
    - a sample of current or proposed labeling.

    Lorillard believes that industry can assist the Agency in collecting information about electronic cigarettes by submitting these confidential reports, which will in turn enhance the Agency's understanding of electronic cigarettes and support responsible and scientifically sound regulatory decision-making.

[41] *See* 79 Fed. Reg. at 23148 ("Because e-cigarettes are not currently subject to FDA jurisdiction (unless they are marketed for therapeutic purposes), FDA currently lacks the authority to collect vital information about these products. Deeming would allow us to collect information . . . .").

[42] The information required in this report could mirror the information required by European regulatory authorities for electronic cigarette manufacturers.

- **Establish GMPs.** Second, FDA could undertake several measures to better ensure consistency and safety in the electronic cigarette market. For example, FDA could develop GMPs for electronic cigarettes. These GMPs should focus specifically on the properties of electronic cigarettes. Lorillard strongly believes that these GMPs should be electronic-cigarette specific, given the substantial differences between electronic cigarettes products and conventional cigarettes. Lorillard believes that the creation of electronic cigarette GMPs would address many of the concerns that FDA expressed about these products in the preamble to the Proposed Deeming Regulation, as well as in its earlier report on electronic cigarettes, such as quality and consistency issues.[43]

- **Create a list of "banned" substances**. Third, FDA could define exposure limits for certain substances (such as DEG and heavy metals), above which these substances would be prohibited in electronic cigarettes. FDA could also undertake to establish recommendations or regulations regarding child-proof and tamper-resistant standards for the nicotine solution used in electronic cigarettes. Lorillard supports FDA's implementation of all of these quality-control measures, which the company believes will give FDA substantial authority in the near term to bring consistency to the electronic-cigarette marketplace and to address those electronic cigarettes that pose a threat to the public health due to insufficient quality and consistency.

C. Developing the Scientific Prerequisites Necessary to Implement other Aspects of the FDCA

There are many aspects of the FDCA, like those described above, that FDA can implement for electronic cigarettes either immediately or relatively quickly, without the need for further scientific development. Other provisions of the FDCA, however, cannot be implemented until certain scientific and methodological tools are established. Absent key scientific tools -- such as validated testing methodologies to compare electronic cigarettes and to measure electronic cigarette HPHCs -- FDA cannot meaningfully implement certain aspects of the FDCA, including the premarket review and HPHC reporting requirements. Accordingly, FDA should undertake a collaborative effort together with industry, academia and the public health community to increase the Agency's scientific understanding of electronic cigarettes to allow the Agency to implement the HPHC reporting and premarket review requirements of the FDCA. As FDA undertakes this process, it should exercise enforcement discretion not to require premarket review or HPHC reporting until the Agency has a sufficient scientific basis for implementing those provisions of the FDCA with respect to electronic cigarettes.

[43] Memorandum from B.J. Westenberger, Deputy Director, CDER/OPS/OTR, Division of Pharmaceutical Analysis, to Michael Levy, Supervisor Regulatory Counsel, CDER, Office of Compliance, Division of New Drugs and Labeling Compliance regarding evaluation of e-cigarettes (May 4, 2009), *available at* http://www.fda.gov/downloads/drugs/scienceresearch/ucm173250.pdf.

1. Scientific process for developing a list of electronic cigarette HPHCs

Given the substantial differences between conventional tobacco products and electronic cigarettes, the Agency should establish an HPHC list specific to electronic cigarettes before implementing the HPHC reporting requirements of Section 904(a)(3) of the FDCA. The Agency's process for developing the HPHC list for conventional tobacco products did not include (and could not have included) an analysis of electronic cigarette HPHCs because such products were not deemed to be under FDA's jurisdiction at the time that list was created. To establish the electronic cigarette HPHC list, the Agency should undertake the following steps, which mirror the steps that FDA undertook to establish the HPHC list for conventional tobacco products:

- Request written submission by interested parties of data and information on electronic cigarette HPHCs and testing methods available to measure these HPHCs;

- Organize public workshops with stakeholders to exchange information about the state of science regarding testing methods and HPHC content in electronic cigarettes;

- Establish a subcommittee of TPSAC to review this information and make preliminary recommendations on electronic cigarette HPHCs and corresponding HPHC testing methods that exist or should be developed;

- Empanel a public meeting of TPSAC to deliberate on the recommendations of the subcommittee;

- Consider TPSAC's recommendations for electronic cigarette HPHCs and HPHC testing methodologies and then publish a proposed list of HPHCs in the Federal Register for public comment;

- Publish a final list of electronic cigarette HPHCs in the Federal Register; and

- Provide for a reasonable compliance period for electronic cigarette manufacturers to undertake to test for and report on HPHC content to FDA, taking into consideration the number of brands and sub-brands on the market and the time commitment and laboratory capacity to conduct such testing.

2. Scientific process for developing analytical methods for evaluating electronic cigarettes

FDA should also undertake a public process to establish standard and validated analytical methods for evaluating electronic cigarettes. At present, there are no standardized or validated methodologies to compare one electronic cigarette to another, nor are there any methodologies to allow FDA to compare electronic cigarettes to conventional cigarettes or to other tobacco products. Filling this gap is fundamental to the ability of FDA's ability to implement premarket review of electronic cigarettes. In contrast to electronic cigarettes, there are fully validated

methodologies to allow for a standardized analysis of conventional cigarettes. These methodologies include (but are not limited to):

- ISO standard 3008:2008
- Canadian Intense

No such methodologies exist for electronic cigarettes and the methods described above cannot be applied to electronic cigarettes.

No longitudinal surveys or other reliable data exist to evaluate population-level usage patterns and effects of electronic cigarettes. Again, such sources of data are critical to implementation of premarket review under Section 910 of the FDCA. With conventional cigarettes, although not longitudinal, numerous databases and surveys track usage patterns and user demographics. These include (but are not limited to):

- National Survey on Drug Use and Health (NSDUH): provides national and state level data on use of tobacco.
- Tobacco Use Supplement to Current Population Survey (CPS-TUS): National Cancer Institute-sponsored survey of tobacco use that has been administered for several decades.
- National Youth Smoking Cessation Survey (NYSCS): A two-year longitudinal telephone study of adolescent and young cigarette smokers (age 16-24).

Again, none of these sources are likely to track electronic cigarette use effectively, even on a cross-sectional basis. Developing reliable data for electronic cigarettes, particularly longitudinal data, will take years.

Without these analytical methods and data sources, manufacturers cannot compile the necessary data to support any type of premarket application. Nor could FDA undertake to apply the premarket review criteria of either Section 905 or 910 of the FDCA. For example, Section 910 requires that the Agency deny approval of a PMTA if the applicant has not shown that permitting the electronic cigarette to be marketed would be appropriate for the public health.[44] Without standardized and validated methodologies to evaluate the public health risks and benefits of an electronic cigarette, FDA cannot make this required determination; nor can an applicant compile data to support this required showing. Similarly, FDA will be unable to evaluate a Section 905(j) substantial equivalence report without methodologies designed to allow the Agency to compare a proposed electronic cigarette to a cited predicate.

To fill these gaps in FDA's scientific understanding, Lorillard proposes that FDA initiate a public process to develop the scientific methodologies necessary for evaluating electronic cigarettes. This process will require a substantial effort on the part of the Agency, industry and

[44] FDCA § 910(c)(2)(A).

other interested parties, but Lorillard believes that a transparent public process for developing these methodologies is in the best interest of the public health. As it has done with other critical public health issues, FDA should begin this process by setting up public workshops to allow all stakeholders to share views and information about how such methodologies and data sources should be established.

As the Agency undertakes these necessary steps, it should exercise enforcement discretion over electronic cigarettes for certain aspects of the FDCA, including the HPHC reporting requirements of Section 904 and the premarket review requirements of Section 910 of the FDCA. Exercising enforcement discretion while analytical methods are developed to measure electronic cigarette HPHCs and while FDA establishes a list of electronic cigarette HPHCs is consistent with the Agency's implementation of these requirements for conventional tobacco product HPHC reporting.[45] Further, exercising enforcement discretion over the premarket review requirements until these scientific gaps are filled is consistent with the phased implementation of the premarket review requirements for traditional tobacco products.

D. Implementation of the Premarket Review Regime for Electronic Cigarettes

Once FDA has developed a robust scientific understanding of electronic cigarettes, the Agency can apply the premarket review provisions of the FDCA to these products. FDA can do so by announcing that it will no longer exercise enforcement discretion after a certain date. Manufacturers of electronic cigarettes would then need to submit premarket applications subject to the issues discussed below, after a reasonable compliance period, for their products to remain on the market after that date. Of course, FDA must provide manufacturers with sufficient time to develop premarket applications, which could take two or more years, depending on the data requirements demanded by the Agency. Accordingly, FDA should set a compliance date for premarket applications at least two and possibly more, years after it announces its intent to no longer exercise enforcement discretion over the premarket review requirements.

In applying the premarket pathways of the statute, FDA should consider the unique characteristics and properties of electronic cigarettes and the recent emergence of the product category. FDA's interpretation of the statutory requirements for premarket review of conventional cigarettes and the data requirements for these applications are not workable for electronic cigarette premarket applications. Nor is the level of data FDA requires for conventional cigarettes commensurate with the risk profile of electronic cigarettes. FDA should therefore establish a premarket review system workable for electronic cigarettes. Doing so will foster innovation in this important area, to the benefit of the public health.

To accomplish these goals, Lorillard recommends that FDA do the following:

[45] *See* Draft HPHC Reporting Guidance, *supra* note 38, at 3, 6 (exercising enforcement discretion for certain small tobacco product manufacturers; choosing to require reporting only for HPHCs with validated testing methods).

- Exercise enforcement discretion not to require premarket review for electronic cigarettes on the market before the effective date of the final deeming regulation;

- Allow the substantial equivalence pathway of Section 905(j) to be available to electronic cigarettes by permitting all electronic cigarettes on the market before the effective date of the final deeming regulation to serve as predicates;

- Establish clear requirements for substantial equivalence that focus on the e-vapor produced by the subject and predicate electronic cigarettes;

- Alternatively, FDA could permit the use of Section 905(j) by establishing a monograph-like system that allows new electronic cigarettes to be compared to a "model" electronic cigarette;

- For PMTAs, FDA should issue an electronic cigarette specific guidance to clarify the requirements for electronic cigarette PMTAs;

- FDA should allow manufacturers to obtain PMTA approvals based on a limited dataset coupled with commitments to collect and report post-market data; and

- FDA should establish a streamlined procedure to permit supplemental PMTA approvals for minor or moderate modifications of electronic cigarettes that do not affect the e-vapor delivered to the consumer.

Each of these issues will be discussed in turn.

1. FDA Should Exercise Enforcement Discretion over Electronic Cigarettes on the Market before the Final Deeming Regulation Becomes Effective

In determining which electronic cigarettes must undergo premarket review, the Agency should exercise enforcement discretion over electronic cigarettes on the market at the time of the effective date of the final deeming regulation. As FDA recognizes, if the Agency enforces the current grandfather date of February 15, 2007, then it will likely prevent electronic cigarettes from utilizing certain existing premarket pathways available to other tobacco products.[46] FDA has specifically asked interested persons to comment on other means of applying the substantial equivalence pathway to deemed products, like electronic cigarettes, that would likely be unable to use this pathway if the statutory grandfather date is enforced.[47]

Whether a product is considered a "new tobacco product" that must undergo FDA review in either the substantial equivalence pathway or PMTA pathway turns on whether the product is considered a "new tobacco product" as defined in the FDCA. A "new tobacco product" is "any

[46] 79 Fed. Reg. at 23144.

[47] *Id.* at 23144.

tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007."[48]

If a product was commercially marketed as of February 15, 2007, then it is not a new tobacco product and is considered "grandfathered."[49] Grandfathered products may stay on the market without seeking premarket review from FDA. Conversely, products that do not qualify as grandfathered products but are instead considered "new tobacco products" must undergo premarket review and, unless exempt, receive either a substantial equivalence order or PMTA order from FDA before a manufacturer may market the product. To obtain a substantial equivalence order specifically, a manufacturer must show that its electronic cigarette is substantially equivalent to a predicate electronic cigarette, which must be an electronic cigarette on the market as of the February 15, 2007 grandfather date.

Congress did not address electronic cigarettes when it enacted the FSPTCA. As FDA recognizes, very few, if any, electronic cigarettes, existed in the United States as of the February 15, 2007 grandfather date.[50] Even if there were electronic cigarettes on the market as of February 15, 2007, they have undergone numerous changes and improvements since that time. For example, changes to electronic cigarettes over the intervening years include: (1) replacing propylene glycol with vegetable glycerin, (2) removing the heating element contact with cotton to prevent avenues for leaching; (3) improving battery management to help prevent failures and overheating; (4) improving the monitoring and assessments of factories, materials, nicotine levels and cross-contamination; and (5) expanding the use of ingredients formulated in the United States.

As a result, if FDA applying the February 15, 2007 grandfather date could have the effect of foreclosing the substantial equivalence pathway to electronic cigarettes altogether, thereby eliminating one of only two premarket pathways available to these products and forcing all electronic cigarettes into the PMTA pathway. Also, by requiring strict adherence to the FSPTCA, FDA's action would result in inferior and potentially more hazardous products remaining on the market, while removing electronic cigarettes that have improved in both technology and reduced harm potential.

When Congress enacted the FSPTCA, it could not have intended that a statutory pathway be wholly unavailable to an entire class of deemed tobacco products. To make the substantial equivalence pathway provided for in the FSPTCA available to electronic cigarettes, FDA should apply enforcement discretion over electronic cigarettes on the market at the time of the effective date of the final deeming regulation. Doing so will give effect to the FSPTCA as enacted and allow electronic cigarettes the same premarket review opportunities as conventional tobacco products.

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[48] FDCA § 910(a)(1)(A).

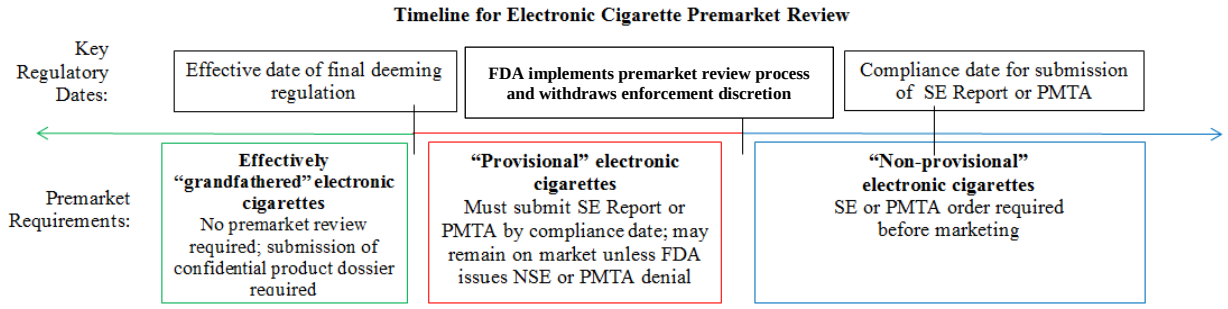
[49] 79 Fed. Reg. at 23174.

[50] *See, e.g.*, 79 Fed. Reg. at 23144, 23145, 23174.

If FDA exercises such enforcement discretion -- that is, to not require premarket review for electronic cigarettes on the market on or before the date when the final deeming regulation becomes effective -- then such products would in effect be considered grandfathered products for which no premarket review would be required unless the product changed after the grandfather date. To ensure that FDA is nonetheless able to regulate effectively grandfathered electronic cigarettes, Lorillard proposes that these products be subject to all of the requirements discussed above in Part 1.III.A.-B, including the submission of a confidential product report to the Agency and HPHC reporting once FDA applies that requirement to electronic cigarettes. This will allow FDA to understand and monitor these grandfathered products notwithstanding the fact that they do not need to undergo premarket review.[51]

For electronic cigarettes entering the market for the first time after the effective date of the final deeming regulation, FDA should establish a provisional process similar to the process established for implementing premarket review of traditional tobacco products. Under this system, electronic cigarettes that enter the market after the effective date of the final deeming can remain on the market until FDA implements the premarket review provisions of the FDCA, at which time manufacturers of provisional electronic cigarettes must submit the required premarket review application. Provisional electronic cigarettes that are the subject of a substantial equivalence report or PMTA could remain on the market unless and until FDA issues a not substantially equivalent (NSE) order or denies the PMTA. "Non-provisional" electronic cigarettes, *e.g.*, those electronic cigarettes introduced after the effective date of the final deeming regulation and after the date on which FDA withdraws its enforcement discretion over the premarket review of electronic cigarettes, must receive a substantial equivalence or PMTA order before they may be lawfully marketed, as reflected in the graphic below.

[51] For clarity, grandfathered products would include not only products actually on the market as of the time of the final deeming regulation, but also products commercially marketed before that date, whether or not the products are actually marketed as of the date of the final deeming regulation.



Lorillard believes that the Agency has ample discretion to apply this grandfather date to electronic cigarettes, contrary to FDA's position in the preamble to the Proposed Deeming Rule.[52] First, FDA has broad discretion under Section 701(a) of the FDCA to "promulgate regulations for the efficient enforcement of [the FDCA]" sufficient to allow FDA to exercise this type of enforcement discretion. Second, past Agency practice supports FDA's ability to exercise enforcement discretion on this issue. For example, FDA has previously exercised enforcement discretion to amend the grandfather date of the re-issued 1996 rule with respect to use of a trade or brand-name of a nontobacco product as the trade or brand-name for a cigarette or smokeless tobacco product. In the FSPTCA, Congress required FDA to reissue the final 1996 rule in identical form to the original rule, with certain enumerated exceptions expressly listed in the statute.[53] Congress did not list the grandfather date for the use of nontobacco brand-names as an exception to the requirement that the 1996 rule be reissued in its original form. Nonetheless, the Agency exercised its enforcement discretion and decided not to enforce the January 1, 1995 grandfather date for the use of a nontobacco brand name.[54] Specifically, FDA stated that it "intend[ed] to exercise its enforcement discretion" while considering the grandfather date issue.[55]

In fact, FDA has exercised enforcement discretion in its implementation of the FSPTCA. For example, FDA has allowed smokeless tobacco manufacturers to market their products without an FDA-approved rotational warning plan as required by the FSPTCA. In this instance, FDA was not able to review and approve, on a timely basis, the rotation plan submissions and permitted manufacturers who had submitted rotation plans in compliance with the FSPTCA to continue to market their products. Further, FDA suspended enforcement of tobacco health document submissions for documents created after December 31, 2009.

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[52] *See* 79 Fed. Reg. at 23174 (stating that the Agency does "not believe that we have the authority to alter or amend this grandfathering date" because the date is established by the statute).

[53] 21 U.S.C. § 387a-1.

[54] *See* CTP, Guidance for Industry and FDA Staff, Enforcement Policy Concerning Certain Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco (May 2010).

[55] *Id*. at 3-4.

FDA has also exercised its discretion to revise statutorily required dates in other contexts. For example, FDA exercised discretion with regard to delaying effective dates in the Food and Drug Administration Amendments Act ("FDAAA").[56] Section 417 of the FDAAA required FDA to establish a Reportable Food Registry via an electronic portal within one year of enactment.[57] FDA twice delayed the implementation of the Section 417 requirements due to issues that arose during implementation.[58] Other agencies have also exercised discretion with regard to statutorily mandated dates.[59] In particular, the Physician Payments Sunshine Act required certain entities to begin collecting data on January 1, 2012 and required the Centers for Medicare and Medicaid Services (CMS) to begin collecting the data from entities on March 31, 2013.[60] In the proposed and final rules, CMS delayed implementation of these statutory dates.[61]

2. FDA Should Enable Electronic Cigarette Manufacturers to Utilize the Substantial Equivalence Pathway

FDA should permit electronic cigarettes commercially marketed before the effective date of the final deeming regulation to serve as predicates. To use the substantial equivalence pathway, FDCA Section 910 requires a manufacturer to identify a predicate product that is substantially equivalent to the proposed new tobacco product and that was commercially marketed as of the specified grandfather date.[62] The manufacturer then submits a report establishing that its new tobacco product is substantially equivalent to the predicate product. To be considered substantially equivalent, a new tobacco product must have "the same characteristics as the predicate product" or "ha[ve] different characteristics" but the "product does not raise different questions of public health."[63]

To serve as a predicate product, a product must have been commercially marketed in the United States as of February 15, 2007.[64] For the reasons described above in Part 1.III.D., FDA should exercise enforcement discretion over electronic cigarettes commercially marketed before the date of the final deeming regulation and allow such products to serve as predicate electronic cigarettes. The availability of qualifying predicate products for electronic cigarettes is essential to the availability of the substantial equivalence pathway for the product category. If there are

[56] 73 Fed. Reg. 30405, 30405-30406 (May 27, 2008); 74 Fed. Reg. 27803, 2780-27804 (June 11, 2009).

[57] 21 U.S.C. § 350f.

[58] 73 Fed. Reg. at 30405-30406; 74 Fed. Reg. at 27804-27805.

[59] *See, e.g.*, 76 Fed. Reg. 78742, 78743 (Dec. 19, 2011); 78 Fed. Reg. 9458, 9459-9460 (Feb. 8, 2013).

[60] 42 U.S.C. § 1320a-7h.

[61] *See, e.g.*, 76 Fed. Reg. at 78742; 78 Fed. Reg. at 9459-9460.

[62] FDCA § 910(a)(2)(i).

[63] *Id.* § 910(a)(3)(A).

[64] *Id.* § 910(a)(2)(i).

no qualifying predicate products for electronic cigarettes, or if all of the qualifying predicate products are substantially different from currently marketed products, electronic cigarette manufacturers will likely be unable to use the substantial equivalence pathway.

To permit electronic cigarette manufacturers to effectively utilize the 905(j) pathway, FDA should exercise enforcement discretion over the requirements of Section 910 for products that can demonstrate substantial equivalence to an electronic cigarette commercially marketed before the effective date of the final deeming regulation. Stated another way, FDA should permit electronic cigarettes on the market prior to the effective date of the deeming regulation to serve as predicates for electronic cigarettes that require premarket review. If the Agency does this, it will open the substantial equivalence pathway to electronic cigarette manufacturers.

FDA should clarify the requirements for substantial equivalence for electronic cigarettes, focusing on the e-vapor. After making the substantial equivalence pathway available to electronic cigarettes, FDA should publish guidance on how the Agency will determine whether one electronic cigarette is substantially equivalent to a predicate product. These substantial equivalence parameters should focus on the deliveries to the consumer from the vapor emitted from an electronic cigarette (e-vapor). The electronic cigarette e-vapor deliveries are the most important characteristic for FDA to evaluate in determining whether a new electronic cigarette raises different questions of public health than its cited predicate.

Alternatively, FDA could implement a monograph approach for electronic cigarettes. If FDA declines to adopt a later grandfather date than February 15, 2007 for electronic cigarettes, the traditional substantial equivalence pathway likely will not be available to electronic cigarettes. The absence of a substantial equivalence pathway would require all electronic cigarette manufacturers to submit PMTAs for all of their electronic cigarettes. The submission of PMTAs for each product would impose an overwhelming burden on manufacturers because of the extensive data requirements that FDA has established for conventional cigarette PMTAs. In addition, the absence of a substantial equivalence pathway will impose an overwhelming burden on FDA to review all of these PMTAs.

Should the Agency decide to enforce the statutory grandfather date, then the Agency should adopt an alternative substantial equivalence pathway for electronic cigarettes. To do so, Lorillard recommends that FDA implement a "monograph"-like system that would allow electronic cigarette manufacturers to utilize the substantial equivalence pathway. The monograph product would serve as a type of qualifying predicate product and it could be used to establish standards for electronic cigarettes. The monograph system would provide electronic cigarette manufacturers with a feasible predicate product, which would otherwise likely be unavailable if FDA enforces the February 15, 2007 grandfather date.

To address the unavailability of predicates, FDA could establish a monograph approach to regulating electronic cigarettes. The monograph system would involve FDA establishing a "model" electronic cigarette that would provide the baseline for electronic cigarettes. Lorillard recommends that the model electronic cigarette adopted by FDA focus on the HPHCs in e-vapor. The emphasis on the electronic cigarette's e-vapor and e-liquid would enable FDA to prioritize review of the electronic cigarette characteristics most relevant to the public health.

FDA could use FDCA Section 907 as a guide for developing its model electronic cigarettes for the monograph system. Specifically, FDA could incorporate the product standards outlined in Section 907 when establishing the characteristics of the model electronic cigarette and when selecting the requirements that electronic cigarettes would be required to satisfy to meet the substantial equivalence threshold. Section 907 outlines tobacco product standards and their content, accordingly, the statutory considerations in Section 907 would provide meaningful guidance for determining the model electronic cigarette.[65]

The proposed monograph system would allow electronic cigarette manufacturers to identify the model cigarette as a predicate to which to compare their products. If a manufacturer can show that its electronic cigarette is "substantially equivalent" to the model established by FDA, *e.g.*, the proposed product delivers less than or equal to the e-vapor delivery standards established for the model electronic cigarette, then FDA could issue a substantial equivalence order. Alternatively, if a substantial equivalence report fails to demonstrate substantial equivalence to the model electronic cigarette, then FDA could issue an NSE order for the proposed product.

3. FDA Should Streamline the PMTA Pathway for Electronic Cigarettes to Encourage Innovation

The PMTA pathway is a pathway available for new tobacco products that are not substantially equivalent to a qualifying predicate product or are otherwise not exempt from the premarket requirements. FDCA Section 910 requires a manufacturer to submit a PMTA and receive a marketing authorization order before its new tobacco product enters the market.[66] Section 910 outlines extensive requirements for the contents of a PMTA. A PMTA must include, among other things, "full reports" on investigations that show the "health risks of such tobacco product" and whether the tobacco product "presents less risk than other tobacco products."[67] The PMTA must support a finding that the tobacco product "is appropriate for the protection of the public health."[68]

FDA previously issued a draft guidance concerning the submission of PMTAs, which provides information regarding the PMTA submission process and the contents of a PMTA.[69] In the PMTA Guidance, FDA outlines the studies required for FDA to find that a tobacco product is appropriate for the public health, including product chemistry studies, clinical studies and

[65] *See id.* § 907.

[66] *Id.* § 910(a)(2).

[67] *Id.* § 910(b).

[68] *Id.* § 910(c)(4).

[69] CTP, Guidance for Industry, Applications for Premarket Review of New Tobacco Products (Sept. 2011) (PMTA Guidance).

nonclinical studies.[70] The PMTA Guidance also requires information regarding the health risks posed by a tobacco product to the individual smoker and to the population as a whole.[71]

To encourage the development of electronic cigarettes, FDA should issue a separate guidance regarding these PMTA requirements for electronic cigarettes. Lorillard believes that the differences between electronic cigarettes and traditional combustible cigarettes necessitate different PMTA requirements. Electronic cigarettes and conventional cigarettes are virtually incomparable; the studies required for approval of a PMTA should reflect the differences between them. The study types and designs required for issuance of a PMTA order should vary depending of the tobacco product seeking approval.

When establishing the guidance for electronic cigarette PMTAs, Lorillard urges that FDA adopt a standard for issuing electronic cigarette PMTA orders based on a finding that the new tobacco product is no more hazardous than currently marketed tobacco products. Lorillard believes that FDA should encourage the introduction of new tobacco products, like electronic cigarettes, into the marketplace if those products potentially diminish risks to smokers, even when those products do not satisfy the standards for an MRTP. Any product that could potentially reduce the risks associated with smoking conventional cigarettes could benefit the public health, and FDA should not discourage the development and introduction of such products into the market.

If FDA issues a guidance specifically concerning electronic cigarettes, Lorillard urges FDA to consider the available and currently unavailable data regarding such products when establishing the required content for a PMTA. The PMTA Guidance states that a PMTA should provide information regarding "whether such tobacco product presents less risk than other tobacco products."[72] Lorillard recommends that FDA allow applicants to utilize the published scientific understanding regarding electronic cigarettes as harm-reduction products to support a PMTA. Lorillard believes that manufacturers should be permitted to rely on the published scientific understanding regarding the relative risks of electronic cigarettes and the use of electronic cigarettes for harm reduction as compared to conventional cigarettes.

To address the recent emergence of electronic cigarettes as a product category and the limited nature of the long-term data available about the product category, Lorillard also recommends that FDA allow the issuance of a PMTA order based on the data submitted in the PMTA and post-marketing commitments from the manufacturer to conduct long-term studies regarding the effects of electronic cigarettes. FDA and the manufacturer could agree to certain long-term studies regarding the product as a condition of the product's approval and the manufacturer could submit the data to FDA after it is developed in the time period agreed to by the applicant and FDA. Lorillard believes that such an agreement would provide FDA with the necessary data regarding the long-term effects of electronic cigarettes while simultaneously permitting these important products to enter the market.

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[70] *Id*. at 16-20.

[71] *Id*. at 16-17.

[72] *Id*. at 9.

4. FDA Should Establish a PMTA Supplement Process to Encourage Electronic Cigarette Innovation

In applying the PMTA process to electronic cigarettes, FDA should consider the continually evolving nature of this product category. To encourage innovation, FDA should create a PMTA supplement process that allows manufacturers to improve their electronic cigarettes without having to undertake the burdensome task of compiling a full PMTA for every product improvement. Establishing this supplement process would be consistent with the supplemental application processes FDA has created for new drug application (NDA) holders and premarket approval (PMA) supplement regimes codified in 21 C.F.R. §§ 314.70 and 814.39.

For example, FDA could categorize minor, moderate and major changes to electronic cigarettes and establish the corresponding amount and type of data and information that must be submitted in a PMTA supplement for each type of change. Any change that does not affect the e-vapor deliveries of the product, *e.g.*, labeling changes, should be considered at most a moderate change for which a full PMTA is not required. The level of data required in each PMTA supplement for minor and moderate changes should be significantly less burdensome than the data required for a full PMTA.

This approach is logical and consistent with how FDA implemented the premarket approval requirements for drugs and medical devices, which allow such manufacturers to make certain changes to an approved product based on a substantially less burdensome application than the original marketing application.[73] Further, FDA's review of these supplemental PMTAs would take less time than review of the original PMTA required, allowing innovative products to reach the market sooner and at a lower cost to Agency resources.

E. FDA Should Permit the Continued Availability of Flavored Electronic Cigarettes

In the preamble to the proposed deeming regulation, FDA requested comments on the effect of flavors used in tobacco products, including electronic cigarettes. FDA's preamble, as well as much of the commentary about flavors in the press, have assumed that flavors in electronic cigarettes necessarily appeal to youth. But, as discussed in Part 2.VI.B of these comments, the current body of science does not support the conclusion that flavors in electronic cigarettes have an effect on appeal or adoption of electronic cigarettes by youth. Moreover, it is axiomatic that adults also might like flavors (indeed, consider the wide array of flavored beverages that are consumed everyday by adult consumers). Accordingly, the assumption that flavors in electronic cigarettes are necessarily intended only to attract youth, is flawed.

In addition, FDA should consider the potentially important role that flavors can play in harm reduction and conventional smoking cessation. Flavors may play an important role in transitioning conventional cigarette smokers to potentially less harmful electronic cigarettes. For

[73] *See, e.g.*, 21 C.F.R. §§ 314.70 (establishing the NDA supplement process); 814.39 (establishing the PMA supplement process).

example, users of flavored electronic cigarettes may be less likely to engage in dual use or less likely to revert to smoking conventional cigarettes because of a preference for the flavor of electronic cigarettes.

CONCLUSION

As described above, electronic cigarettes hold the promise of aligning the interests of the tobacco industry, public health advocates, and regulatory agencies such as FDA to meaningfully address the negative health effects of traditional tobacco products. Electronic cigarettes present an unprecedented opportunity to move consumers of traditional tobacco products to lower-risk alternatives. The product category is evolving and expanding rapidly, as existing smokers move to electronic cigarettes in increasing numbers.

FDA's regulation of this product category, therefore, should be appropriately calibrated to the risks and opportunities presented by electronic cigarettes. Moreover, FDA should not unduly impose requirements, such as premarket review and HPHC reporting, without the scientific prerequisites necessary for meaningful regulation. A calibrated regulatory system implemented in stages will both advance the public health and allow the agency to develop the science needed for an appropriate regulatory system.

Accordingly, Lorillard urges FDA to consider and adopt the suggested regulatory approaches described above. Lorillard stands ready to work collaboratively with FDA to advance the science surrounding electronic cigarettes and to implement a thoughtful regulatory system for this product category.

PART 2: COMMENTS ON THE SCIENTIFIC ISSUES ASSOCIATED WITH ELECTRONIC CIGARETTES

In this Part of Lorillard's comments, Lorillard presents a comprehensive discussion of the science available to date on electronic cigarettes.[74] Although the scientific understanding of electronic cigarettes is still emerging, the data to date suggest that electronic cigarettes have a vastly different safety profile than conventional cigarettes. Available information indicates that electronic cigarettes: (1) do not promote initiation of smoking; (2) help people reduce smoking; and (3) may help some people quit smoking. These early data suggest that electronic cigarettes have significant potential to reduce harm at both the individual and population levels.[75]

In its preamble to the Proposed Deeming Regulation, FDA "recognizes that there may be the potential for varying levels of harm and negative effects on public health for different categories of tobacco products."[76] Furthermore, FDA notes that

> while all tobacco products are potentially harmful and potentially addictive, different categories of tobacco products may have the potential for varying effects on public health. For example, some have advanced views that certain new noncombustible tobacco products (such as electronic cigarettes) may be less hazardous, at least in certain respects, than combustible products given the carcinogens in smoke and the dangers of secondhand smoke.[77]

FDA has therefore requested data on the potential effect of electronic cigarettes on the public health. Specifically, FDA has raised questions regarding the following topics:

- Chemical and toxicological laboratory analyses,
- Health effects,

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[74] Lorillard's comments generally do not cite research available only in abstract form for several reasons, including lack of peer review and insufficient detail. However, a few abstracts *are* cited in this section because of the importance of safety information and the relative limited number of published studies.

[75] A very recent literature review by Hajek et al. (2014) supports Lorillard's comments. These authors found that long-term use of electronic cigarettes is likely to be much less, if at all, harmful to users and bystanders than conventional cigarettes. They also found that electronic cigarettes are associated with smoking reduction and there is little evidence that they deter smokers from quitting. Finally, they reported that regular use of electronic cigarettes by nonsmokers is rare and no migration from electronic cigarettes to smoking has been documented. With respect to regulation of electronic cigarettes, Hajek et al. concluded that "regulatory decisions will provide the greatest public health benefit when they are proportional, based on evidence and incorporate a rational appraisal of the likely risks and benefits."

[76] 79 Fed. Reg. at 23144.

[77] *Id*. at 23152.

- Addiction and dependence,
- Smoking reduction and cessation,
- Patterns of use, especially dual use,
- Youth issues, and
- Marketing and consumer perceptions of risk.

The following sections address FDA's scientific comments and questions.

I. Chemical and Toxicological Laboratory Analyses

In the preamble to the Proposed Deeming regulation, FDA discusses the potential presence of toxicants in electronic cigarette aerosol and exhaled electronic cigarette vapor.[78] To address FDA's discussion and questions regarding these issues, Lorillard summarizes below the existing information on the chemistry and toxicology of electronic cigarette e-liquids and aerosols, including the aerosol-forming excipients in electronic cigarettes as well as potentially hazardous compounds found in these products (TSNAs, PAHs, carbonyls, metals, volatile organic compounds (VOCs), particulate matter). This section also addresses the data regarding the nicotine levels in electronic cigarettes as well as the data available regarding the existence of potential toxicants in exhaled electronic cigarette vapor.

When interpreting the available chemical and toxicological data for electronic cigarettes, several limiting factors must be considered. First, electronic cigarettes are rapidly evolving; consequently, the composition of samples obtained years ago does not necessarily reflect the composition of products on the market today. Further, drawing generalized conclusions about the chemistry and toxicology of electronic cigarette liquids and aerosols is difficult given the large number of brands (466 according to a recent study by Zhu et al. 2014) and varieties of electronic cigarettes sold. Finally, there are no standardized protocols for creating electronic cigarette aerosol or for measuring potentially harmful constituents in either e-liquids or aerosols.

Although some of the data summarized below reveal the existence of potentially harmful constituents in e-liquids or aerosols, most of these data show that the levels of these toxicants are low. Toxicant levels in electronic cigarettes are usually significantly lower than those found in conventional cigarette smoke and estimated exposures to toxicants from electronic cigarette use are typically below those specified as American Conference of Industrial Hygienists (ACGIH) Threshold Limit Values (TLV) (Burstyn 2014). Although TLVs are intended to provide a basis for inhalation safety for workplaces rather than for general populations, the TLVs available for the relatively few toxicants that have been reported in electronic cigarette e-liquids and aerosols provide broad points of reference as an initial evaluation of exposures from active or passive exposure to electronic cigarette aerosols. A review of the available literature by Burstyn (2014)

[78] 79 Fed. Reg. at 23157.

calculated exposure values for potentially harmful constituents and compared them to TLVs. The vast majority of predicted exposures are <<1% of TLV, while predicted exposures to certain carbonyls are typically <5% TLV. Burstyn concludes that the mixture of contaminants in electronic cigarettes does not pose a risk to health and that exposure to bystanders poses no apparent concern.

A few studies have compared electronic cigarette related indoor air levels of respirable airborne particulates (PM2.5) and volatile compounds such as formaldehyde to the guidance limits recommended as 24-hour averages for indoor air by the World Health Organization (WHO 2010). The interpretation of such comparisons is hampered by the fundamental chemical and physical differences between the rapidly-evaporating liquid droplet aerosols produced by electronic cigarettes and the stable particulate aerosols that are the subject of the WHO indoor air guidance limits for PM2.5 of 24-hr average of 25 $\mu g/m^3$ (WHO 2005).

Toxicology studies generally show that some electronic cigarette samples have low levels of cytotoxicity in certain cell lines, but they are substantially less cytotoxic than conventional cigarette smoke. The limited *in vitro* information on inflammatory, mutagenic and genotoxic properties of electronic cigarette shows few effects. The relatively few studies to date on room air emissions and "passive vaping" are entirely consistent with a very low order of bystander exposure and negligible risks from electronic cigarette usage relative to the exposures that may result from secondhand/passive cigarette smoking.

A. Chemical Composition of Electronic Cigarette E-Liquids and Aerosols

This section summarizes studies on the chemical composition of electronic cigarette cartridges, e-liquids and inhaled aerosol, with a focus on the presence of propylene glycol and vegetable glycerin (aerosol-forming excipients), TSNAs, PAHs, carbonyls, metals, VOCs, nicotine and particulate matter.[79] With regard to terminology, the term "refill liquids" is used to refer to e-liquids that are added by the consumer into the electronic cigarette, while the term "cartridge" refers to the e-liquids in a prefilled cartridge. When a study author does not specify whether the liquid is a refill liquid or a prefilled cartridge, the term e-liquid is used. Generally, comparisons of the chemical composition of electronic cigarettes are made to conventional cigarettes or nicotine replacement therapies (NRTs) rather than providing absolute concentration values because studies use varying methods and report their results in different units.

1. Major electronic cigarette aerosol-forming excipients are safe and nontoxic

The two aerosol-forming excipients most commonly found in e-liquids are propylene glycol (PG) and glycerol (commonly vegetable glycerin or VG). Both compounds have well-established safety profiles and are considered to be nontoxic. Detailed safety profiles of PG and

[79] Some studies also examined constituents in indoor air after vaping; these results will be discussed later in the section on passive vaping.

VG are described by Fowles et al. (2013) and SIDS (2012), respectively. Further, both Farsalinos et al. (2013a) and Bahl et al. (2012) reported that neither PG nor VG are cytotoxic, consistent with their widespread use in foods as well as in oral, topical, parenteral and inhalational therapeutic formulations. PG is often used as a solvent in aerosolized drug delivery systems such as metered-dose inhalers and nebulizers (Schripp et al. 2013 citing Montharu et al. 2010). Glycerin is used less in such inhalers due to its poorer solvent properties, but is listed along with ethyl alcohol as an excipient in at least one asthma inhaler formulation (Clenil Modulite) that is marketed in the United Kingdom (UK) (electronic Medicines Compendium 2014).

A 2009 study by FDA (Westenberger 2009) has been cited frequently for raising concerns after finding diethylene glycol (DEG) in a single electronic cigarette cartridge. The presence of DEG is of concern given its potential for toxicity (Schep et al. 2009). However, at least five subsequent studies that looked for DEG in e-liquids failed to detect the chemical in any sample (Etter et al. 2013, Monakhova et al. 2014, McAuley et al. 2012, Lauterbach et al. 2012, Foster et al. 2013). Thus, FDA's early finding is likely not representative of the current market and may have been a result of product contamination.

Several published reports have described modest *in vitro* cytotoxic properties for e-liquids and aerosols that the authors attributed to certain flavoring ingredients, including some derived from extracted tobacco (Bahl et al. 2012, Farsalinos et al. 2013a, Romanga et al. 2013). Given the very low cytotoxicity of the other major e-liquid ingredients (water, VG, PG and nicotine), it is not surprising that flavoring ingredients appeared to account for the majority of the effects reported. In all instances where such comparisons have been made, the cytotoxicity of e-liquids and aerosols were reported to be markedly lower than that of conventional cigarette smoke extracts tested under comparable conditions.

2. Electronic cigarettes as a source of tobacco-specific nitrosamines (TSNAs)

FDA has expressed concern about TSNAs in electronic cigarettes, though the Agency agrees that the levels reported to date have been low and are "similar to those in nicotine replacement therapies."[80]

To date, nine studies have reported on TSNAs in electronic cigarette cartridges, refill liquids and aerosols; the results of these studies are summarized in Appendix 1. The evidence shows that TSNAs are present in some electronic cigarettes at levels from 8 to 380 times lower than in conventional cigarettes. Evidence from Laugesen (2008b) indicates that the levels of TSNAs are more comparable to levels in a nicotine medicinal patch and are 200 times lower than in Swedish snuff. Laugesen (2008b) also reported that e-liquids with a higher concentration of nicotine contained more TSNAs, an expected finding considering TSNAs are derived from nicotine in tobacco. The data show that TSNAs are present in some electronic cigarette aerosols at

[80] 79 Fed. Reg. at 23157.

significantly lower concentrations than in conventional tobacco cigarettes and at levels more comparable to a nicotine medicinal patch.

3. Electronic cigarettes as a source of polycyclic aromatic hydrocarbons

FDA has expressed concerns about the presence of polycyclic aromatic hydrocarbons (PAHs), citing a study that found "e-cigarettes increased indoor air levels of polycyclic aromatic hydrocarbons."[81] The presence of PAHs is concerning because many are known or suspected carcinogens. In addition, chronic exposure to PAHs has been linked to negative effects on the pulmonary, gastrointestinal, renal and dermatologic systems (ATSDR 2014).

To date, there are five studies that address electronic cigarettes as a source of PAHs, the results of which are summarized in Appendix 2. These studies show that the level of PAHs in electronic cigarettes ranged from not detected to 56 times lower than in conventional cigarette smoke. Only one study (McAuley et al. 2012) reported that PAH levels in some samples tested exceeded those in conventional cigarette smoke; however, the values obtained were extremely variable and this likely reflects quality control or analytical chemistry issues. Most data show that the levels of PAHs in electronic cigarettes are significantly lower than those found in conventional cigarettes.

4. Electronic cigarettes as a source of carbonyls

FDA is concerned about carbonyls in electronic cigarettes because they can be cytotoxic, carcinogenic and irritating and also can cause pulmonary emphysema and dermatitis (Goniewicz et al. 2013b). Specifically, FDA noted the presence of "toxic chemicals such as formaldehyde and acetaldehyde" in electronic cigarette cartridges and aerosol.[82]

There are 13 studies addressing electronic cigarettes as a source of carbonyls and the results of these studies are summarized in Appendix 3. To date, the evidence shows that carbonyl exposure from electronic cigarettes is much lower than from conventional cigarettes and may not differ from concentrations encountered from their ubiquitous presence in normal indoor air. Studies generally found that carbonyl levels in aerosols were 1.9 to 807 times lower than those in cigarette smoke. Shihadeh and Eissenberg (2013) and Kosmider et al. (2014) note that higher voltages and dripping liquid directly onto a heater surface produce greater amounts of carbonyls. The "dry puff" phenomenon described by Farsalinos et al. (2013a) is similarly associated with elevated levels of pyrolysis products in electronic cigarette aerosols when inadequate quantities of e-liquid are delivered to the heating element. The growing popularity of user-adjustable voltage and liquid feed models of electronic cigarettes may facilitate a greater understanding of the aerosol generation dynamics that could lead to further lowering of the levels of carbonyls in electronic cigarettes.

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[81] *Id.* It should be noted that although FDA cites both Schober et al. (2013) and Schripp et al. (2013) with respect to PAHs, Schripp et al. does not investigate those compounds.

[82] *Id.*

One clinical study, reported in an abstract by McRobbie et al. (2014), measured levels of an acrolein metabolite in vapers who switched from smoking cigarettes to electronic cigarettes. The study found that acrolein levels were significantly decreased in urine samples after four weeks of either complete or partial substitution of smoking with electronic cigarettes. The authors concluded that substituting electronic cigarettes for conventional cigarettes significantly reduced acrolein exposure. Similar studies are the next logical steps to assess user exposure to these constituents.

5. Electronic cigarettes as a source of metals

FDA has expressed concerns about metals in electronic cigarette liquids and aerosols, specifically citing studies that found "lead, nickel and chromium."[83] The presence of metals in conventional cigarette smoke is well documented and many are known to be carcinogenic or neurotoxic, or to cause other harmful effects (Bernhard et al. 2005).

While more data are needed concerning electronic cigarettes as a source of metal exposure, much of the data indicate that if metals are present, they are present at levels significantly lower than in conventional cigarette smoke. Some data, however, do indicate a cause for concern. Approximately six studies address the presence of metals in electronic cigarette cartridges and aerosol. The results of these studies are summarized in Appendix 4. All but two of these studies found low concentrations of metals that were comparable to the levels in a nicotine inhaler or 17 to 60 times lower than that from a conventional cigarette. In contrast, Williams et al. (2013) found substantial concentrations of metals in the aerosol and metal and silicate particles in the cartridge liquid of certain electronic cigarettes. These metal and silicate particles are likely the result of quality control, design, or materials problems that result in corrosion of metallic components in contact with e-liquids, or leaching of metals from stainless steel components or the nickel-chromium alloy used in the heating elements of many electronic cigarettes. Some product designs have solder joints in contact with e-liquids, which likely account for the tin compounds and particulates reported in the study. Another Williams study (2014) reported that eight metals were, in general, less abundant in electronic cigarette aerosols than conventional cigarette smoke, while 12 metals were more abundant in electronic cigarette aerosol than conventional cigarette smoke. Information on specific levels of metals was not provided in the abstract.

Four of the metals reported in this study (lead, chromium, nickel, copper) have specified Permissible Daily Exposure limits for inhalational drugs (USP 2013). Whereas certain electronic cigarette products sampled from the marketplace may have quality control or design issues that result in high or variable presence of metals relative to others, the findings reported by Williams et al. (2013) suggest that the daily metals exposures resulting from typical use of many of the leading, contemporary electronic cigarette products are below those specified by USP for inhalational drug products. Additional refinement of some electronic cigarette designs could further reduce the presence of inorganic contaminants in e-liquids and, potentially, in aerosols.

[83] *Id*.

6. Electronic Cigarettes as a source of volatile organic compounds

FDA has expressed concerns over the presence of VOCs in electronic cigarette liquid and aerosols. VOCs are a challenging category to summarize because there is no uniform definition of a VOC. The VOCs included in this analysis have a wide range of health effects, with some merely considered irritating and others considered carcinogenic. VOCs are found in both indoor and outdoor air samples.

Eight studies analyzed electronic cigarettes as a source of VOCs. The results of these studies are summarized in Appendix 5. Studies that compared electronic cigarettes to cigarette smoke generally found that the levels of VOCs were significantly lower for electronic cigarettes than conventional cigarettes (Lauterbach et al. 2012, McAuley et al. 2012) and sometimes the levels were indistinguishable from the blank sample (McAuley et al. 2012).

7. Nicotine levels in electronic cigarettes

FDA has noted that the "amount of nicotine . . . varies among brands"[84] and that "[r]esearchers have identified instances of poor quality control and significant variability in nicotine content when testing certain e-cigarette cartridges."[85] Lorillard fully supports reasonable nicotine-content limits in electronic cigarettes and the requirement that nicotine levels be accurately represented on product labeling. Lot-to-lot variability in nicotine or other ingredients should likewise be held within practical and technically achievable limits.

About a dozen studies have compared the amount of nicotine labeled on a cartridge or refill liquid to the actual nicotine content. Due to the large number of studies, Lorillard will note the overall results rather than discuss each individual study. While many studies report wide variation between the labeled amount and actual amount of nicotine (*e.g.*, Trehy et al. 2011, Goniewicz et al. 2013a, Goniewicz et al. 2013b), others have reported that labels were reasonably accurate (Etter et al. 2013). A recent study by Davis et al. (2014) reported analyses of numerous electronic cigarette refill fluids and reported that 35 of 54 liquids analyzed contained nicotine levels that differed by 10% or more from labeled concentrations, with 46 of 50 being in excess of labeled values. The authors noted some recent improvements in lot-to-lot consistency for some manufacturers, but also noted a need for further improvement. Voluntary industry standards for the accuracy of nicotine content and labeling and other measures of product consistency have recently been advanced by some industry trade associations (*e.g.*, American E-Liquid Manufacturing Standards Association (AEMSA), Electronic Cigarette Trade Association of Canada (ECTA)) and these could assist FDA in developing appropriate, industry-wide standards to ensure that labeled nicotine levels reflect measured nicotine concentrations.

Early analyses conducted by FDA (Westenberger 2009, Hadwiger et al. 2010, Trehy et al. 2011) found that nicotine was present in some samples of zero-nicotine e-liquids. For example, a recent analysis of nicotine in zero-nicotine e-liquids by Kubica et al. (2013) shows only trace

[84] *Id*. at 23155.

[85] *Id.* at 23157.

quantities present, with a maximum concentration of 338 μg/g liquid. Similarly, Davis et al. (2014) confirmed the absence of nicotine in 5 commercial products labeled as zero-nicotine refill liquids. It is entirely appropriate for FDA to enforce standards to ensure that electronic cigarette cartridges and refill liquids labeled as being nicotine-free should in fact contain no measurable nicotine.

Many studies have measured the amount of nicotine delivered in electronic cigarette aerosols. Authors have reported that the amount of nicotine in electronic cigarette aerosols is significantly lower than in conventional cigarette smoke (Laugesen 2009, McAuley et al. 2012, Lauterbach et al. 2012, Romagna et al. 2012, Czogala et al. 2013, Goniewicz et al. 2014a). Shihadeh and Eissenberg (2013) found that higher electronic cigarette voltage is related to greater nicotine delivery. Surprisingly, Goniewicz et al. (2014a) found that the variation of nicotine content of the cartridges has very little impact on the nicotine in the aerosol. Additional study in this area is necessary.

8. Electronic cigarettes as a source of particulate matter

Many researchers have investigated airborne particulate matter in electronic cigarette aerosol. Particle size of electronic cigarette aerosol is an important area of research because particle size determines whether a particular particle is respirable and whether it can be deposited in the lungs. The studies that investigate particulate matter generally refer to PM10, PM2.5 and PM1.0, particles with a diameter of less 10, 2.5 and 1.0 microns, respectively. PM2.5 is most generally taken as representing respirable airborne particulate matter. Generally, particulate matter is discussed in the context of ambient outdoor air pollution and the National Ambient Air Quality Standards are set by the EPA to provide public health protection. WHO concluded that its prior guideline for outdoor air particulate matter could be reasonably extended to indoor air exposures and so that guideline limit for PM2.5 of 25 $\mu g/m^3$ (for a 24-hour average) is commonly used as a point of reference (WHO 2005).

Czogala et al. (2013) showed that the PM2.5 concentration was seven times lower after vaping than after conventional cigarette smoking (151.7 $\mu g/m^3$ vs 819.3 $\mu g/m^3$). Schober et al. (2013) similarly found a mean PM2.5 concentration of 197 $\mu g/m^3$ after vaping. Though these values are higher than the recommended 25 $\mu g/m^3$, it is difficult to make a meaningful comparison since the WHO limit is a 24-hour average while these studies measured concentrations immediately after vaping. It should be noted that these particles appear to be much more transient than particles from conventional cigarette smoke, which makes measuring the particles and making realistic comparisons to air quality standards challenging. Czogala et al. (2013) measured the change in PM2.5 concentration and found that the particles from electronic cigarettes dissipated quickly. The authors note that although some studies suggest that electronic cigarette aerosol and secondhand smoke have comparable aerosol particle size distribution and deposition patterns, the "concentration of e-cigarette aerosol particles tends to decrease rapidly when diluted in air."

Several authors have performed studies to characterize the particles in electronic cigarette mainstream aerosols (Ingebrethsen et al. 2012, Fuoco et al. 2014, Zhang et al. 2013, Marini et al. 2014, Pelligrino et al. 2012, Williams et al. 2013, Rabinowitz and Leischow 2014). These studies were performed using a smoking machine and measured the particle number, average

particle diameter and overall particle size distribution. These studies mostly found respirable particles that would fall into the category of PM1.0, having a particle diameter of less than 1 micron. The study of Ingebrethsen et al. (2012) reported electronic cigarette aerosols to be slightly larger (250-450 nm), possibly due to the application of methods that were less affected by the rapid evaporation of the generated particles. All extant studies in this area are in broad agreement that electronic cigarette aerosol droplets are broadly similar in size to those in conventional cigarette smoke and would therefore be anticipated to be deposited and retained in the respiratory tract to a generally similar extent. It is possible that certain inhaled aerosol characteristics such as hygroscopic particle growth may be measurably different between the electronic cigarette aerosol and conventional cigarette smoke, but additional research is necessary to confirm any such differences. The studies are beginning to develop a particulate profile for electronic cigarette aerosol, but more research and standard protocols need to be implemented before any conclusions can be drawn.

B. *In-Vitro* Toxicological Analyses of E-Liquids and Aerosols

Eight *in vitro* studies have been conducted (two on genotoxicity and six on cytotoxicity) of electronic cigarette liquids or aerosols. These studies are summarized in Appendix 6 and discussed briefly below. One genetic toxicity abstract reports very early findings and therefore no firm conclusions can be drawn, while the other genetic toxicity abstract reports that while several cigarette smoke extract (CSE) preparations were genotoxic, electronic cigarette aerosol preparations were not. The cytotoxicity studies report a range of results; however, the two studies that used standard protocols report very low cytotoxicity and significantly lower cytotoxicity than cigarette smoke. Additionally, one of the cytotoxicity studies also examined inflammatory endpoints and found while cigarette smoke provoked a substantial inflammatory response, electronic cigarette aerosol did not.

Park et al. (2014) reported studies involving the *in vitro* treatment of transformed cells with culture medium that had been conditioned with high-nicotine and low-nicotine electronic cigarette aerosols or combustible cigarette smoke. These authors found enhanced anchorage-independent colony grown from the high-nicotine electronic cigarette and combustible cigarette medium treatments. No increase in the invasive behavior of the test cultures (human bronchial epithelial cells that had been immortalized for *in vitro* growth by P53 gene silencing and KRAS gene activation) was seen for any treatment. Some similarities and some differences among the treatment groups were reported in the meeting presentation, but full study details are unavailable.

Leverette et al. (2014) described in a meeting abstract a genetic toxicity assessment of e-liquids and collected aerosols, accompanied by comparisons to extracts of cigarette smoke, smokeless tobacco products and a NRT lozenge product. Under the experimental conditions used to evaluate traditional tobacco burning cigarettes, electronic cigarette liquids and aerosols, similar to the NRT lozenge and smokeless tobacco product, did not produce any meaningful genetic toxicity in the Ames bacterial mutagenesis test or the mammalian CHO cell micronucleus test. All of the conventional cigarette smoke preparations, at comparable exposures, were found to be markedly genotoxic.

Six studies examining the *in vitro* cytotoxicity of electronic cigarette aerosol and e-liquid in various cell lines have shown mixed results. Three (Farsalinos et al. 2013a, Romagna et al. 2013, Leverette et al. 2014) compared the cytotoxicity of electronic cigarette aerosol extract with that of cigarette smoke extract, while three others examined the cytotoxicity of e-liquids. The studies that compared electronic cigarette aerosol to cigarette smoke generally found that electronic cigarette aerosol exhibited very low overall cytotoxicity, significantly less than that of cigarette smoke. The Farsalinos and Romagna studies both used a standard protocol (ISO 10993-5) that defines cytotoxicity as viability of less than 70% (compared to untreated cells). Of the four samples found to be cytotoxic by Farsalinos et al. (2013a), three of them were made using cured tobacco leaves and subsequently filtered (most tobacco-flavored liquids are made a different way using tobacco absolute extract). Given this production method, it is not surprising that these e-liquids were significantly more cytotoxic than the other 17 e-liquids tested. The single sample not made from cured tobacco leaves was only slightly under the threshold for cytotoxicity (64.8% viability). Romagna et al. (2013) found that only one sample was cytotoxic, but was still 795% less cytotoxic than cigarette smoke extract.

Leverette et al. (2014) described in a meeting abstract an extensive cytotoxicity assessment of multiple e-liquids and collected aerosols, accompanied by comparisons to extracts of cigarette smoke, smokeless tobacco products and a NRT lozenge product. Under the experimental conditions used to evaluate traditional tobacco burning cigarettes, electronic cigarette liquids and aerosols did not produce any meaningful cytotoxicity in the mammalian cell neutral red uptake assay and did not produce any meaningful toxic effects as measured by IL-8 (inflammation), in which conventional cigarette smoke preparations, at comparable exposures, are markedly cytotoxic and inflammatory.

The three other cytotoxicity studies did not use a standard cytotoxicity protocol or compare to conventional cigarette smoke, so comparing the results is challenging. Williams et al. (2013) found small metal and silicate particles in the cartomizer fluid, which the authors deduced came from the wires and solder joints in the electronic cigarette hardware. The authors found greater inhibition of cell growth and attachment by the e-liquids with particulate contaminants and concluded that the presence of these particles demonstrates the need for improved quality control. Behar et al. (2014) investigated the specific cytotoxicity of cinnamon flavored e-liquids and found that embryonic cell lines were more sensitive than adult cell lines and that the cinnamon flavorings in refill fluids appear to be linked with cytotoxicity. Commenting on Behar et al. (2014), Farsalinos et al. (2014c) noted that the study has serious flaws such as undiluted flavoring being confused for refill liquid and pointed out that direct extrapolation of *in vitro* cytotoxicity findings for cinnamaldehyde to other conditions of exposure is questionable in light of the long history of uneventful use of the compound in diverse flavoring applications.

Further *in vitro* and *in vivo* assessments of electronic cigarette liquids and aerosols studies are warranted to more fully characterize any toxicological properties that these formulations may have.

C. Electronic Cigarettes and Passive Vaping

Passive vaping is the electronic cigarette analog to secondhand smoking. Unlike conventional cigarettes, electronic cigarettes do not produce emissions between puffs. Therefore passive vaping refers only to bystanders breathing in exhaled electronic cigarette aerosol rather than exhaled cigarette smoke in addition to emissions produced between puffs. Passive vaping is generally a concern in indoor air. WHO has advanced guidelines "for the protection of public health from risks due to a number of chemicals commonly present in indoor air" (WHO, 2010). These chemicals include several that have been reported to be present in side-stream cigarette smoke emissions, such as benzene, carbon monoxide, formaldehyde and polycyclic aromatic hydrocarbons. Similar to TVLs, OSHA PELs (Occupational Safety and Health Administration's permissible exposure limits) are the legal limits for exposure of an employee to a chemical substance. These values are generally expressed as a time weighted average (TWA) for an 8-hour work day.

Schripp et al. (2013) reports that many parameters can affect passive vaping, including type of electronic cigarette, length of puff, indoor climate, airflow conditions and the age, sex, health status and diet of the user. Though FDA did not express specific concerns regarding passive vaping in the proposed deeming regulation, FDA did raise concerns about the existence of toxicants in the exhaled aerosol,[86] which would correspond to passive vaping.

Only four studies have analyzed the air in a room after a vaping session has occurred. These studies generally compared the levels of various components in room air after vaping with those after cigarette smoking, or with the air in a control room where no vaping or smoking has occurred (intended to represent the "normal" composition of indoor air).

This distinction between passive vaping studies and those that analyze the mainstream aerosol is significant, as Schripp et al. (2013) notes that during "inhalation of the e-cigarette vapor, the aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles. This effect is also caused by evaporation of the liquid particles in the lung and also in the environment after exhalation."

The passive vaping studies compared indoor air concentrations of PAHs, VOCs, carbonyls and metals after vaping to those in a control setting and/or after conventional cigarette smoking. Some other parameters such as total organic carbon (TOC), particulate matter and carbon monoxide (CO) levels are sometimes reported. The results of these studies are summarized in Appendix 7.

In general, the results show that vaping releases a much smaller amount of potentially harmful components into indoor air than conventional cigarette smoking. Further, the results often show that the concentration of harmful components after vaping is not significantly higher than normal indoor air levels. Schober et al. (2013) reported elevated levels of PAHs in an experimental room occupied by electronic cigarette users, but a subsequent published letter by Farsalinos

[86] *Id*. at 23157.

(2014b) questioned whether the infiltration of ambient urban air PAH may have accounted for this finding. The author's response (Schober et al. 2014) dismissed this contention and further investigation may be needed to determine why room air PAH levels reported by Schober and coworkers (2013) are inconsistent with the majority of laboratory analyses of electronic cigarettes that have reported very low to undetectable PAH emissions.

Data from the Schober et al., Schripp and Romagna studies discussed above on compounds that were found to be elevated in indoor air after vaping (PAHs, methylethylketone, acrolein, acetone, formaldehyde, acetaldehyde and aluminum) were compared to OSHA PELs.[87] All reported values were substantially lower than the OSHA limits. Benzaldehyde concentrations were not compared to OSHA PELs because OSHA does not have an established PEL for this compound, however benzaldehyde was only slightly elevated by vaping (5.0 $\mu g/m^3$ vs 3.7 $\mu g/m^3$ without vaping) and so this level is unlikely to cause a problem.

In addition to the four studies in which aerosol was generated by a person using an electronic cigarette, one additional study (McAuley et al. 2012), collected mainstream electronic cigarette aerosols generated by a smoking machine to develop estimates of potential room air emissions. Technical problems, including apparent cross-contamination among samples, were encountered by the investigators. Results from this study were provided to a toxicologist, who then assessed health impact using two widely accepted risk metrics: the Total Cumulative Hazard Indices (HIs) and the Excess Lifetime Cancer Risk (ELCRs). HIs below the defined risk limit will not likely result in adverse non-cancer health effects over a lifetime of exposure. Similarly, ELCRs below the defined risk limit will not likely result in an increased incidence of cancer over a lifetime of exposure. McAuley et al. (2012) found that both HIs and ELCRs for electronic cigarettes were substantially lower than the risk limit. McAuley et al. concluded that there are very low indoor air quality impacts from the use of an electronic cigarette and there is no apparent risk to human health from electronic cigarette emissions based on the compounds analyzed.

D. Conclusions about Chemical and Toxicological Laboratory Analyses

Chemical and toxicological analyses of electronic cigarette liquids and aerosols are accumulating, but additional and more intensive research is warranted. Thus far, most studies have shown that electronic cigarettes expose the user to much lower levels of potentially harmful chemicals than conventional cigarette smoke. Many *in vitro* studies have also shown that electronic cigarettes are much less cytotoxic than conventional cigarettes. Additional *in vitro* studies have found that electronic cigarettes are much less genotoxic and mutagenic and cause less inflammation than conventional cigarettes. Only a limited number of studies have analyzed indoor air after vaping has occurred; these passive vaping studies have shown that the amount of

[87] The data on VOCs must be considered separately, due to the large number of VOCs tested and the lack of consistency in VOCs tested from study to study. For this reason OSHA PELs were not consulted and further investigation should be conducted on VOCs of particular interest.

harmful constituents is often similar to that in background indoor air and that passive vaping is not expected to pose risk to human health.

II. HEALTH EFFECTS OF USING ELECTRONIC CIGARETTES

In the preamble, FDA asks for "any health and behavioral data about the effects of using electronic cigarettes."[88] In response, Lorillard conducted a comprehensive survey of the published literature on health effects, and identified the following:

- Clinical studies examining the acute physiological effects of electronic cigarettes;
- Studies conducted for another purpose (including smoking cessation) that collected longer-term data on adverse events that occurred while using electronic cigarettes;
- Case reports and case series;
- Information on accidental or intentional poisoning from exposure to nicotine-containing electronic cigarette liquids; and
- FDA's adverse event database.

This section summarizes Lorillard's review of the available data. As an initial matter, Lorillard notes that the research is still in the early stages due to the relatively recent emergence and rapid technology advancement of electronic cigarettes. The available data do not yet permit firm conclusions about long-term safety or overall population effects. Despite these limitations, short-term clinical studies, smoking cessation studies, surveys and case reports have provided little evidence of significant short-term health or safety issues.[89] These findings, in conjunction with the observation from laboratory and toxicological studies that exposure of electronic cigarette users to hazardous substances is negligible compared to that of smokers, have led Farsalinos and Polosa (2014) to conclude that the potential for harmful consequences of electronic cigarette use has been largely exaggerated. In fact, surveys of longer-term use describe a number of perceived health benefits among people who have reduced or replaced conventional cigarette smoking with electronic cigarette use.

Further research is needed and long-term survey projects (such as the Population Assessment of Tobacco and Health, or PATH study) may provide the basis for more sound and refined estimates of current and projected electronic cigarette use (FDA and NIH 2014).

[88] 79 Fed. Reg. at 23143. The preamble cites very few references related to health effects.

[89] According to a recent systematic review, approximately 6% of all adults in the US had tried an electronic cigarette as of 2011 (Pepper and Brewer 2013). While the precise number of regular users is not known, the Tobacco Vapor Electronic Cigarette Association reported that there were 2.5 million users in 2012 (Wells Fargo 2012, citing TVECA) and there has been no evidence of significant short-term health effects or safety issues.

A. Clinical Studies of Health Effects among Electronic Cigarette Users

Lorillard has found and reviewed 16 clinical studies on the health effects of electronic cigarettes that have been conducted to date. A summary of each study is provided in Appendix 8.[90] Generally, these studies are small, with most involving fewer than 50 subjects and short term. Endpoints were typically evaluated before and after a single use of an electronic cigarette lasting just a few minutes. Only two studies involved use of the electronic cigarettes over longer periods (2-4 weeks). The studies were designed to examine respiratory, cardiovascular and inflammatory endpoints, as well as clinical symptoms. Approximately half of the studies involved only smokers or former smokers, with some of the subjects having pre-existing diseases such as chronic obstructive pulmonary disease (COPD) or asthma and the other half included small numbers of never-smokers. Some studies included comparator products, including conventional cigarettes or electronic cigarettes with no nicotine.

While these studies do not permit any conclusions about the health effects of long-term use, they begin to characterize the acute physiological effects of brief electronic cigarette exposure. The results suggest that acute effects are minor and are generally less severe than those associated with use of conventional cigarettes. The findings are summarized below by general endpoints:

> **Respiratory Effects.** Six studies examined respiratory effects. One study (Flouris et al. 2013) found that brief vaping had no effect on basic pulmonary parameters (including fraction of exhaled nitric oxide, or FeNO), while conventional cigarette smoking affected acute lung function. A second (Vardavas et al. 2012) reported decreased FeNO and increased peripheral airway resistance and impedance in smokers after 5 minutes of vaping. In contrast, a small study of 9 subjects found increases in FeNO after 2 hours of vaping (Schober et al. 2013). A fourth study (Marini et al. 2014) found decreases in FeNO after smoking or using an electronic cigarette. An abstract by Palamidas et al. (2014) reported that brief use of an electronic cigarette was associated with increased airway resistance and a concomitant decrease in specific airway conductance, although the authors speculated that this could be due to the vaporizing liquid rather than the inhaled nicotine. Finally, 13 heavy smokers who switched to electronic cigarettes for 2 weeks had lower carboxyhemoglobin levels and increased oxygen saturation and most perceived improvements in their health (Van Staden et al. 2013).
>
> **Cardiovascular Effects.** Four papers (three available only as abstracts) describe studies that evaluated various cardiovascular parameters after brief use of an electronic cigarette, including cardiac output, systemic vascular resistance, myocardial function, elasticity of the aorta and coronary microcirculation. In general, these studies found no or minimal adverse effects of brief vaping. One uncontrolled clinical study (Battista et al. 2013) concluded that "…e-cigarettes appear less harmful than tobacco smoking…", but also that inhalation of nicotine vapor produces "…the same pathophysiological cardiovascular

[90] Seven of the 16 studies are available only as abstracts, and therefore, there are few details available.

effects as traditional cigarette smoking." This statement by the authors apparently refers only to their demonstration of some of the well-characterized effects of nicotine on cardiovascular measures and not to changes in blood oxygen saturation, carboxyhemoglobin levels, or systemic inflammatory effects that have been previously described from conventional cigarette smoking. In the three studies that included a conventional cigarette comparator condition, vaping did not lead to the adverse effects known to be associated with smoking (Farsalinos et al. 2014d, 2013e, 2013f).

Hematologic Measures. Two studies evaluated effects vaping on complete blood count, blood chemistry and other hematologic measures (Flouris et al. 2012, Miura et al. 2011). No effects on normal blood counts were noted.

Inflammatory Markers. One abstract describes a study in which subjects had brief exposure (active and passive) to an electronic cigarette and a conventional cigarette (Tzatzrakis et al. 2013). The results showed that active and passive conventional cigarette smoking led to acute increases in inflammatory markers (interleukins, TNFz, EGF, etc.), while active and passive vaping did not.

Clinical Symptoms. Two studies evaluated the effects of 10 minutes of use of an electronic cigarette (11 mg/mL nicotine) on clinical symptoms and vital signs, as well as some measures of airway inflammation (Tsikrika et al. 2014, Vakali et al. 2014). Both reported that even a single use of an electronic cigarette increased heart rate and symptoms like cough and sore throat. Vakali et al. (2014) also concluded that the increased heart rate and palpitations were related to nicotine in the electronic cigarette, but that airway symptoms and inflammatory markers (decreased FeNO, increased exhaled CO) were independent of nicotine use.

Memory. A single study (Dawkins et al. 2013b) found that nicotine delivered via electronic cigarette can improve prospective memory in abstinent smokers, suggesting efficient delivery of nicotine. No significant effects were demonstrated in another test of cognitive function (a letter cancellation task) in this study. A considerable number of studies of conventional cigarette smoking or nicotine delivered by other routes have previously reported improvement in certain domains of cognitive function (Heishman et al. 2010).

Thus, these very early studies are beginning to describe the acute physiological effects that occur in small groups of electronic cigarette users, most of whom are smokers. The effects were generally minor and much less than those that occur after a brief exposure to either active smoking or environmental tobacco smoke. Additional research is needed to further characterize the long-term health effects of using electronic cigarettes.

B. Other Studies of Human Subjects

Studies conducted for purposes other than specifically investigating the health effects of electronic cigarettes also provide some evidence that side effects and adverse events are minor. Some of these studies involved use of electronic cigarettes for longer periods of time than the

acute studies discussed above. These studies also show that users (who are typically substituting electronic cigarettes for conventional cigarettes) experience a number of benefits in terms of general health.

Smoking Cessation Studies. Several studies that investigated the efficacy of electronic cigarettes for smoking cessation also collected data on side effects or adverse outcomes. None of these studies identified any serious product-related adverse events.

- **Randomized controlled trials.** Two randomized controlled trials (RCTs) followed electronic cigarette users for 6 months or longer. Bullen et al. (2013b) conducted a 6-month RCT of 657 smokers who were assigned to a 16 mg nicotine Elusion® electronic cigarette, a 0 mg nicotine Elusion® electronic cigarette, or a 21 mg nicotine patch for 12 weeks. There were no significant differences in adverse events between the groups, with no evidence of an association between adverse events and any of the study products. A 12-month RCT conducted by Caponnetto et al. (2013a) followed 300 smokers who used the Categoria® electronic cigarette three different strengths of nicotine cartridges (0 mg for 12 weeks; 7.2 mg for 12 weeks; or 7.2 mg for 6 weeks followed by 5.4 mg for 6 weeks). There were no serious adverse events. The authors noted that adverse events were common before using the electronic cigarette (dry cough, mouth irritation, shortness of breath, throat irritation, headache) and that all adverse effects decreased substantially during the follow-up period.

- **Two-year observational study.** Polosa et al. (2013b) evaluated the effectiveness and tolerability of the Categoria® electronic cigarette among 40 smokers in a 2-year, prospective observational study. There were no serious adverse events; only some mouth irritation, throat irritation and dry cough were reported.

- **Short-term intervention study.** Nides et al. (2014) investigated short-term smoking reduction among 25 smokers after a 1-week trial of using the NJOY® King electronic cigarettes. The product was well-tolerated. The most common adverse events were local irritation of the mouth, throat, or airways; cough, dry throat; burning sensation on the lips; and headache; most of these resolved within a few days of use.

Surveys of Electronic Cigarette Users. Many surveys of electronic cigarette users provide information about health effects (both positive and negative) under conditions of real-life use over longer periods of time. The observations are not collected under controlled conditions (many were obtained via online questionnaires) and these surveys are diverse in terms of quality of methods and numbers of subjects. In general, the surveys show that electronic cigarette users experience low levels of adverse effects (most commonly mouth and throat irritation), which tend to lessen over time. Improvements in overall health are reported by many electronic cigarette users, including improved breathing and cough, better exercise ability and improved senses of taste and smell (Heavner et al. 2009, Dawkins et al. 2013a, Farsalinos et al. 2013b).

The largest and most recent survey was conducted by Farsalinos et al. (2014b) (this and the other studies are summarized in Appendix 9). An online questionnaire was used to survey more than 19,000 electronic cigarette users who had used electronic cigarettes for a median of 10 months (81% were former smokers and 19% were current smokers). Side effects were reported by 59.8% of the users, with the most common being sore/dry mouth and throat. Side effects were generally mild and more than 90% resolved either partially or completely over time. Users reported experiencing significant benefits in overall physical health and reduction of symptoms associated with pre-existing diseases common among smokers (chronic obstructive lung disease, asthma). According to the authors, more than half of the subjects reported better breathing, senses of taste and smell, endurance and physical status in general.

Studies of Nicotine Delivery. Several short-term clinical studies that focused on nicotine delivery of electronic cigarettes also found few adverse events. Bullen et al. (2010) conducted a single-blind, randomized cross-over trial of 40 subjects to assess the effect of 1 day's use of the Ruyan® electronic cigarette on pharmacokinetics, withdrawal symptoms, acceptability and adverse effects. The 16 mg/mL nicotine electronic cigarette was well-tolerated, with some reports of mouth and throat irritation, but fewer than reported by subjects in the comparator condition (Nicorette® inhalator). Dawkins and Corcoran (2013) evaluated plasma nicotine levels in 14 regular electronic cigarette users over 12 hours, with few reported adverse effects (lightheadedness and throat irritation were most common). Farsalinos et al. (2014a) compared nicotine absorption from first- and new-generation electronic cigarette models among 23 experienced electronic cigarette users and found a low score for negative effects. Vansickel et al. (2012), which describes a small study of abuse liability, stated that no adverse effects of electronic cigarettes were observed in their current or earlier studies (*e.g.*, Vansickel et al. 2010, Eissenberg 2010).

C. Case Reports/Case Series

There are a limited number of case reports in the literature that describe both positive and negative health effects occurring among electronic cigarette users (summarized in Appendix 10). Several describe adverse effects (subacute bronchial toxicity, lipoid pneumonia and eosinophilic pneumonia); one describes health benefits associated with smoking cessation accomplished by using an electronic cigarette (reversal of chronic idiopathic neutrophilia) and one appears to be due to incorrect use of an electronic cigarette (atrial fibrillation).

Polosa et al. (2014) describe harm reversal in a series of 18 asthmatic smokers who switched partly or completely to electronic cigarettes. The authors conducted a retrospective analysis of their clinic records to identify patients who had standard clinical exams to evaluate their asthma at baseline (prior to switching) and at two follow-up visits (6 and 12 months after switching). Eight individuals quit smoking completely and 10 reduced their cigarette consumption but were dual users. These patients had significant improvements in spirometry data, asthma control and airway hyperreactivity. There were no adverse events, only occasional reports of dry mouth and throat irritation.

Case reports provide only anecdotal evidence and no firm conclusions can be drawn about causal relationships between the use of electronic cigarettes and the reported health effects. Further complicating the interpretation of these cases is the fact that most of these individuals had long smoking histories before using electronic cigarettes. However, it is worth noting that the number of reports is small given the increasingly large number of electronic cigarette users, the number is not growing as electronic cigarettes become increasingly popular and there is nothing in these case reports that suggests a "signal" or a particular body system that is affected.

D. Data on Accidental and Intentional Poisoning

FDA raises concerns about the potential for acute toxicity with electronic cigarettes, noting recent increases in calls to poison control centers, especially those involving young children.[91] The recent addition of reporting categories for electronic cigarettes, cartomizers and refill fluids to the database maintained by the American Association of Poison Control Centers (AAPCC) will permit more accurate accumulation of information on poisoning incidents than was possible in earlier years when reporting of such incidents may have been inconsistent. Conclusions regarding trends in acute intoxication events should be developed with consideration of the evolving categorization scheme for nicotine-containing therapeutic products, tobacco and non-tobacco product categories that are employed by the AAPCC (Bronstein et al. 2012). The potential for accidental nicotine overdose by ingestion of e-liquids does exist; however, Lorillard believes that the available data show that such incidents to date have been overwhelmingly resolved without serious consequence and only occasional brief hospitalizations for follow-up observation have occurred. Furthermore, safety packaging can mitigate risks of accidental e-liquid ingestion.

While it has long been recognized that nicotine can have toxic effects, there is a new understanding that the estimated lethal dose for an adult human is likely much higher than the 30-60 mg long reported. A very recent analysis by Mayer (2014) traced the previous estimate to a poorly-documented self-experiment conducted by a German researcher in the 19th century and developed a new, more realistic estimate for a human lethal dose of 500 mg or higher. Mayer concludes that "Nicotine is a toxic compound that should be handled with care, but the frequent warnings of potential fatalities caused by ingestion of small amounts of tobacco products or diluted nicotine-containing solutions is unjustified and needs to be revised in light of overwhelming data indicating that more than 0.5 g of oral nicotine is required to kill an adult." By comparison, the one-piece disposable electronic cigarette product sold by Lorillard contains up to 24 mg nicotine; the highest level of nicotine in an individual cartridge is 16 mg.

This new understanding is supported by a very recent analysis commissioned by the Electronic Cigarette Industry Trade Association (ECITA) that showed that the European Union has wrongly been labeling e-liquid as extremely toxic. According the Classification, Labelling, and Packaging (CLP) categories, European officials have considered nicotine e-liquids as CLP

[91] 79 Fed. Reg. at 23157.

category 2 products (*e.g.*, strychnine) or category 3 products (*e.g.*, formaldehyde). This analysis showed that the acute oral and dermal toxicity of the strongest nicotine e-liquids (containing up to 50 mg/mL nicotine) only merit classification as CLP category 4 (the lowest category, with product such as soap), while e-liquids with less than 25 mg/mL (which are the vast majority of e-liquids) do not require any type of formal hazard warning.

The few case reports of accidental or intentional ingestions of nicotine-containing e-liquids support this higher estimate for a lethal dose. A 10-month-old infant who ingested a "small" amount of e-liquid containing 18 mg/mL of nicotine developed vomiting, tachycardia, grunting respirations and truncal ataxia, but did not require antidote therapy and recovered within 6 hours after the ingestion (Bassett et al. 2014). Three other individuals used nicotine-containing e-liquids in attempts to commit suicide. In the first two reports (Christensen et al. 2013, Valento 2013), the liquids were orally ingested in doses ranging from 360-1500 mg. Symptoms (nausea, vomiting, dizziness) developed within minutes after ingestion; the individuals were treated at the hospital and survived. The third report describes a 29-year-old man who injected himself intravenously with e-liquid. He was hospitalized and treatment was attempted, but he was declared brain dead. His serum nicotine and cotinine were 2000 ng/mL and 2100 ng/mL, respectively (Thornton et al. 2014).

Analyses of data from the AAPCC show that while reports of electronic cigarette exposures have increased in recent years, the incidents are not generally serious. The Centers for Disease Control and Prevention (CDC) reported 2,405 calls about electronic cigarette exposures (either the device or the e-liquid) between 2010 and 2014, mostly among children under age 5 and adults over age 20. Exposures were via ingestion (68.9%), inhalation (16.8%), eye (8.5%) and skin (5.9%) and the most common adverse effects were vomiting, nausea and eye irritation (Chatham-Stephens et al. 2014). Reports from two statewide poison control centers provide additional detail. In California, there were 35 cases from 2010 to 2012 (14 in children age 8 or younger). In Texas, there were 79 exposures from 2009-2013 (39 were age 19 or younger). Exposures were via various routes (ingestion, inhalation, dermal, ocular). Most were managed without presentation at a hospital and there were no deaths. The authors of both papers concluded that exposure to electronic cigarettes does not generally result in serious toxicity (Cantrell 2013a, Ordonez et al. 2013).

Many common household substances such as cleaning products have the potential for acute toxicity if ingested, or if ingested in high enough amounts. For example, ingestion of each of the following has been documented to be fatal to a child: 10 adult iron tablets; 7 60-mg tablets of pseudoephedrine; 1 teaspoon of oil of wintergreen; 1-2 ounces of cologne; 2-3 g of boric acid; a single mouthful of kerosene or gasoline if aspirated; or 0.1 mL of food contaminated with botulinum toxin (Morris-Kukoski and Egland 2014). Lorillard supports the use of child-resistant packaging on all nicotine-containing e-liquids to prevent accidental ingestions.

E. FDA's Adverse Event Database

The FDA regularly receives voluntary reports of adverse events involving consumer products (including electronic cigarettes) from consumers and health professionals. As of the first quarter of 2012, 47 adverse events had been reported, including hospitalization for illnesses such as

pneumonia, congestive heart failure, disorientation, seizure, hypotension, possible aspiration pneumonia, second-degree burns to the face after the product exploded, chest pain and rapid heartbeat, possible infant death due to choking on an electronic cigarette cartridge and loss of vision requiring surgery (Chen 2012). FDA states very clearly that it is not known whether electronic cigarettes may have caused the reported events and that some of them could be related to pre-existing medical conditions or other causes. As additional adverse event data accumulate, FDA may be able to identify certain products, components, packaging, or e-liquids that may be associated with specific events in order to determine whether specific follow-up actions may be warranted.

F. No Signal from Increasingly Widespread Use

In addition to the information presented in published papers, it can be noted that despite increasingly widespread use, there is no evidence of significant health problems associated with electronic cigarette use. According to early market participants, electronic cigarettes were first introduced in the US in mid-2007 and use has increased rapidly since that time. There were an estimated 2.5 million users in the US in 2012 and the number has certainly increased since that time (Wells Fargo 2012, citing TVECA).

G. Conclusions about Health Effects among Electronic Cigarette Users

Review of the available literature demonstrates that research into the health effects of electronic cigarettes is still in the early stages. Results obtained to date do not provide evidence of significant health or safety issues. These findings, in conjunction with the observation from laboratory and toxicological studies that exposure of electronic cigarette users to hazardous substances is negligible compared to that of smokers, has led Farsalinos and Polosa (2014) to conclude that the potential for harmful consequences of electronic cigarette use has been largely exaggerated.

III. ADDICTION AND DEPENDENCE

In the preamble to the Proposed Deeming Regulation, FDA poses several questions and comments about nicotine addiction and dependence with respect to tobacco products in general and electronic cigarettes in particular. First, FDA asserts that **"**all tobacco products containing nicotine are addictive, and FDA is not currently aware of any tobacco products that do not contain nicotine."[92] In light of this assertion, FDA asks for "comments, including supporting research, facts, and other evidence, as to whether all tobacco products should be required to carry an addiction warning and, if yes, whether different warnings should be placed on different categories of products."[93] For electronic cigarettes, FDA asks whether such products could serve

[92] *Id*. at 23144. Lorillard produces electronic cigarettes that do not contain nicotine. Because such devices do not contain any ingredient derived from tobacco, they are not tobacco products.

[93] *Id*.

as a path to nicotine addiction for non-tobacco users, stating "experts have expressed concern that e-cigarettes may draw more consumers to nicotine-containing products."[94]

Lorillard agrees with FDA that nicotine, including nicotine delivered by electronic cigarettes, is addictive. Lorillard further agrees that addiction warnings are necessary and that all products delivering nicotine should carry the same addiction warning until there is a sound scientific basis for a different approach. Lorillard notes, however, that there is some evidence that users are less dependent on electronic cigarettes than conventional cigarettes.

Although FDA has noted concerns that electronic cigarettes could be a path to nicotine addiction for non-tobacco users, these concerns are speculative and without scientific support. Lorillard has found no evidence that electronic cigarettes are a path to nicotine addiction for non-tobacco users. Instead, a number of large surveys report that very few never-smokers use electronic cigarettes. There is also no evidence that the very small percentage of never-smokers who try or use electronic cigarettes will transition to use of conventional tobacco products, or that electronic cigarettes are likely to cause relapse to smoking for former smokers.

A. Nicotine is Addictive

It is well-recognized that nicotine is an addictive substance. Nicotine can affect the neurochemistry of the brain and may act with other sensory and behavioral components of smoking to render it addictive (Rose et al. 2010, Benowitz 2014). Lorillard agrees that nicotine, regardless of the delivery product, is addictive. Nicotine as delivered in electronic cigarette vapor is addictive.

B. Warnings on Products Delivering Nicotine

Lorillard agrees that all products delivering nicotine should carry a standard addiction warning, including nicotine-containing electronic cigarettes.

FDA has asked whether there is evidence to support the use of different warnings on different categories of products, as has been discussed by some authors (*e.g.*, Fagerström and Eissenberg 2012). Lorillard believes that, for the purposes of product labeling, a consistent addiction warning should be used on all products that deliver nicotine until there is a sound scientific basis for different warnings. As summarized below, however, the available scientific evidence indicates that people may be less dependent on electronic cigarettes than conventional cigarettes.

Electronic cigarette users tend to decrease the levels of nicotine they use over time. For example, a recent worldwide survey of more than 19,000 electronic cigarette users who had used electronic cigarettes for a median of 10 months showed that participants initiated use of electronic cigarettes with a median nicotine level of 18 mg/mL but reduced the level over time to 12 mg/mL at the time of the survey (Farsalinos et al. 2014b). This was confirmed by a second

[94] *Id*. at 23159.

study of 111 individuals who had completely substituted electronic cigarette use for smoking for at least 1 month. Among these subjects, nicotine levels in the electronic cigarettes used declined significantly from a median of 18 mg/mL at initiation to 12 mg/mL at the time of the interview (Farsalinos et al. 2013b).

Three studies have directly evaluated aspects of dependence on electronic cigarettes vs. conventional combustible cigarettes. The Farsalinos et al. (2013b) study of 111 electronic cigarette users estimated the dependence potential of the two products using two measures: time to first cigarette or electronic cigarette after waking and use of a 100-point visual analogue scale to estimate past and current dependence. The median (interquartile range) score for time to first use was 2 (2-3) for tobacco cigarettes and 2 (1-2) for electronic cigarettes. The median (interquartile range) score on the visual analogue scale about dependence was 83 (77-89) for conventional cigarettes and 59 (49-66) for electronic cigarettes. Electronic cigarette dependence as assessed using this method was significantly lower than that of conventional cigarettes for both metrics ($p<0.001$).

A small clinical study of the "abuse liability" of electronic cigarettes was conducted by Vansickel et al. (2012). The study used a multiple choice procedure that has been used previously to evaluate the "abuse liability," or drug reinforcement, of conventional cigarettes. In this study, 20 smokers tried an electronic cigarette with an 18 mg/mL nicotine cartridge and then made a series of discrete choices comparing the relative value of the electronic cigarette with that of conventional cigarettes and of money. The authors reported that electronic cigarettes delivered clinically significant amounts of nicotine, suppressed smoking abstinence symptoms and appeared to have lower potential for abuse relative to conventional cigarettes.

Foulds and colleagues (2014) have been working to develop a brief questionnaire measure of nicotine dependence that is suitable for use across products and that can be used to compare dependence on conventional cigarettes with electronic cigarettes. Early results with this questionnaire have shown that current electronic cigarette users are significantly less dependent on electronic cigarettes than they were on smoking prior to switching. Other authors have suggested that such efforts to develop multi-product dependence assessment instruments should be abandoned in favor of behavior-based instruments that are product-specific (Fagerström and Eissenberg 2012).

C. Electronic Cigarettes as a Path to Nicotine Addiction

As noted above, FDA questions whether electronic cigarettes could serve as a path to nicotine addiction for non-tobacco users, stating "experts have expressed concern that e-cigarettes may draw more consumers to nicotine-containing products."[95] This concern is speculative. The available literature shows convincingly that very few adult never-smokers use electronic cigarettes.[96] Further, there are no scientific data that support a hypothesis that the very low

[95] 79 Fed. Reg. at 23159.

percentage of never-smokers who try or use electronic cigarettes transition to use of conventional tobacco products.

Nine surveys were identified that provide data on the number of electronic cigarette users who have never smoked (see Appendix 11). Most involved large populations (two-thirds had more than 10,000 respondents) and they covered the US, UK and parts of Europe. Ever-use of electronic cigarettes by never-smokers ranged from 0.4% to 3.8%, with most estimates of ever-use at around 1% or lower. Current use of electronic cigarettes by never-smokers is even less common, with almost all estimates lower than 0.3%.

Thus, the available literature clearly and consistently shows that the number of never-smokers who use electronic cigarettes is very low. Furthermore, it is not known whether any of these individuals could be using electronic cigarettes that do not contain nicotine. Concerns that electronic cigarettes serve as a pathway to nicotine addiction and gateway to conventional tobacco products are simply not justified by the available scientific data.

D. Concern that Electronic Cigarettes Could Lead to Smoking Relapse by Former Smokers

Another theoretical concern is whether former smokers who have successfully quit smoking could first take up electronic cigarette use and then relapse to smoking conventional cigarettes. No studies have formally evaluated this hypothesis. One large survey of electronic cigarette users (Farsalinos et al. 2014b) found that 0.5% (or 88) of the participants reported that they were not smokers at the time of electronic cigarette use. However, 7 of them responded to the questions of the Fagerström Test for Nicotine Dependence and 11 more reported past attempts to quit smoking, suggesting that they were actually former smokers who quit smoking shortly before beginning electronic cigarette use.

One small recent study also provided some limited information on this issue in a report on conventional and electronic cigarette use among a special population of persons with mental health conditions (Cummins et al. 2014). These authors concluded that the studied subjects' motivations for using electronic cigarettes were similar to those of other users and further stated that "[e]qually clear is the fact that e-cigarettes appeal to smokers, but not to those who have never smoked or who quit smoking for more than a year."

Based on the limited data available, smoking relapse of former smokers related to use of electronic cigarettes appears to be a very rare occurrence.

[96] Data on the prevalence of electronic cigarette among adolescent never-smokers are presented and discussed in Part 2.VI. on Youth Issues.

E. Conclusions about Addiction and Dependence

Lorillard agrees with FDA that nicotine is addictive, that all products delivering nicotine should carry an addiction warning and that the warning should be the same for all such products until a sound scientific basis supports a different approach. It must be noted, however, that there is some evidence that people are less dependent on nicotine-containing electronic cigarettes than conventional cigarettes. The current body of scientific evidence reports that very few never-smokers use electronic cigarettes and there is no evidence that the very small percentage of never-smokers who try or use electronic cigarettes will transition to use of conventional tobacco products. Lorillard believes that addiction warnings on nicotine-containing electronic cigarettes will provide an additional safeguard against the possibility that consumers will not understand that electronic cigarettes are addictive.

IV. SMOKING REDUCTION AND CESSATION

In the preamble to the Proposed Deeming Regulation, FDA focuses on whether electronic cigarettes help smokers reduce or quit smoking.[97] FDA discusses whether electronic cigarettes can deliver sufficient nicotine in a manner that reduces nicotine withdrawal symptoms and craving,[98] or provide other sensory aspects beneficial in smoking reduction and cessation.[99] In its discussion, FDA notes the limited nature of the data on these issues.[100]

This section summarizes the available information on whether electronic cigarettes are effective in helping people to reduce or stop smoking.[101] The body of literature on the efficacy of electronic cigarettes for smoking reduction and cessation is growing rapidly. Many of the observational studies show that conventional cigarette smokers are very interested in alternatives to smoking. The available evidence suggests that current models of electronic cigarettes, especially when used by experienced vapers, can deliver adequate nicotine to suppress abstinence symptoms. In addition, a growing body of literature reports that electronic cigarettes

[97] 79 Fed. Reg. at 23152 ("several recent studies of limited numbers of users suggest that e-cigarettes may have the potential to help smokers"); *id.* ("some researchers believe that e-cigarettes are at least capable of suppressing the urge to smoke.").

[98] *Id.* ("e-cigarettes may have the potential to help with cessation by delivering a sufficient nicotine dose, particularly for experienced e-cigarette users").

[99] *Id.* ("sensory aspects associated with e-cigarettes may also have the potential to provide some short-term smoking reduction benefits").

[100] *Id*. at 23147 ("the number of cigarette smokers who actually quit tobacco product use with e-cigarettes is low"); *id*. at 23152 ("There is no evidence to date that e-cigarettes are effective cessation devices"); *id.* ("several large studies appear to raise questions as to whether e-cigarettes are effective cessation aids in real-world use"); *id*. at 23166 ("possible reduced usage of cigarettes that may be associated with e-cigarettes and the limitation of existing studies.").

[101] Lorillard makes no claims regarding the use or efficacy of electronic cigarettes for smoking reduction or cessation. This review merely summarizes the research conducted to date.

help smokers make statistically significant reductions in the number of cigarettes smoked per day and help some smokers quit smoking.

A. Studies of Nicotine Delivery, Withdrawal and Craving

If electronic cigarettes are to serve as an effective replacement for conventional cigarettes, they must deliver enough nicotine to suppress withdrawal symptoms and relieve cravings. Two recent FDA reviews emphasize that nicotine delivery depends on device characteristics and user experience (Schroeder and Hoffman 2014, Evans and Hoffman 2014) and thus these factors must be considered when attempting to draw conclusions from the literature.

Ten small acute clinical studies have examined nicotine delivery, as well as relief of withdrawal symptoms and craving, after using electronic cigarettes. These studies are summarized in Appendix 12. Early studies conducted with smokers who were not experienced in using electronic cigarettes reported poor nicotine delivery (Bullen et al. 2010, Vansickel et al. 2010). More recent studies have reported that experienced users who use their preferred devices are able to obtain reliable levels of nicotine (Dawkins and Corcoran 2013, Etter 2014a, Vansickel and Eissenberg 2013). Even electronic cigarettes that deliver less nicotine than conventional cigarettes suppress some abstinence symptoms (Dawkins et al. 2012).

Early clinical studies also reported that puffing topography is important, as individuals who puff more often can obtain nicotine in amounts similar to those obtained with smoking (Etter and Bullen 2011b). A more recent clinical study examined vaping topography by videotaping volunteers using both conventional and electronic cigarettes. This analysis showed that inhalation duration was lower and puff duration was longer in experienced vapers (Farsalinos et al. 2013d).

The design of electronic cigarettes continues to evolve and new-generation devices appear to deliver nicotine more efficiently than the early products. However, in a study of 23 experienced e-cigarette users, even the newer devices did not deliver nicotine to the bloodstream as rapidly as smoking (Farsalinos et al. 2014a).

Thus, the information available to date suggests that current models of electronic cigarettes, especially when used by experienced vapers, can provide adequate nicotine levels to suppress abstinence symptoms. In addition, other sensory cues provided by the devices (using an object that is much like a cigarette, smoking-associated behaviors of holding the electronic cigarette and inhaling, etc.) may also play a role in suppressing some withdrawal symptoms (Fagerström 2012).

B. Studies of Electronic Cigarettes for Smoking Reduction and Cessation

A growing body of literature shows that electronic cigarettes are effective in helping people cut down and possibly even quit smoking. Relevant information comes from:

- Randomized controlled clinical trials;
- Intervention studies;

- Observational epidemiology studies;
- Surveys of electronic cigarette users;
- Case reports and case series; and
- Studies that are planned or in progress.

The first three categories of studies (randomized controlled trials, intervention studies and observational epidemiology studies) are the most methodologically rigorous. These studies are summarized in Appendix 13. The remaining categories of studies (surveys of electronic cigarette users and case reports) are less rigorous in nature; they provide anecdotal, although still useful, evidence about the real-life use of electronic cigarettes. This literature provides consistent evidence that smokers who use electronic cigarettes have significant reductions in the number of cigarettes smoked per day. The data regarding smoking cessation are less consistent. However, quitting smoking is very difficult and smokers are very interested in additional cessation aids, particularly electronic cigarettes. Electronic cigarettes are reported to help some people quit smoking.

Randomized controlled trials. Two randomized controlled trials followed electronic cigarette users for 6 months or longer. In a 6-month trial in New Zealand, 657 smokers who wanted to quit were assigned to a 16 mg nicotine Elusion® electronic cigarette, a 21 mg nicotine patch for 12 weeks, or a 0 mg nicotine placebo electronic cigarette (Bullen et al. 2013b). Continued abstinence at 6 months (objectively verified) was 7.3% with the nicotine electronic cigarette; 5.8% with patches; and 4.1% with placebo electronic cigarettes. The statistical power was insufficient to conclude that the nicotine electronic cigarette was superior to the other conditions. However, 57% percent of the nicotine electronic cigarette users reduced their cigarettes per day by at least half at 6 months; this was significantly higher than the patches group (41%; p=0.0002) and non-significantly higher than the placebo group (45%; p=0.08). The authors concluded that electronic cigarettes, with or without nicotine, were modestly effective in helping smokers quit.

The ECLAT study, a 12-month, randomized controlled trial followed 300 smokers who used the Categoria® electronic cigarette with 3 different strengths of nicotine cartridges (0 mg for 12 weeks; 7.2 mg for 12 weeks; or 7.2 mg for 6 weeks followed by 5.4 mg for 6 weeks) (Caponnetto et al. 2013a). The number of cigarettes smoked per day decreased significantly in all three groups ($p<0.001$ compared to baseline), with no consistent differences between study groups. Overall smoking reduction (>50% fewer cigarettes per day) was 22.3% at week 12 and 10.3% at week 52. Overall abstinence (not even a puff since the previous study visit) was 10.7% at week 12 and 8.7% at week 52. The authors concluded that, in smokers not intending to quit, the use of electronic cigarettes (with or without nicotine) decreased cigarette consumption and elicited enduring tobacco abstinence.

A small prospective study (intended as a pilot study for a future randomized controlled trial) provides evidence that electronic cigarettes can help schizophrenic smokers reduce cigarette consumption. Schizophrenic smokers are reported to be less successful in quitting than the general smoking population. This prospective, 12-month study

examined the impact of electronic cigarette use in 14 smokers with chronic schizophrenia who did not intend to quit. Subjects were given the Categoria® electronic cigarette; they then attended 6 visits during the year at which smoking reduction and abstinence were encouraged. At week 52, 2 subjects had achieved sustained smoking abstinence and another 7 had reduced the number of cigarettes smoked per day by half. There was no negative impact on schizophrenic symptoms (Caponnetto et al. 2013b).

Intervention studies. Two short-term and one long-term intervention studies (in which electronic cigarettes were provided to smokers) have been conducted. A 2-year prospective study provides evidence that electronic cigarettes are effective and tolerable under "real-life" conditions (Polosa et al. 2013b). During the initial 6-month intervention phase of this study, subjects (40 adult smokers who did not intend to quit) were given the Categoria® electronic cigarette and monitored. No cartridges were provided after 6 months. At 24 months, 17 subjects were lost to follow-up. Eleven of 40 subjects (27.5%) had achieved a sustained 50% reduction in number of cigarettes/day and 5 of 40 (12.5%) had achieved total smoking abstinence (not a puff for 30 days, objectively verified). Five subjects stopped using the electronic cigarette and stayed quit, while 3 relapsed to smoking. Withdrawal symptoms were uncommon. The authors concluded that long-term electronic cigarette use can decrease smoking substantially in smokers not intending to quit.

Two small pilot studies showed that a brief intervention (providing smokers with an electronic cigarette to use for 1 week) led to reductions in conventional cigarette use. In both studies, smokers who did not intend to quit were instructed how to use an electronic cigarette and allowed to use it ad lib for 1 week. Nides et al. (2014) evaluated smoking reduction among 25 smokers after a 1-week trial of the NJOY® King electronic cigarette. They found that use of the electronic cigarette resulted in a decrease in cigarettes smoked among 89% of the participants; cigarettes per day were reduced by a mean of 39%. Wagener et al. (2013) investigated changes in readiness and confidence to quit among 20 smokers not interested in quitting. After 1 week of electronic cigarette use, the subjects reported a statistically significant (44%) reduction in cigarettes smoked per day, as well as substantially increased readiness and confidence to quit smoking. Both groups of investigators concluded that larger, longer-term studies are needed.

Observational epidemiology studies. Nine observational epidemiology studies examined the relationship between electronic cigarette use and smoking reduction or cessation in either cross-sectional or longitudinal analyses. The three studies that examined smoking reduction obtained different results. A longitudinal analysis of the International Tobacco Control Four-Country Survey found that current electronic cigarette users were more likely have reduced the number of cigarettes smoked per day than smokers who did not use electronic cigarettes ($p<0.05$) between waves of data collection (Adkison et al. 2013). However, in two other longitudinal analyses (Choi and Forster 2014b, Grana et al. 2014), baseline electronic cigarette use was not associated with a statistically significant change in cigarette consumption.

All nine studies assessed cessation, using a number of different measures, such as motivation to quit, quit attempts, quit duration and successful quitting. In general, these studies found some evidence that electronic cigarette users were more likely to have attempted to quit smoking (*e.g.*, Brown et al. 2014a), but they were not more likely to have been successful in doing so (Adkison et al. 2013, Choi and Forster 2014b, Grana et al. 2014, Popova and Ling 2013, Vickerman et al. 2013). An exception to this general finding was a recent large, cross-sectional study by Brown et al. (2014b) that assessed the real-world effectiveness of aids to cessation by comparing the success rates with different methods and adjusting statistically for a wide range of factors that could bias the results, such as nicotine dependence. The authors found that electronic cigarette users were statistically significantly more likely to report abstinence from smoking than those who used either NRT purchased over the counter or those who used no aid.

Some important points made by authors of these studies must be considered when interpreting the results. First, alternative tobacco products, including electronic cigarettes, are attractive to smokers who want to quit (Popova and Ling 2013). Noting that electronic cigarette users were more motivated to quit, had longer recent quit durations and were more likely to have used FDA-approved smoking cessation products in the past than those who did not use electronic cigarettes, Pokhrel et al. (2013) concluded that smokers who use electronic cigarette are serious about wanting to quit. Adkison et al. (2013) stated that, because trial of electronic cigarettes was associated with nondaily smoking and a desire to quit smoking, electronic cigarettes may have the potential to serve as a cessation aid. Addressing the inconsistency between attempting to quit but not being able to do so, Vickerman et al. (2013) point out that this could be due to confounding variables; some of these people may have been more heavily dependent on smoking or may have been exposed to other factors (such as tobacco users at work or home) that interfered with quitting.

Surveys of Vapers. Many surveys of electronic cigarette users provide testimonials about the efficacy of the products for reducing or quitting smoking under real-life circumstances (*e.g.*, Heavner et al. 2009, Etter 2010, Foulds et al. 2011, Siegel et al. 2011, Dawkins et al. 2013a, Farsalinos et al. 2013b). The observations are not collected under controlled conditions (many were obtained via online questionnaires) and the surveys vary in terms of quality of methods and numbers of subjects (those cited above included from 81 to 1,347 participants). However, the subjects consistently reported that they quit or greatly reduced their use of conventional cigarettes because of electronic cigarettes. Many had tried to quit multiple times unsuccessfully before finding electronic cigarettes. Selection bias is likely; but despite this, the studies provide a picture of dedicated users who are convinced of the efficacy of electronic cigarettes.

Larger surveys support these findings. For example, in a survey of 3,587 visitors to websites and online discussion forums dedicated to electronic cigarettes and smoking cessation, most former smokers (96%) said electronic cigarettes helped them quit smoking and most current smokers (92%) said electronic cigarettes helped them to reduce their smoking (Etter and Bullen 2011a). A longitudinal internet survey that examined use of conventional and electronic cigarettes over 12 months found that electronic cigarettes

provided an alternative to smoking, helped current smokers stop smoking and helped former smokers avoid relapse (Etter and Bullen 2013).

The largest and most recent survey, a worldwide survey of more than 19,000 consumers, (Farsalinos et al. 2014b) reported that 81% of the participants had completely substituted electronic cigarettes for smoking. Current smokers reduced the number of cigarettes smoked per day from 20 to 4. Electronic cigarettes were effective in reducing the number of cigarettes per day even for heavy smokers.

Case Reports/Case Series. Two publications describe cases in which electronic cigarettes were successfully used by five long-term heavy smokers (two of whom had established histories of depression) to quit smoking. All five individuals had been treated repeatedly at a smoking cessation clinic with nicotine patches, bupropion and counseling, but relapsed each time. Each was able to quit on his/her own within a few months of trying electronic cigarettes and each remained abstinent from tobacco for at least 6 months (confirmed objectively) (Caponnetto et al. 2011a, Caponnetto et al. 2011b).

A recent retrospective analysis by Polosa and colleagues (2014) evaluated subjective and objective asthma parameters in 18 asthmatic smokers who quit or reduced tobacco use by using electronic cigarettes. Ten of these subjects completely switched to electronic cigarettes and the remaining 8 were dual users of both conventional and electronic cigarettes. However, both groups showed statistically significant improvements in spirometry data, asthma control and airway hyperresponsiveness after beginning use of electronic cigarettes. The authors concluded that electronic cigarettes may be a valid option for asthmatic smokers.

Studies that are Planned or In Progress

A consistent conclusion stated in the early literature is that larger, longer studies are needed to determine the efficacy of electronic cigarettes for reducing or quitting smoking under real-life conditions and with specific populations of subjects. The following are planned or in progress:

- A multi-center cohort study initiated in June 2013 in Italy will follow 1500 subjects for 5 years to evaluate long-term efficacy and safety of electronic cigarettes. Three groups of subjects will be enrolled: those who have used electronic cigarettes only, conventional cigarettes only or both for at least 6 months. The study will evaluate adherence to electronic cigarette use, efficacy for reducing and/or quitting smoking and will compare the health effects of electronic cigarette use to both smoking and dual use of conventional and electronic cigarettes (Manzoli et al. 2013).

- A 12-month, randomized controlled clinical trial is planned to evaluate smoking reduction, smoking abstinence and adverse events among 153 schizophrenic individuals not intending to quit. The SCARIS study (Smoking Cessation and

Reduction in Schizophrenia) will have three arms: a popular electronic cigarette with either 24 mg or 0 mg nicotine, or the PAIPO nicotine-free inhalator (Caponnetto et al. 2014).

- A 12-month, open-label randomized clinical trial of 1,600 smokers in New Zealand will evaluate whether electronic cigarettes are more effective for quitting smoking than short- or long-term use of existing NRTs (ANZCTR 2012).

C. Conclusions about the Efficacy of Electronic Cigarettes for Smoking Reduction and Cessation

The body of literature on the efficacy of electronic cigarettes for smoking reduction and cessation continues to grow rapidly. As many of the observational studies show, smokers are very interested in alternatives to smoking. Currently available electronic cigarettes, especially when used by experienced vapers, can deliver adequate nicotine to suppress abstinence symptoms. A growing number of studies show that electronic cigarettes are effective in helping smokers make statistically significant reductions in the number of cigarettes smoked per day. Electronic cigarettes also appear to help some smokers quit smoking.

V. PATTERNS OF USE AND DUAL USE

This section summarizes the available information on the prevalence of electronic cigarette use among the general population of adults in the United States and among the population of current and ex-smokers.[102] This section also addresses the dual use of conventional and electronic cigarettes. As noted elsewhere in these comments (*see* Part 2.III., Addiction and Dependence), electronic cigarettes are rarely used by never-smokers.[103] By definition, dual use occurs among individuals who are current or former smokers. Thus, the discussion that follows generally involves information obtained from current and former smokers.

The available information shows that use of electronic cigarettes among the general population of adults in the United States is low but increasing. Almost all electronic cigarette users are current or former smokers. Although dual use of conventional and electronic cigarettes has not been studied specifically, it appears that dual use is a common and often temporary condition that occurs when an individual is transitioning from being a smoker to reducing or quitting smoking by using electronic cigarettes. Any substitution of electronic cigarettes for smoking, even partial, lessens an individual's exposure to harmful constituents found in conventional cigarettes. Nutt et al. (2014) recently estimated that electronic cigarettes have only 4% of the maximum relative harm of conventional cigarettes, so any substitution of electronic cigarettes for

[102] Prevalence of use by adolescents is discussed in Part 2.VI. on Youth Issues.

[103] Data from nine large surveys show that ever-use of electronic cigarettes by never-smokers is approximately 1% or lower. Current use of electronic cigarettes by never-smokers is even less common, with almost all estimates lower than 0.3%.

conventional cigarettes is likely to benefit the user's health. While there is little information to date on the effect of flavors in electronic cigarettes on the behavior of users, it appears that flavors reflect personal preferences and may aid in smoking cessation.

A. Prevalence of Use of Electronic Cigarettes among United States Adults

While electronic cigarettes are not widely used by the general population of US adults, awareness is high and the prevalence of use appears to be increasing. A national, consumer-based survey showed that 57.9% of US adults were aware of electronic cigarettes in 2011 (King et al. 2013). A recent systematic review of 49 studies reported that prevalence of use in the US in 2011 was about 6% (Pepper and Brewer 2013). More recent estimates of prevalence come from small, although nationally representative populations. A US population survey with a national probability sample of 10,041 adults reported that 8.1% had tried electronic cigarettes and 1.4% were current users (Zhu et al. 2013). Data from 3,627 adults in the 2012 RTI National Adult Tobacco Survey showed that 0.4% were exclusive users of electronic cigarettes and 1.9% used both conventional and electronic cigarettes (Lee et al. 2014).

As mentioned previously, the vast majority of electronic cigarette users are current or former smokers. A very recent paper by Giovenco et al. (2014) documented the prevalence of use of electronic cigarettes in a nationally representative survey of 2,136 current and former cigarette smokers in the US in June 2013. These authors argue for the use of a different metric ("established use") because the commonly used "current use" likely includes people who have recently tried but do not continue to use electronic cigarettes. Among their population of current and former smokers, 46.8% had used electronic cigarettes (tried even once), 16.1% were current users (used at least once in the past 30 days) and 3.8% were established users (used in past 30 days and more than 50 times in life). Established use of electronic cigarettes was significantly higher among former smokers (8.3%) than current daily smokers (2.8%) (OR=3.24; 95% CI:1.13-9.30, $p<0.05$).

Prevalence of use of electronic cigarettes is higher in some other countries. As of 2014, approximately 2.1 million adults in Great Britain used electronic cigarettes. Among current smokers, 51.7% had ever used electronic cigarettes and 17.7% were current users. Among ex-smokers, 11.8% had ever used electronic cigarettes and 4.7% were current users (ASH 2014). A general population survey of smokers in Great Britain reported current electronic cigarette use by 21.9% of current smokers and 18.8% of recent ex-smokers (Brown et al. 2014a).

B. Dual Use of Conventional and Electronic Cigarettes

One of the most commonly raised concerns about electronic cigarettes is that of dual use of conventional and electronic cigarettes (*e.g.*, Drummond and Upson 2014). Dual use is not a well-characterized behavior and has not been studied specifically. The prevalence and duration of dual use are not well understood, nor is it clear how great the reduction in cigarette use is during the period of dual use. However, it appears to be a common and often temporary condition that occurs when an individual is transitioning from being a smoker to reducing or quitting smoking by using electronic cigarettes.

According to a systematic review, dual use of conventional and electronic cigarettes is not commonly reported in population surveys, but it is fairly commonly observed among convenience samples of subjects who use electronic cigarettes (Pepper and Brewer 2013). For example, two probability samples of US adults in 2010 found that 6% (Regan et al. 2013) and 4% (Pearson et al. 2012) of current smokers had used electronic cigarettes in the past 30 days. A study that specifically evaluated the prevalence of multiple tobacco product use among US adults in 2012 reported that dual use of conventional and electronic cigarettes occurred among only 1.9% (Lee et al. 2014).

While dual use was not specifically studied in the two randomized clinical trials of smoking reduction and cessation conducted to date, it was fairly common. At 52 weeks of follow-up in the ECLAT study, 29 of 200 smokers in the two groups that used an electronic cigarette with nicotine cartridges were "reducers" (people who had $\geq$50% reduction in smoking) and 12 of 100 in the no-nicotine cartridge group were "reducers" (Caponnetto et al. 2013a). In the trial conducted by Bullen et al. (2013b), subjects who continued to smoke and use electronic cigarettes at 6 months were noted to have reduced cigarette consumption. As described in Part 2.IV., Smoking Reduction and Cessation, these and numerous other studies have reported statistically significant reductions in conventional cigarette use among dual users.

Surveys of vapers also provide information on the extent and nature of dual use. In a survey of 104 vapers, 40% quit smoking within 2 months of beginning vaping, while 14% continued dual use (Foulds et al. 2012). Among a group of 1,347 vapers, 74% had not smoked for several weeks to several months since using their electronic cigarettes (Dawkins et al. 2013a). Among a group of 3,587 visitors to websites and online discussion forums dedicated to smoking cessation, 65.2% said they had ever used both an electronic cigarette and tobacco on the same day; however, those who reported dual use also stated that the median duration of dual use was 5 days (Etter and Bullen 2011a). In a longitudinal internet survey to assess behavior change over 12 months in electronic cigarette users, 22% of dual users stopped smoking after 1 month and 46% stopped after 1 year (Etter and Bullen 2013). In a worldwide survey of more than 19,000 electronic cigarette users, approximately 19% were current smokers. Almost one-third of these smoked less than daily, while the daily smokers reduced consumption from 20 to 4 cigarettes per day (Farsalinos et al. 2014b). Finally, a very recent analysis of the duration of electronic cigarette use among 159 users found that increased duration of electronic cigarette use was associated with fewer cigarettes smoked per day (Lechner et al. 2014).

C. Health Effects of Dual Use

The health effects of dual use have not been studied specifically, but numerous studies have shown that electronic cigarettes deliver far fewer and much lower levels of the harmful or potentially harmful constituents delivered in cigarette smoke. Therefore, any time conventional cigarettes are replaced by electronic cigarettes, the user is exposed to fewer harmful chemicals.

As described in more detail in (see Appendix 10, referenced in Part 2.II., Health Effects), surveys describe a number of perceived health benefits among smokers who have reduced smoking with electronic cigarette use, most commonly better breathing, senses of taste and smell, endurance and physical status in general. Smokers with pre-existing diseases generally reported

improvements after initiating electronic cigarette use (*e.g.*, Farsalinos et al. 2014b). As would be expected, in the worldwide survey of more than 19,000 electronic cigarette users mentioned above, the beneficial health effects were more apparent in former smokers (who had completely substituted electronic cigarettes for smoking) than in electronic cigarettes users who continued to smoke (Farsalinos et al. 2014b).

Studies are planned to specifically evaluate the health effects of dual use, including a large multi-center cohort study initiated in June 2013 in Italy. The study is following 1,500 subjects for 5 years to evaluate long-term efficacy and safety of electronic cigarettes. Three groups of subjects will be enrolled: those who have used electronic cigarettes only, conventional cigarettes only, or both for at least 6 months. The study will evaluate efficacy for reducing and/or quitting smoking and will compare the health effects of electronic cigarette use to both smoking and dual use of conventional and electronic cigarettes (Manzoli et al. 2013).

The potential harm from electronic cigarettes was recently estimated to be only 4% of the maximum relative harm (MRH) of conventional cigarettes (by comparison, NRTs were rated at about 2% of the MRH). This was determined by an international expert panel convened by the Independent Scientific Committee on Drugs, which developed a multi-criteria decision analysis model of 14 types of harms to the user and to others from various nicotine-containing products. Not surprisingly, conventional cigarettes were the most harmful. The authors concluded that attempts to use other forms of nicotine such as electronic cigarettes to reduce cigarette smoking should be encouraged, as the harms of such products are much lower (Nutt et al. 2014).

D. Smokers Who Might Otherwise Have Quit

One of FDA's comments raises the question of whether the existence of electronic cigarettes might keep smokers who would otherwise have quit from doing so: "FDA cautions that long-term studies are not available to . . . establish what effects e-cigarettes have in users who might have otherwise quit, but instead engage in dual use of e-cigarettes and another tobacco product."[104]

The concern that the existence of electronic cigarettes will keep smokers from quitting is speculative. There are no data suggesting that the availability of electronic cigarettes keeps smokers from quitting. It is not clear how the theoretical occurrence of failure to quit because of dual use could even be studied, other than to ask current smokers what their intentions are with respect to quitting and whether the existence of electronic cigarettes would affect their plans. Such data would be of questionable value, however, as it is commonly recognized that many smokers often talk about intentions to quit smoking without ever following through on their stated intent.

On the other hand, there is some anecdotal evidence that the existence of electronic cigarettes might keep former smokers from relapsing to smoking. In a study of 3,585 visitors to websites and online discussion forums dedicated to electronic cigarettes and smoking cessation, most

[104] 79 Fed. Reg. at 23152.

former smokers (79%) feared they might relapse to smoking if they stopped using the electronic cigarette (Etter and Bullen 2011a).

E. Role of Flavors in Adult Use of Electronic Cigarettes

Few studies have specifically examined the role of flavors in electronic cigarette use or the behavior of adult electronic cigarette users. No studies have addressed the role of flavored electronic cigarettes on later initiation of conventional cigarettes. The literature that exists suggests that flavors reflect personal preferences and may aid in smoking cessation.

An early study reported that flavors are appealing to electronic cigarette users. In an 2009 internet survey of 81 electronic cigarette users, one of the most frequently mentioned positive features of electronic cigarettes was the taste and variety of flavors (Etter 2010). The preferred flavor was tobacco (46 of 78 responses), followed by mint, fruit, vanilla, coffee and tea. A more recent online survey of 1,347 electronic cigarette users examined preferred flavors (Dawkins et al. 2013a). Tobacco was the most popular flavor (53%), although results differed by gender. Men preferred tobacco-flavored liquids, while women preferred chocolate or other sweet flavors.

Lorillard's data on sales of flavored cartridges for blu™ electronic cigarettes confirm that flavors are popular. Of approximately 1.4 million flavored cartridges sold via blucigs.com in the 12 months ending April 30, 2014, about 36% were classic tobacco flavor, 15% were menthol and the remaining 48% were other flavors (cherry, vanilla, java, pina colada, peach schnapps). The vast majority (86%) of flavored cartridges were purchased by people age 25 to 64. People age 18-24 purchased only 3% of flavored cartridges, while people age 65 and older purchased 10% of flavored cartridges.

However, a worldwide survey of more than 19,000 electronic cigarette users shows that the preference for flavors does not appear to be a strong factor in the initiation of electronic cigarette use (Farsalinos et al. 2014b). Respondents were given 5 reasons for initiating use of electronic cigarettes and asked to rate them from 1 (not important) to 5 (most important). The two most important reasons were reducing or quitting smoking (rated 5) and reducing smoking exposure to family members (rated 4). Enjoying the variability in flavors was rated 3 (neither important nor unimportant). Economic reasons was also rated 3, while avoiding smoking bans in public places was rated 2.

Two studies suggest that users perceive flavored electronic cigarettes to be helpful in smoking cessation. In a focus group conducted with 11 electronic cigarette users, flavors played a role in one of the themes ("hobby") that helped explain why users perceive electronic cigarettes to be more efficacious than NRTs for smoking cessation (Barbeau et al. 2013). The authors speculated that having a variety of flavors, devices and nicotine levels available reinforces the motivation to quit smoking and helps prevent relapse.

The second study was done specifically to examine and understand the impact of flavors on the electronic cigarette experience of a group of more than 4,500 dedicated users (Farsalinos et al. 2013c). On average, these individuals used 3 different flavors on a regular basis, with former smokers (who had quit after using electronic cigarettes) switching between flavors more

frequently than current smokers. Tobacco flavors were most popular at the time of electronic cigarette initiation, while fruit and sweet flavors were more important at the time of the survey. Flavor variability was rated very important (4 on a scale from 1 to 5) with respect to reducing or quitting smoking. The majority said that restricting the availability of flavors would make the electronic cigarette experience less enjoyable and almost half said it would increase craving for tobacco cigarettes and would make reducing or quitting smoking less likely. Logistic regression showed that the number of flavors regularly used was significantly associated with complete smoking abstinence in this group ($p=0.038$). The authors speculated that the improvement in taste and smell that occurs in people who have quit smoking could lead to more pleasure perceived from different flavors and an aversion to tobacco flavor. Such a phenomenon may contribute to lower relapse to smoking; however, the authors caution that this should be specifically studied before drawing any conclusions.

F. Conclusions about Patterns of Use and Dual Use

The prevalence of electronic cigarette use in the US is low but appears to be increasing. At the same time, a decrease in the size of the conventional cigarette market was noted, which does not appear to be fully attributable to past smoking cessation trends. Electronic cigarettes are used almost exclusively by current and former smokers, with most studies suggesting that never-smokers make up less than 1% of users (Pepper and Brewer 2013). Dual use of conventional and electronic cigarettes does occur; in fact, it appears to be a common and often temporary, condition that reflects the migration from exclusive smoking to reducing or quitting smoking. While the health effects of dual use have not yet been studied specifically, any substitution of electronic cigarettes for smoking lowers an individual's exposure to potentially harmful constituents. It was recently estimated that electronic cigarettes have only 4% of the maximum relative harm of conventional cigarettes, so any substitution of electronic cigarettes for conventional cigarettes is likely to bring significant benefits not only to the user, but also to nonsmokers and to society as a whole (Nutt et al. 2014). Emerging literature suggests that flavors reflect personal preferences and may aid in smoking cessation.

VI. YOUTH ISSUES

This section addresses issues raised by FDA in the preamble to the Proposed Deeming Regulation related to the use of electronic cigarettes by young people, and includes a discussion of:

- Increasing prevalence of use;
- The role of flavors (in electronic cigarettes and in general) and their effect on subsequent tobacco use patterns in young people;
- Electronic cigarettes as a gateway to smoking;
- Electronic cigarettes as a gateway to nicotine addiction; and

- Whether young people are uniquely susceptible to nicotine addiction.[105]

A. Prevalence of Use of Electronic Cigarettes among Young People

While electronic cigarettes are not commonly used by young people, awareness of them by youth is high and the prevalence of use appears to be increasing (Durmowicz 2014). The National Youth Tobacco Survey (NYTS), a cross-sectional, nationally representative sample of US students in grades 6-12, reported that ever-use of electronic cigarettes increased from 3.3% in 2011 to 6.8% in 2012 (Corey et al. 2013). Since ever-use likely reflects some degree of experimentation, a more relevant metric may be current use of electronic cigarettes. From 2011 to 2012, current use increased from 1.1% to 2.1%. Data from the UK suggest that regular use of electronic cigarettes among young people is confined almost entirely to current or former smokers (ASH 2013b); however, Durmowicz concluded that use is not limited to conventional cigarette smokers. Current dual use of electronic cigarettes and conventional cigarettes in the NYTS increased from 0.8% in 2011 to 1.6% in 2012 (Corey et al. 2013).

According to a recent review by Carroll Chapman and Wu (2014), no studies have addressed reasons for use of electronic cigarettes by adolescents (ages 13-18) or young adults (age 20-28 or of college age), although they note that adolescence is a time when individuals often experiment with and initiate substances. The only common correlate associated with use of electronic cigarettes found in this review was cigarette smoking.

B. Effect of Flavors on Young People

In its proposed rule, FDA raises questions about the role that flavors might play in youth behavior, stating that: "flavors can be especially attractive to youth" and "FDA is also seeking research regarding the long-term effects of flavored tobacco product usage including data as to the likelihood of whether users of flavored tobacco products initiate cigarette usage and/or become dual users with cigarettes."[106]

While many authors (*e.g.* Etter 2010) have suggested that flavored electronic cigarettes might appeal to young people and thus facilitate initiation of nicotine dependence, this hypothesis has not been tested. There are no actual studies on the effect of flavors in electronic cigarettes on the subsequent tobacco use behaviors of young people.

Two studies present some information on electronic cigarette flavor preferences of young people. Pepper et al. (2013) conducted a small, cross-sectional online survey of 228 teenage boys (age 11 to 19) in 2011. Although only 2 boys (<1%) had ever tried electronic cigarettes, 18% said they would try one if it was offered by one of their best friends. Willingness to try plain versus flavored varieties did not differ, leading the authors to suggest that candy or fruit flavors do not increase the attractiveness of electronic cigarettes to adolescents. The authors speculated that

[105] *Id*.

[106] *Id*. at 23144.

future marketing of flavored electronic cigarettes directed to young people could increase their appeal relative to unflavored electronic cigarettes.

Choi et al. (2012) held focus groups with 66 young adults (age 18-26) and found that they had generally positive perceptions of novel products (snus, dissolvable tobacco products and electronic cigarettes), especially the flavored ones. The authors hypothesized that eliminating flavors in these products may reduce young adults' intentions to try these products.

Research not involving electronic cigarettes has shown that improving the flavor of a smoking cessation aid (nicotine chewing gum) did not increase abuse liability among young adults. In a randomized, placebo-controlled, double-blind study, 24 subjects (including 12 who were between the ages of 18 and 21) compared original nicotine gum with mint-flavored gum; amphetamine and confectionary gum were included as positive controls for abuse liability and palatability. The mint gum was rated more palatable than the original nicotine gum and substantially lower than the confectionary gum, but neither flavor of nicotine gum increased ratings of traditional abuse liability predictors. The authors concluded that improved flavor of nicotine gum did not increase abuse liability in either young adults or older subjects, but could be associated with enhanced reduction of craving (Houtsmuller et al. 2002).

C. Electronic Cigarettes as a Gateway to Tobacco Smoking

While many authors have speculated that use of electronic cigarettes could be a gateway to later tobacco use, there is currently no evidence to support this hypothesis. To test the hypothesis, a longitudinal study is needed. Such a study would identify young people before use of any products (either electronic cigarettes or any type of tobacco product) and record information on product use over time, which would then permit a useful examination of temporal relationships.

Two analyses of a single longitudinal study (Choi and Forster 2014a, 2014b) that provide data on the temporal relationship between smoking and electronic cigarette use do not suggest that electronic cigarettes are a gateway to smoking. The study was not done to examine order of use of tobacco and electronic cigarettes; rather, it investigated what beliefs predict experimentation with electronic cigarettes by young adults (mean age 24). The initial analysis involved 1,379 young people in the Minnesota Adolescent Community Cohort who (by self-report) had never used an electronic cigarette. When they followed up with the same young people 1 year later, 7.4% (or 102 people) had tried one. Among the 102 who had tried electronic cigarettes, there were:

- Seventy-four who were current or former smokers at baseline. Thus, the majority of electronic cigarette users at follow-up (72.5% of those who had tried an electronic cigarette) had smoked before ever using an electronic cigarette.

- Twenty-eight who were nonsmokers at baseline (defined as "never smoked $\geq$100 cigarettes in their lifetime and none in the past 30 days). They represent 2.0% of the total study population, 2.9% of the baseline nonsmokers and 27.5% of those who had tried an electronic cigarette.

The authors didn't provide information on whether the 28 baseline nonsmokers smoked regular cigarettes after the baseline interview and before they tried electronic cigarettes and there is no way to know if they went on to try cigarettes in the future after first trying electronic cigarettes. However, this study, although done for the purpose of studying beliefs about electronic cigarettes, does not provide strong support for a gateway hypothesis. In fact, it was criticized by Knight-West et al. (2014) for not reporting smoking status at follow-up, thereby making it impossible to determine any relationship between electronic cigarette use and smoking.

In response, Choi and Forster (2014b) conducted a second analysis of the same longitudinal cohort specifically to examine the gateway hypothesis. At the 1-year follow-up, 10% of nonsmokers who had tried electronic cigarettes at baseline became current cigarette smokers at follow-up compared to 5% of nonsmokers who had never tried electronic cigarettes (OR=2.11, 95% CI:0.48-9.26, p=0.32). The authors incorrectly state "these data are consistent with the possibility that electronic cigarette experimentation is acting as a pathway to cigarette smoking." This conclusion is not justified by the data, which clearly do not show a statistically significant difference.

This was a small study and there were few electronic cigarette users in the population; thus, additional studies are needed. However, the first longitudinal study of the relationship between electronic cigarette use and smoking does not support the hypothesis that electronic cigarettes are a gateway to smoking for young people.

Ecological data (data derived from populations rather than individuals) also fail to find support for a gateway hypothesis. As pointed out by Siegel (2014), enough young people are experimenting with electronic cigarettes that, if the gateway hypothesis were correct, there would be an increase in smoking prevalence as electronic cigarette experimenters are converted to smokers. Instead, while electronic cigarette experimentation among high school students doubled from 4.7% 2011 to 10.0% in 2012 (Corey et al. 2013, based on the National Youth Tobacco Survey), smoking prevalence among high school students fell from 18.1% in 2011 to 15.7% in 2013 (CDC 2014, based on the Youth Risk Behavior Survey). These data argue against a gateway hypothesis.

Two cross-sectional surveys examined use of both electronic cigarettes and conventional cigarettes, but results must be interpreted with caution as cross-sectional data cannot address order of use. An analysis of data from the National Youth Tobacco Survey concluded that use of electronic cigarettes "does not discourage and may encourage" use of conventional cigarettes (Dutra and Glantz 2014). These authors examined the relationship between conventional and electronic cigarette use among 39,882 students in grades 6-12 in 2011 and 2012. They reported that use of electronic cigarettes was associated with higher odds of ever or current smoking and higher odds of established smoking. The authors acknowledge that their cross-sectional analysis does not allow them to determine whether most youth initiate with conventional cigarettes and then move on to electronic cigarettes or vice versa; consequently, their conclusion is not justified by the data.

A similar analysis of cross-sectional survey data on electronic cigarette use by Korean adolescents concludes that the products "inhibit rather than promote cessation" (Lee et al. 2013).

This analysis used data from the 2011 Korean Youth Risk Behavior Survey of 75,643 students age 13-18. A total of 9.4% had ever used electronic cigarettes (8% were ever-users of both conventional and electronic cigarettes) and 4.7% were current electronic cigarette users. Smokers and those who smoked more frequently were more likely to be current electronic cigarette users. Former smokers were rare among current electronic cigarette users, which the authors interpreted as suggesting that electronic cigarettes inhibit cessation. Again, their conclusion about a temporal relationship is not warranted, based on the cross-sectional nature of the data.

While additional longitudinal studies with larger numbers of subjects are needed, to date there is no evidence that electronic cigarettes serve as a gateway to conventional cigarette smoking among young people.

D. Electronic Cigarettes as a Path to Nicotine Addiction

As noted above, FDA raises the possibility that electronic cigarettes could serve as a path to nicotine addiction for non-tobacco-using adolescents, stating that "[m]ore youth who report they would never have used a tobacco product are experimenting with e-cigarettes."[107] This concern can be addressed by the available literature, which shows that the prevalence of electronic cigarette use among adolescents who have never smoked is very low. Furthermore, available literature does not indicate that electronic cigarette users progress to conventional cigarettes smoking.

Eight surveys were identified that provide data on the prevalence of ever and current electronic cigarette use among adolescents who have never smoked (see Appendix 14). Estimates are generally low (about 3% or less) although a few are higher (9.3%-16%, mostly among college students).

Most of the surveys involved fairly large populations (several in excess of 10,000 respondents) and were conducted in the US, UK, Europe and South Korea. Ever-use of electronic cigarettes by never-smokers ranged from 0.4% to 16%, with most estimates under 4%. The prevalence of ever-use was lower among adolescents under age 18 (typically under 4%) and higher among college and university students (ranging from 3% to 16%). Current use (as opposed to ever-use) of electronic cigarettes by never-smokers is quite uncommon, with almost all prevalence estimates lower than 1%. The large difference between estimates of ever-use and current use suggests that it may be common for young people to experiment with, but not become regular users of, electronic cigarettes.

Two of the studies cited in Appendix 14 analyzed data from the US National Youth Tobacco Survey, but arrived at fairly different estimates of the prevalence of ever-use among never-smokers in grades 6-12 in 2012. Corey et al. (2013) reported that, of an unspecified number of students, 9.3% who had ever used an electronic cigarette had never smoked a conventional cigarette. Dutra and Glantz (2014) found that, of 22,529 students, 4.1% who had ever used an

[107] *Id*. at 23147.

electronic cigarette had never smoked a conventional cigarette. It is not clear why the authors of these studies reported such different results.

The available literature shows that the number of adolescent never-smokers who have ever used electronic cigarettes is low, although not quite as low as the estimates among adults (see Appendix 11, referenced in Addiction and Dependence). Perhaps this is not surprising, as adolescence is known to be a period of experimentation and risk-taking. Furthermore, it is not known whether any of these adolescents could be using electronic cigarettes that do not contain nicotine. As discussed above, there are no data indicating that users of electronic cigarettes are more likely to progress to conventional cigarettes. Concerns that electronic cigarettes serve as a pathway to nicotine addiction do not appear to be justified by the current scientific literature.

FDA also states that "e-cigarettes that deliver very low levels of nicotine may be effective starter products for non-tobacco product users. Such risks could be mitigated by the establishment of an FDA regulatory approach for these products that focuses on limiting youth initiation."[108] blu does not market and is not aware of any electronic cigarettes that are designed to serve as "starter products."

Lorillard supports efforts to prevent youth access to electronic cigarettes through a number of initiatives, including banning sales to those under age 18 and website age verification.

E. Susceptibility of Youth to Nicotine Addiction

FDA raises concerns that adolescents are uniquely susceptible to nicotine addiction, stating that "there are data suggesting that the adolescent brain is more vulnerable to developing nicotine dependence than the adult brain. There is also evidence to suggest that these brain changes are permanent."[109] FDA cites two studies to support this concern, Torres et al. (2008) and Schochet et al. (2008). Both of these studies were conducted on rats.

In Torres et al. (2008), the authors observe behavior that is similar to nicotine self-administration in rats using the conditioned place preference (CPP) test. Briefly, rats were given nicotine injections when they were placed in a specific chamber of a two-chambered box. When the same rats were placed in the opposite chamber, they were given injections of saline. After many injections, a test was performed to see if the rats preferred to stay in the nicotine-injection chamber or the saline-injection chamber. From this experiment, the authors generated a "difference score," which reflects how much more a rat prefers to stay in the nicotine-injection chamber at the end of the study than it did at the beginning of the study. The authors found that for moderate doses of nicotine, adolescent rats have significantly higher difference scores (and therefore, CPP) than adult rats. They also found that adolescent rats were less avoidant of higher, potentially noxious doses of nicotine than adult rats. This latter effect was true whether the adolescents had encountered nicotine before the experiment or not.

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[108] *Id*. at 23158 (citations omitted).

[109] *Id*. at 23153.

While use of the CPP test is accepted in the study of lab animals, its relevance for understanding human health is uncertain according to some researchers. In a review of the CPP protocol, Dr. Michael Bardo and Dr. Rick Bevins write that "a lingering criticism of CPP is that it has not been validated as a protocol for measuring drug reward in either humans or non-human primates…until it is demonstrated that humans prefer an environmental context previously associated with a drug US [unconditioned stimulus] over an unpaired context, the validity of CPP for understanding drug reward in humans will remain speculative" (Bardo and Bevins 2000).

In the study by Schochet et al., the authors found that expression of the mRNA that encodes the protein dendrin is increased one hour after rats have been injected with nicotine. This increase was greater in adolescent rats (about -10% to +33%, depending upon brain region) than in adult rats (about 0% to +10%, depending upon brain region). However, this change was no longer apparent two hours after the nicotine injection. The regulatory response by a specific gene to a given stimulus can differ enormously between two species as divergent as rats and humans, and there are no available data that show if or how dendrin expression responds to nicotine in humans. Furthermore, even if it were clear that humans show a change, similar to that in rats, in dendrin mRNA expression after exposure to nicotine, it is questionable whether this finding would be meaningful because dendrin has never been shown to serve an important function in the nervous system. Therefore, it is inappropriate to extrapolate the findings of Schochet et al. to the neural development or function of humans.

In a very recent human study, Morales et al. (2014) recruited smokers and non-smokers aged 16-21 to determine if measures of tobacco use and dependence correlate with the thickness of the insular cortex of the cerebrum, which is hypothesized to contribute to tobacco dependence. The authors imaged the participants' brains using magnetic resonance imaging (MRI), and constructed virtual, three-dimensional models from these data. From these models, data concerning the thickness of the insular cortex were extracted. Using analysis of co-variance (ANCOVA), the authors looked for potentially confounding correlations between insular thickness and the co-variables of sex, alcohol use, and marijuana use. They then looked for correlation between insular cortex thickness and smoking-related variables (pack-years and cigarette dependence score). Morales et al. found no difference in insular cortex thickness between young adult smokers and nonsmokers.

The studies cited by FDA do not provide adequate scientific support for the hypothesis that youth are uniquely susceptible to nicotine dependence. Further, the Morales et al. study casts additional doubt on the validity of the hypothesis.

F. Conclusions about Electronic Cigarettes and Youth Issues

Lorillard appreciates and shares FDA's concerns about use of electronic cigarettes by adolescents. While regular use of electronic cigarettes by young people is currently uncommon, the prevalence has increased in recent years. A mounting body of evidence shows that very few young never-smokers use electronic cigarettes. There are still many unknowns, and there is little longitudinal information about the relationship between use of electronic cigarettes and later

tobacco use. Lorillard supports a ban on sales to those under age 18 and believes that addiction warnings on nicotine-containing electronic cigarettes will provide an additional safeguard against the possibility of young people becoming addicted to nicotine through use of electronic cigarettes.

VII. MARKETING AND CONSUMER PERCEPTIONS OF RISK

This section addresses issues related to marketing and consumer perception of electronic cigarettes, including:

- Marketing practices related to electronic cigarettes (especially the marketing of flavored electronic cigarettes); and
- Consumer beliefs about the safety and efficacy of electronic cigarettes.

A. blu Follows Responsible Practices in the Marketing of Electronic Cigarettes

Lorillard is in favor of reasonable, science-based regulation of electronic cigarettes and marketing restrictions. We believe that FDA should institute regulations that mirror the continuum of risk. In the absence of regulations, blu has voluntarily implemented many responsible measures and has engaged in the promotion to state governments for sales restrictions that prevent youth access.

Lorillard acknowledges that "e-cigarettes are widely available in retail outlets such as kiosks in shopping malls and on the Internet."[110] Lorillard believes that responsible and feasible marketing practices should be implemented that mirror the continuum of risk among nicotine-containing products and is in favor of a regulatory framework that ensures the prohibition of sales and marketing to youth. Lorillard strongly believes that responsible and feasible marketing parameters prohibiting the marketing and sales of electronic cigarettes to youth may be achieved without establishing unnecessary obstacles that prevent traditional smokers from having access to the product.

FDA asserts that "some e-cigarettes . . . are being marketed with flavors that may be attractive to young people."[111] While Lorillard encourages FDA to institute reasonable, scientifically-based marketing parameters, scientific data regarding the role of flavors in electronic cigarettes is unclear. Regardless, Lorillard supports a ban on sales to those under age 18. blu takes reasonable and feasible measures to support and reinforce its belief and policy that electronic cigarettes are not a product for youth and any usage of electronic cigarettes by youth is unacceptable. Such measures include age certification and age verification for blu's website; marking each package of its products with the following, or similar, warning: "NOT FOR SALE TO MINORS" in a prominent position, clearly legible on the package; and various marketing restrictions, as outlined in Part 1.I. of this response.

[110] *Id*. at 23146.

[111] *Id.* at 23147-23148.

Lorillard is committed to taking a leadership role in demonstrating how manufacturers in an emerging but largely unregulated category can and should be responsible. Lorillard is in favor of a regulatory framework that ensures that sales and marketing to youth is prohibited. blu has demonstrated its commitment to this by establishing, implementing and abiding by a series of age-related restrictions to limit youth exposure, as outlined in Part 1.I. of this response.

blu is also committed to ensuring that no promotional materials or advertising includes implied or express claims that electronic cigarettes are healthy, including claims that electronic cigarettes may help consumers quit smoking conventional cigarettes. Packaging for blu™ electronic cigarettes also includes the following warning: "Warning: This product contains nicotine, a chemical known to the state of California to cause birth defects or other reproductive harm."

B. Consumer Perceptions about the Safety and Efficacy of Electronic Cigarettes

FDA is concerned that consumers have beliefs about electronic cigarettes that are not substantiated by the scientific evidence. Specifically, the Proposed Deeming Regulation states:

- "Many consumers believe that e-cigarettes are 'safe' tobacco products or are 'safer' than cigarettes"; and

- "[M]any consumers have strong, but to date unsubstantiated, beliefs that e-cigarettes are a safe and effective way for quitting cigarette use and many consumers start consuming e-cigarettes because of those unsubstantiated beliefs."[112]

There is evidence that consumers, especially those who use electronic cigarettes, do believe that electronic cigarettes are safer than conventional cigarettes and that they can be an effective aid in reducing or quitting smoking. A recent systematic review that summarizes 49 studies examining awareness, use, reactions and beliefs about electronic cigarettes supports this, finding that the most common reasons for using electronic cigarettes are to use a product that is healthier than cigarettes and to quit smoking (Pepper and Brewer 2013).

1. Consumer Beliefs about the Safety of Electronic Cigarettes

There is ample evidence that many adult consumers believe that electronic cigarettes are safer than conventional cigarettes. The review by Pepper and Brewer (2013) cited above reported that many electronic cigarette users consider the products to be healthier than smoking both for themselves (*e.g.*, Etter 2010, McQueen et al. 2011, Barbeau et al. 2013, Dawkins et al. 2013a, Goniewicz et al. 2013c,) and for others (Foulds et al. 2011, Farsalinos et al. 2014b). For example, in a survey of 19,353 electronic cigarette users, 2,124 (11%) said that electronic cigarettes were absolutely harmless and 17,063 (88.2%) said they were less harmful than tobacco cigarettes (Farsalinos et al. 2014b). Few electronic cigarette users in these surveys raised concerns about safety and toxicity (*e.g.*, Etter and Bullen 2011a).

[112] *Id*. at 23158.

Surveys that included adult respondents who did not use electronic cigarettes (typically surveys of current and former smokers) also found that many believe the products to be less harmful than cigarette smoking (Pearson et al. 2012, Adkison et al. 2013, Li et al. 2013, Zhu et al. 2013, Brown et al. 2014a). For example, an analysis of data from 5,939 current and former smokers in the International Tobacco Control Four-Country Survey collected from July 2010 to June 2011 showed that the vast majority of respondents who were aware of electronic cigarettes reported that they were less harmful than traditional cigarettes (Adkison et al. 2013).

Students and younger adults also believe that electronic cigarettes are safer than conventional cigarettes (*e.g.*, Choi et al. 2012, Goniewicz and Zielinska-Danch 2012, ASH 2013b, Choi and Forster 2013, Sutfin et al. 2013). Choi and Forster (2014a) describe a longitudinal study of 1,379 young adults (mean age 24.1) in the Minnesota Adolescent Community Cohort who had never used electronic cigarettes at baseline. Logistic regression showed that participants who believed that electronic cigarettes were less harmful than traditional cigarettes and who believed that they help people quit smoking were significantly more likely to experiment with electronic cigarettes than those who did not hold those beliefs.

2. Consumer Beliefs about the Efficacy of Electronic Cigarettes

As discussed by Pepper and Brewer (2013), numerous surveys of adult electronic cigarette users show that the majority believe the products helped them quit or reduce smoking (*e.g.*, Etter 2010, Foulds et al. 2011, Etter and Bullen 2011a, McQueen et al. 2011, Dawkins et al. 2013a, Goniewicz et al. 2013c, Farsalinos et al. 2014b). Focus groups with electronic cigarette users have helped to clarify the reasons they believe electronic cigarettes help people quit, including: they mimic smoking a real cigarette; they allow a user to stop smoking but not eliminate use of nicotine; and they become part of a vaper's social identity (Barbeau et al. 2013).

Similarly, surveys that included adult respondents who did not use electronic cigarettes (typically surveys of current and former smokers) also found that many believe the products help people quit smoking (Pearson et al. 2012, Li et al. 2013, Zhu et al. 2013). For example, in a survey of 1,380 smokers in Great Britain, 55% thought electronic cigarettes "might help me cut down on cigarettes" and 51% thought "they might help me give up smoking entirely" (Dockrell et al. 2013).

Interest in electronic cigarettes is common among smokers who wish to quit, suggesting that they perceive the products as beneficial cessation aids. A recent survey of practitioners and clients at the UK's Stop Smoking Services showed that almost all practitioners had been asked about electronic cigarettes (95%) and almost all had clients who had used them (90%). The main reasons for use were to cut down or quit smoking, or as an alternative to smoking (Beard et al. 2014). As noted above in the Choi and Forster (2014) longitudinal study of 1,379 young adults, the belief that electronic cigarettes help people quit smoking is a significant predictor of experimentation with electronic cigarettes.

C. Conclusions about Marketing and Consumer Perceptions of Risk

Lorillard is in favor of reasonable, science-based regulation of electronic cigarettes and supports marketing restrictions that mirror the continuum of risk among nicotine-containing products. In the absence of current regulations, blu has voluntarily implemented and follows responsible practices, including the prohibition of sales and marketing of electronic cigarettes to youth.

The available information supports the conclusion that many users of electronic cigarettes, as well as many individuals who are aware of the products but do not currently use them, believe them to be safer than cigarettes and a useful aid in reducing or quitting smoking. While any smoke reduction claims made by manufacturers should be substantiated, Lorillard believes it would not help smokers seeking to quit with electronic cigarettes if FDA dissuades them from the attempt, as some smokers may respond better to electronic cigarettes than to NRTs.

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Appendix 1 – Studies of TSNAs in Electronic Cigarettes

Citation	Sample	Findings
Lauterbach et al. 2012	Aerosol	TSNA levels were 122 to 267 times lower than in CS
McAuley et al. 2012	Aerosol	TSNA levels were 8 to 10 times lower than in CS
Laugesen 2009	Aerosol	No TSNAs were detected (LOD unknown)
Goniewicz et al. 2013b	Aerosol	TSNAs levels were 40 to 380 times lower than in CS TSNAs were not detected in the nicotine inhaler
Westenberger 2009	Cartridge	TSNAs were detected, but could not be measured (LOQ = 21 to 75 ppb)
Cheah et al. 2014	Cartridge	No TSNAs were detected (LOD unknown)
Laugesen 2009, Laugesen 2008b	Cartridge	The maximum TSNA level found was 8 ng/g cartridge liquid and was comparable to the amount found in a nicotine medicinal patch The TSNA content was 200 times less than in Swedish snuff More TSNAs were present in higher nicotine e-cigarettes
Schober et al. 2013	Refill liquid	TSNAs were not detected (LOD unknown)
Kim and Shin 2013	Refill liquid	Highly variable levels found TSNA levels ranged from 0.09 µg/L to 62.19 µg/L

Abbreviations: CS: cigarette smoke
LOQ: limit of quantitation
LOD: limit of detection

Appendix 2 – Studies of PAHs in Electronic Cigarettes

Citation	Sample	Findings
Lauterbach et al. 2012	Aerosol	PAH level was 56 times lower than in CS
Laugesen 2009	Aerosol	No PAHs were detected (LOD unknown)
McAuley et al. 2012	Aerosol	Some levels of PAHs in e-cigarette aerosol exceeded those in CS. Problems with the analytical methods were evident and were discussed by the authors.
Laugesen 2008a, Laugesen 2008b, Laugesen 2009	Cartridge	Benzo(a)pyrene was not detected (LOD = 1 ng) PAHs found were all Group 3 IARC and are not classified as carcinogens PAHs were present in e-cigarette liquid between 0.3% and 1.4% of PAHs in smoke of an equivalent number of tobacco cigarettes
Cheah et al. 2014	Cartridge	No PAHs were detected (LOD unknown)

Abbreviations: CS: cigarette smoke
LOD: limit of detection
IARC: International Agency for Research on Cancer

Appendix 3 – Studies of Carbonyls in Electronic Cigarettes

Citation	Sample	Findings
Goniewicz et al. 2013d (abstract)	Aerosol	Acrolein levels were about 4 times lower than in CS
Laugesen 2009	Aerosol	Acrolein was not detected (LOD unknown) Acetaldehyde was detected; author noted this could be artifact from ethanol
Laugesen 2008a	Aerosol	Acrolein was not detected (LOD = 10 ppb) Acetaldehyde, acetone and formaldehyde were detected between 0.16 ppm and 0.34 ppm
Goniewicz et al. 2013b	Aerosol	Carbonyl levels were 9 to 450 times lower than in CS Carbonyl levels were higher in e-cigarette aerosol compared to a nicotine inhaler
Kosmider et al. 2014	Aerosol	Carbonyl levels from lower voltage e-cigarette produced formaldehyde and acetaldehyde levels 13 to 807 times lower than in tobacco smoke Carbonyl levels were similar to those generated by a nicotine inhaler (compared to data in Goniewicz et al. 2013b) Higher voltage produced higher carbonyl levels
McAuley et al. 2012	Aerosol	Carbonyl levels were 10 to 92 times lower than in CS Blank carbonyl level exceeded any level found in aerosol
Lauterbach et al. 2012	Aerosol	Carbonyl levels were 10 and 110 times lower than in CS
Uchiyama et al. 2013	Aerosol	Carbonyl levels were at least 1.9 to 47 times lower than those found in CS (compared to data in Lauterbach et al. 2012, which used a similar protocol)
Shidadeh and Eissenberg 2013 (abstract)	Aerosol	Dripping liquid directly onto a heater surface produced higher carbonyl levels in aerosol
Sobczak et al. 2013 (abstract)	Aerosol	Carbonyls were detected at levels 12 to > 1000 times lower than in CS
Sobczak et al. 2013 (abstract)	Refill liquid	Traces of acetaldehyde were detected (0.081 µg/mL)
Lim and Shin 2013	Refill liquid	Levels were relatively low
Laugesen 2008a Laugesen 2008b Laugesen 2009	Cartridge	Two headspace analyses were conducted (Feb 08, Aug 08) Acetaldehyde and acrolein were detected in Feb (9.2 and 1.0 ppm). Acetaldehyde and acrolein were detected in Aug (5.1 and < 0.33 ppm)

Abbreviations: CS: cigarette smoke

Appendix 4 – Studies of Metals in Electronic Cigarettes

Citation	Sample	Findings
Laugesen 2009	Aerosol	Mercury was the only metal detected Mercury level (0.17 ng per e-cigarette) was 17 to 60 times less than in a cigarette (compared to literature data by Kowalski and Wiercinski 2009)
Goniewicz et al. 2013b	Aerosol	Metal levels were similar to or slightly above those of the nicotine inhaler Metals detected in blank sample was sometimes higher than in e-cigarette sample
Williams et al. 2013	Aerosol	Metal levels in aerosol were often higher than found in CS
Williams et al. 2014 (abstract)	Aerosol	Of 62 elements screened, 21 were present in EC aerosols. Al, B, Ba, Na, Pb, Si, Sr, Zi were less abundant than in CS Ag, Ca, Cr, Cu, Fe, Mg, Mn, Ni, Se, Sn, Ti, Zn were more abundant than in CS
Williams et al. 2013	Cartridge	Metal was found but not quantified in cartridge
Laugesen 2008a, Laugesen et al. 2008, Laugesen 2008b, Laugesen 2009	Cartridge	As, Cd, Cr, Cu, Pb, Mn, Ni not detected (LOD < 0.3 ppm) Sb and Co not detected (LOD = 1, 0.5 ppm) The carcinogenic heavy metals, including As, Cd, Cr, Ni, Pb were not detected (LOD = 2 μg/g)

Abbreviations: CS: cigarette smoke
LOD: limit of detection

Appendix 5 – Studies of VOCs in Electronic Cigarettes

Citation	Sample	Findings
Sobczak et al. 2013 (abstract)	Aerosol	No VOCs were detected (LOD unknown)
Laugesen 2008a	Aerosol	VOC levels ranged from not detected (LOD = 10 ppb) to 0.29 ppm Ethanol was detected at 100 ppm
Laugesen 2009	Aerosol	No VOCs were detected (LOD unknown)
McAuley et al. 2012	Aerosol	Some VOC concentrations were much lower than found in the blank sample VOC levels were 11 to 343 times lower than found in CS Analytical chemistry difficulties were encountered in this study
Goniewicz et al. 2013b	Aerosol	One VOC concentration (*p,m*-xylene) was similar to the control measurements Other VOC (toluene) concentration was 120 times lower than found in CS
Lauterbach et al. 2012	Aerosol	VOC levels were 28 to 297 times lower than found in CS
Laugesen 2009	Cartridge	No VOCs (benzene, cresols, xylenes, or styrene) were detected in headspace (LOD = 0.01 ppm) Toluene was detected in the liquid at trace quantities
Laugesen 2008a	Cartridge	Two headspace analyses were conducted (Feb 08, Aug 08) Benzene and cresols were detected in Feb (1.2 and 0.19 ppm). Benzene and cresols were not detected (upper limit of 0.3 ppm) in Aug (Author notes that after the February analysis, tests linked the benzene to a flavoring. The formula was changed to eliminate this contaminant; the new formulation was tested in August.)

Abbreviations: CS: cigarette smoke
LOD: limit of detection

Appendix 6 – *In-Vitro* Studies of E-Liquid and Aerosols

Citation	Sample	Findings
Genetic Toxicity		
Park et al. 2014 (abstract)	Collected Aerosol	Increased cell division after exposure to high nicotine e-cigarette aerosol and CSE (compared to low nicotine e-cigarette aerosol and the untreated groups). Some changes is cell morphology were similar for CSE and e-cigarette treatments.
Leverette et al. 2014 (abstract)	Cigarette smoke and e-cig aerosol, Collected aerosols and e-liquids	Several CSE preparations were markedly genotoxic in the Ames bacterial mutagenicity test and a mammalian CHO cell micronucleus test. Neither e-cigarette liquids nor collected aerosols produced any meaningful effects in either test at comparable or substantially higher dose levels. Similarly, direct cigarette smoke exposures produced clear mutagenic activity in the Ames test, while direct e-cigarette aerosol exposures did not.
Cytotoxicity		
Farsalinos et al. 2013a	Aerosol	4 of 20 samples were cytotoxic Aerosol extract was significantly less cytotoxic compared to CSE
Romagna et al. 2013	Aerosol extract	1 of 21 samples was cytotoxic Cytotoxic sample was 795% less cytotoxic than CSE
Williams et al. 2013	Cartomizer fluid	Fluids that contained small tin particles significantly inhibited cell attachment and proliferation while fluids without particles did not. Fluids both with and without particles inhibited cell survival in hPF assay, but the effect was greater for fluids with particles.
Bahl et al. 2012	E-liquid	Depending on the cell line, 23-69% had low cytotoxicity, 28-61% had moderate cytotoxicity and 3-31% had high cytotoxicity Different cell lines had different sensitivity to the e-liquids, with increased sensitivity seen in embryonic cell lines. Cytotoxicity appeared to be correlated with the number and concentration of the chemical flavorings rather than the nicotine concentration
Behar et al. 2014	Cinnamon e-liquid	The cytotoxicity of cinnamon flavored e-liquids was correlated with cinnamaldehyde (a cinnamon flavor additive).
Leverette et al. 2014 (abstract)	Cigarette smoke and e-cig aerosol, Collected aerosols and e-liquids	Human embryonic stem cells were more sensitive than human adult cells. Several CSE preparations were markedly cytotoxic to human lung epithelial carcinoma A-549 cells in the Neutral Red Uptake assay and promoted the release of an inflammatory mediator (IL-8). Neither e-cigarette liquids nor collected aerosols produced any meaningful effects in either test at comparable or substantially higher dose levels. Similarly, direct exposures of A-549 cells to cigarette smoke evoked the release of IL-8, while direct e-cigarette aerosol exposures did not.

Abbreviations: CSE: cigarette smoke extract
hPF: human pulmonary fibroblasts

Appendix 7 – Studies of Passive Vaping

Substance	Findings
PAHs	PAH levels after vaping were significantly higher than control[2] PAH levels were significantly lower than OSHA PEL[1,2] PAH levels were lower than after cigarette smoking[1]
Carbonyls	Carbonyl levels did not always exceed background concentrations[2] Carbonyl levels were significantly lower than the OSHA PEL[1,2,3] Carbonyl levels were lower than after cigarette smoking[3] Acrolein levels were lower than after cigarette smoking[1]
Metals	Most metals were not significantly higher than control[2] Aluminum level (elevated by vaping) was significantly lower than OSHA PEL[2]
VOCs	VOC levels did not always exceed background concentrations[2,3,4] Some VOCs were significantly higher than after cigarette smoking[1] Some VOCs were significantly lower than after cigarette smoking[1,3,4]
TOC	Vaping produces 9 times less TOC than after cigarette smoking[1] 11 minutes of cigarette smoking produces as much TOC as 5 hours of vaping[1]
CO	CO levels were not significantly increased by vaping[1,2,4]
Particulate Matter	Higher temperature released smaller diameter particles[3] Significantly fewer particles resulted from nicotine e-liquids compared to nicotine-free e-liquids[2] Vaping produced significant concentrations of PM10, PM2.5 and PM1.0[2]

[1] Romagna et al. (2012)
[2] Schober et al. (2013)
[3] Schripp et al. (2013)
[4] Czogala et al. (2013)

Appendix 8 – Clinical Studies of the Physiological Effects of Electronic Cigarette Use (n=16)

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
RESPIRATORY EFFECTS (n=6)				
Flouris et al. 2013 (Chorti et al. 2012 appears to be early results of this study)	Lung function (spirometry) Serum cotinine Exhaled CO and fraction of exhaled NO (FeNO)[113]	Non-randomized repeated-measures controlled study Active smoking: 15 smokers underwent a control condition (smoke an unlit cigarette), smoked 2 of their own cigarettes and used an e-cigarette (Giant, Nobacco®; 11 mg/mL) for a specified number of puffs Passive smoking: 15 never-smokers underwent a control condition (room air), a passive tobacco smoke session for 1 hr and a passive e-cigarette session for 1 hr	Neither active nor passive e-cigarette use significantly affected lung function. In contrast, active tobacco smoking (but not passive tobacco smoke exposure) undermined lung function (decreased FEV1/FVC). E-cigarettes and tobacco cigarettes resulted in similar elevations of serum cotinine levels after both active and passive smoking. There was no effect on FeNO after active e-cigarette vaping.	**Short-term active and passive e-cigarette exposure did not significantly interfere with lung function, while active and passive tobacco cigarette smoking significantly undermined lung function.**

[113] The significance of alterations in FeNO levels is unclear. FeNO is generally reduced in long-term smokers. While an increase is commonly considered to be a marker for airway inflammation and respiratory disease, there is evidence that certain types of airway inflammation can lower FeNO. Interpretation of FeNO levels in the clinical setting FeNO is complicated and requires adjustments for gender, age, height, smoking status, respiratory infection and allergies. Consequently, the validity of this measure is questionable. (Palazzolo 2013, Schober et al. 2014).

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Marini et al. 2014	Exhaled nitric oxide (NO) Exhaled smoke and vapor were characterized in terms of particle number concentration and size distribution	Single group, within-subject design 25 healthy smokers underwent 4 conditions at least 1 day apart: a control condition (e-cigarette without cartridge); smoking a tobacco cigarette of their own choice, using a nicotine-free e-cigarette for 5 min; and using an e-cigarette with 18 mg/mL nicotine for 5 min	There were similar decreases in exhaled NO after smoking or using the e-cigarettes and all were significantly lower than the control condition. Mainstream aerosols generated by e-cigarettes were similar to those of regular cigarettes in terms of the distribution of particles; the amount of particles emitted varied as a function of nicotine content.	**E-cigarettes are not safer than tobacco cigarettes when effects related to exhaled NO reduction are considered.**
Palamidas et al. 2014 (abstract) (early results were reported by Gennimata et al. 2012)	Lung function (lung volumes, airway resistance, specific airway conductance and slope in phase III)	Study design not described 60 subjects used an e-cigarette with 11 mg/mL nicotine. There were 9 never-smokers and 51 smokers (24 with no overt airways disease, 11 with asthma, 16 with COPD) 10 never-smokers used a nicotine-free e-cigarette	After using the nicotine e-cigarette, there was a significant increase in airway resistance in smokers and never-smokers and a significant decrease in specific airway conductance. Increased slope in phase III was shown only in asthmatic patients. After using the nicotine-free e-cigarette, there was also a significant increase in airway resistance and a significant decrease in specific airway conductance.	**Using the e-cigarette was associated with increased airway resistance and a concomitant decrease in specific airway conductance, which could be due to the vaporizing liquid but not the inhaled nicotine.**

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Schober et al. 2013	Exhaled nitric oxide (FeNO) and carbon monoxide (CO), urinary metabolites	9 healthy volunteers (occasional smokers) consumed first a nicotine-free e-cigarette and one day later a nicotine-containing e-cigarette for 2 hrs	7 of 9 individuals showed a slight but statistically significant rise of FeNO after vaping a nicotine e-cigarette, but not when nicotine-free liquids were used. Exhaled CO levels (known to be elevated with smoking) were not increased after use of the e-cigarettes. Analysis of urinary metabolites confirmed the uptake of nicotine and acrolein via e-cigarette consumption.	**Physiologic effects, though difficult to interpret, are suggested by the slight increase in FeNO after vaping nicotine-containing liquids.**
Van Staden et al. 2013	Carboxyhemoglobin (COHb) levels Venous cotinine, oxygen saturation	Single group, within-subject design 13 heavy smokers switched to Twisp e-cigarettes for 2 weeks	Arterial and venous COHb levels were significantly reduced after 2 weeks of using the e-cigarette. Cotinine levels decreased and oxygen saturation increased.	**E-cigarettes may be an aid to smoking cessation and/or a healthier alternative to tobacco smoking.**
Vardavas et al. 2012	Respiratory function (spirometry) Fraction of exhaled nitric oxide (FeNO)	Controlled clinical study 30 healthy smokers used an e-cigarette (Nobacco®; 11 mg/mL) for 5 min 10 of these subjects also used the e-cigarette with the cartridge removed for 5 min	Using the nicotine e-cigarette led to a significant decrease in FeNO and significant increases in respiratory impedance and respiratory flow resistance.	**E-cigarettes have immediate adverse pulmonary effects similar to some of those of smoking.**
CARDIOVASCULAR EFFECTS (n=4)				
Battista et al. 2013 (abstract)	Cardiac output Blood pressure Systemic vascular resistance (SVR)	Uncontrolled clinical study 12 healthy volunteers used their own e-cigarettes (4-9 mg/mL nicotine) for 4 min	Cardiac output increased and SVR decreased after 2 and 4 min of e-cigarette use, while diastolic blood pressure and mean arterial pressure increased at 4 min. Oxygen saturation did not change.	**E-cigarettes appear less harmful than tobacco smoking, but inhalation of nicotine vapor produces the same pathophysiological cardiovascular effects as traditional cigarette smoking.**

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Farsalinos et al. 2014d	Myocardial function (echocardiography)	Uncontrolled clinical study 36 healthy heavy smokers smoked 1 cigarette 40 e-cigarette users (ex-smokers) used an 11 mg/mL nicotine e-cigarette for 7 min (Nobacco® battery with Alter Ego atomizer)	Isovolumetric relaxation time (IVRT) and corrected-to-heart rate IVRT were prolonged, diastolic velocity and strain rate were decreased, and myocardial performance index was elevated after smoking a cigarette. No differences were observed after e-cigarette use.	**Acute smoking caused a delay in left ventricular myocardial relaxation, but there were no such immediate effects after use of an e-cigarette.**
Farsalinos et al. 2013e (abstract)	Elasticity of the aorta	Randomized crossover study 51 healthy smokers smoked 2 of their own cigarettes or an e-cigarette with 18mg/mL nicotine for 10 min 57 healthy daily e-cigarette users (who had quit smoking for 10.5 $\pm$8.7 months) just used the e-cigarette	No adverse effects were observed after using the e-cigarette. Significantly decreased aortic elasticity and elevated stiffness of ascending aorta were observed after smoking regular cigarettes.	**E-cigarettes may be useful in reducing the adverse vascular effects associated with smoking.**
Farsalinos et al. 2013f (abstract)	Coronary microcirculation, including coronary flow velocity reserve (CFVR), coronary vascular resistance index (CVRI), COHb	Randomized crossover study 30 healthy smokers smoked 2 of their own cigarettes or an e-cigarette with 9mg/mL nicotine for 15 min 30 healthy ex-smokers who used e-cigarettes daily just used the e-cigarette	No differences were observed in any parameters after e-cigarette use in either smokers or ex-smokers. In contrast, there were significant elevations in COHb and CVRI and decreases in CFVR in smokers after smoking 2 cigarettes.	**E-cigarettes may have the potential to reduce the adverse vascular effects associated with smoking.**
HEMATOLOGIC MEASURES (n=2)				

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Flouris et al. 2012	Complete blood count	Randomized crossover study Active smoking: 15 smokers underwent a control condition (smoke an unlit cigarette), smoked 2 of their own cigarettes and used an e-cigarette (Giant, Nobacco®; 11 mg/mL) for a specified number of puffs Passive smoking: 15 never-smokers underwent a control condition (room air), a passive tobacco smoke session for 1 hr and a passive e-cigarette session for 1 hr	CBC indices were unchanged after active and passive e-cigarettes exposure in smokers and never-smokers. In contrast, both active and passive tobacco smoking resulted in increases in white blood cell count, lymphocyte and granulocyte count for at least 1 hr.	**Acute active and passive smoking using the e-cigarettes tested in the current study does not affect complete blood count indices in smokers or never-smokers.**
Miura et al. 2011 (only abstract is in English)	Blood pressure, hematologic data, blood chemistry	Uncontrolled clinical study 32 smokers used 1 e-cigarette cartridge (0.25 g glycerin aqueous solution) per day for 4 weeks	There were no abnormal changes in blood pressure, hematological data, or blood chemistry. A trace amount of acrolein was detected in the vapor collected from a single cartridge, but it was less than the minimum amount in the mainstream smoke from a single tobacco cigarette.	**E-cigarettes containing glycerin aqueous solution may be a safe alternative to smoking.**
MARKERS OF INFLAMMATION (n=1)				
Tzatzrakis et al. 2013 (abstract)	Inflammatory markers (interleukins, TNFz, EGF, etc.)	Repeated measures controlled study Active smoking: 10 smokers underwent a control condition, smoked their own cigarette, or used an e-cigarette. Passive smoking: 10 never-smokers underwent a control session, a passive tobacco cigarette smoke session and a passive e-cigarette vaping session.	Active and passive smoking of the e-cigarette did not affect inflammatory markers. In contrast, active tobacco smoking produced acute increases in IL2 and EGF, while passive tobacco smoking produced acute increases in TNFa.	**Active and passive tobacco smoking led to acute increases in inflammatory markers, while active and passive vaping did not.**
CLINICAL SYMPTOMS (n=2)				

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Tsikrika et al. 2014 (abstract)	Clinical symptoms, vital signs (heart rate, oxygen saturation), exhaled CO	Uncontrolled clinical study 62 smokers used an e-cigarette with 11 mg/mL nicotine for 10 min. There were 10 nonsmokers and 52 smokers (24 with no overt airways disease, 16 with COPD, 12 with asthma)	Cough and sore throat were present in both smokers and nonsmokers after using the e-cigarette; both symptoms were reported by 90% of asthmatics and 63% of those with COPD. A significant increase in heart rate with palpitations was also noted with a decrease in oxygen saturation mainly in smokers. There was a significant increase in exhaled CO in nonsmokers.	**Even a single use of an e-cigarette increased heart rate and symptoms like cough and sore throat.**

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
CLINICAL SYMPTOMS (n=2) (continued)				
Vakali et al. 2014 (abstract)	Clinical symptoms, vital signs (heart rate, oxygen saturation), indices of airway inflammation (exhaled NO, airways temperature)	Controlled clinical study 41 subjects (12 never-smokers and 29 healthy smokers) used an e-cigarette with 11 mg/mL nicotine for 10 min. 23 subjects (14 never-smokers and 9 healthy smokers) used an e-cigarette with 0 mg nicotine for 10 min.	All subjects reported symptoms, but respiratory (sore throat, cough) and cardiovascular symptoms (palpitations) were reported more often by those using the nicotine e-cigarette than the 0 mg e-cigarette. Dizziness was more commonly reported by nonsmokers using the 0 mg e-cigarette. Increased heart rate was noted with the nicotine e-cigarette, but not the 0 mg product. Decreased exhaled NO was found in those using the 0 mg product. An increase in airways temperature was reported in smokers using the 11 mg e-cigarette.	**Increased heart rate and palpitations and decreased oxygen saturation are related to the use of a nicotine-containing e-cigarette, but airways symptoms and inflammatory markers are independent of nicotine use.**
MEMORY (n=1)				
Dawkins et al. 2013b	Prospective memory, mood, craving	Double-blind, placebo-controlled, within-subjects study 20 smokers abstained for 8-10 hrs, used a Tornado e-cigarette for 10 min with nicotine (18 mg) or placebo cartridges (0 mg)	Compared to placebo, the nicotine e-cigarette reduced desire to smoke and tobacco withdrawal symptoms and improved time-based (but not event-based) prospective memory.	**Nicotine delivered via e-cigarette can improve prospective memory in abstinent smokers, suggesting efficient nicotine delivery.**

Appendix 9 – Positive and Negative Effects Reported in Surveys of Electronic Cigarette Users (n=8)

Citation	Description of Survey and Subjects	Positive Effects	Negative Effects
Dawkins et al. 2013a	Online survey of 1,347 e-cigarette users (83% former smokers, 16% current smokers, <1% never-smokers)	Improved breathing (72.4%) Improved cough (70.3%)	There were few adverse effects (most common were throat irritation and mouth irritation). Less than 16% reported experiencing any degree of negative effect and less than 3% reported a high level of side effects.
Etter 2010	Internet survey of 81 ever-users of e-cigarettes (63% former smokers, 37% current smokers)	There were 134 comments about beneficial effects; the most frequently cited were improved breathing and respiration, less cough/less expectoration/fewer sore throats, improved health and physical fitness, did not cause unpleasant odors or bad breath.	There were 61 comments about undesirable effects; the most frequently cited were dry mouth and throat, vertigo, headache, or nausea.
Etter et al. 2011	Internet survey of 3,587 e-cigarette users (70% former smokers, 30% current smokers)	Not addressed	22.1% agreed that they burn the throat 26.2% agreed that they cause a dry mouth/throat.
Farsalinos et al. 2013b	Personal interviews with 111 vapers (100% former smokers who completely substituted smoking with e-cigarette use for at least 1 month)	Improved olfactory and gustatory senses (81.9%) Better exercise capacity (76.6%) Less morning cough (58.6%) Better sleep (22.3%)	Side effects were mild and temporary: Throat irritation (27%) Cough (13.5%) Gastrointestinal discomfort (7.2%) Palpitations (5.4%) Other negative effects were reported by <5% of subjects.

Citation	Description of Survey and Subjects	Positive Effects	Negative Effects
Farsalinos et al. 2014b	Online survey of 19,441 e-cigarette users (81.0% former smokers, 19% current smokers, 0.5% never-smokers)	More than 73.5% of respondents reported better physical status in general, better endurance, better smell, better taste and better breathing. Between 16.2 % and 38.1% of users reported improvements in appetite, sexual performance, mood, memory and quality of sleep. Of respondents with various health conditions (diabetes, hypertension, hypercholesterolemia, thyroid disease, coronary artery disease, asthma, COPD), between 35.0% and 75.7% reported improvements after initiating e-cigarette use.	57.9% reported at least one adverse symptom that they attributed to e-cigarette use. The most common was sore or dry mouth and throat (38.9%). All other side effects were reported in less than 15% of users. Side effects were mild and in most cases were subsequently resolved (partially or completely).
Goniewicz et al. 2013c	Web-based survey of 179 e-cigarette users (66% former smokers, 34% current smokers)	Not addressed	Sometimes/often headaches (21%) Sometimes/often cough during the day (27%) Sometimes/often phlegm production (25%) Other side effects were reported by <20% of subjects.
Heavner et al. 2009	Online survey of 303 e-cigarette users (79% former smokers, 21% current smokers)	The majority of respondents reported that their general health (91%), smoker's cough (97%), ability to exercise (84%) and sense of smell (80%) and sense of taste (73%) were better since using e-cigarettes.	No one reported declines in general health, smoker's cough, ability to exercise, sense of smell, or sense of taste.
Hua et al. 2013	Analysis of original posts on 3 online e-cigarette forums (a total of 405 symptoms were reported)	78 positive symptoms were reported; these were most frequently related to the respiratory system.	326 negative symptoms were reported; negative effects occurred most often in the mouth and throat and in the respiratory, neurological, sensory and digestive systems.

Appendix 10 – Case Reports and Case Series Involving Electronic Cigarette Users

Citation	Description of Case	Outcome of Case
Camus et al. 2014	A 49-year-old female smoker's **ulcerative colitis** symptoms were kept in remission for many years while she was a smoker. One week after she switched to an e-cigarette, her condition relapsed.	The authors interpreted this as a case of smoking-dependent ulcerative colitis which recurred after replacing smoking with nicotine-containing e-cigarettes.
Farsalinos and Romagna 2013	A male smoker was diagnosed with **chronic idiopathic neutrophilia** (CIN) at age 28. He was advised to quit smoking and after 2 failed attempts over the following years using conventional methods, eventually did so within 10 days of starting an e-cigarette.	Within 6 months, the abnormal lab values had resolved. The most probable explanation for reversal of the CIN was smoking cessation. The authors noted that "despite the daily use of electronic cigarette by this patient, the beneficial effects of smoking cessation were maintained."
Hureaux et al. 2014	A 43-year-old man (45-pack-year smoking history) with stage II COPD and recent lung cancer tried to quit smoking with an e-cigarette and developed **subacute bronchial toxicity**.	Symptoms improved within 1 week of ceasing use of e-cigarettes.
McCauley et al. 2012	**Lipoid pneumonia** occurred in a 42-year-old woman (smoking history not specified) who had used e-cigarettes for about 7 months.	Symptoms improved after ceasing use of e-cigarettes. The suspected source of the patient's condition was recurrent exposure to glycerin-based oils in the e-cigarette vapor.
Monroy et al. 2012	A 70-year-old woman with a 40-pack-year smoking history experienced **atrial fibrillation** following total hip arthroplasty, each time after using an e-cigarette.	The woman had not filled her e-cigarette cartridge properly (nicotine dose was likely too high). There were no further episodes of atrial fibrillation after ceasing use of e-cigarettes.
Thota and Latham 2014	A 20-year-old man (smoking history not specified) developed respiratory symptoms shortly after initiating e-cigarette use; he was diagnosed with **eosinophilic pneumonia**.	The patient was treated with prednisone and his symptoms resolved in 1 week.
Polosa et al. 2014	18 **asthmatic smokers** switched partly (n=8) or completely (n=10) to e-cigarettes	At 12 months of follow-up, subjects had significant improvements in spirometry data, asthma control, and airway hyperresponsiveness.

Appendix 11 – Estimates of Electronic Cigarette Use by Adult Never-Smokers (n=9)

Short Citation	Prevalence of Use by Never-Smokers	Population
Action on Smoking and Health 2014	**1.1%** of never-smokers had ever used e-cigarettes **0.1%** of never-smokers currently use e-cigarettes	Survey of 12,269 adults (6081 never-smokers) in Great Britain (2014)
Choi and Forster 2013	**2.7%** of never-established smokers had ever used e-cigarettes	Survey of 2,624 US Midwestern adults (age 20-28); 1,835 had ever used e-cigarettes (2010-2011)
Dawkins et al. 2013a	**0.3%** of vapers had never smoked	Online survey of 1,347 vapers; 72% of respondents were European, with a mean age of 43 (2011-2012)
Dockrell et al. 2013	**0.4%** of never-smokers had tried e-cigarettes but do not use anymore **0.1%** of never-smokers had tried e-cigarettes and still use	Survey of 12,432 adults (5,866 never-smokers) in Great Britain (2012)
Farsalinos et al. 2014b	**0.5%** of e-cigarette users were not smokers when they initiated e-cigarette use	Worldwide online survey of 19,441 e-cigarette users (2013)
King et al. 2013	**1.2-1.3%** of never-smokers had ever used an e-cigarette	Survey of 10,739 US adults (2010-2011)
Pearson et al. 2012	**0.8%** of never-smokers had ever used e-cigarettes **0.3%** of never-smokers had used e-cigarettes in the past 30 days	Online survey of 2,649 US adults (2010)
Regan et al. 2013	**3.8%** of never-smokers had ever tried e-cigarettes **2.2%** of never-smokers had used e-cigarettes in the past month	Survey of 10,328 US adults (2010)
Zhu et al. 2013	**1.04%** of never-smokers had ever used e-cigarettes **0.04%** of never-smokers currently use e-cigarettes	Survey of 10,041 US adults (3,254 never-smokers) (2012)

Appendix 12 – Clinical Studies of Nicotine Delivery, Withdrawal and Craving Use (n=10)

Citation	Endpoints	Study Design and Subjects	Authors' Conclusions
Bullen et al. 2010	Change in desire to smoke Withdrawal symptoms Serum nicotine	Clinical study (single-blind randomized cross-over trial) of 40 adult smokers Four conditions: usual cigarette; nicotine inhalator; Ruyan® V8 e-cigarette (0 mg nicotine); Ruyan® V8 e-cigarette (0 mg nicotine)	The 16 mg e-cigarette alleviated desire to smoke. It had a pharmacokinetic profile more like the Nicorette inhalator than a conventional cigarette. There was no difference in desire to smoke between the 16 mg e-cigarette and the nicotine inhalator.
Dawkins and Corcoran 2013	Plasma nicotine Withdrawal symptoms Urge to smoke	Clinical study of 14 regular e-cigarette users who used the SKYCIG® e-cigarette	Plasma nicotine rose significantly after ad lib use of the e-cigarette (comparable to NRTs, snuff and chewing tobacco). Nicotine-related withdrawal symptoms and urge to smoke were substantially reduced. Reliable plasma nicotine concentrations were achieved with a first-generation e-cigarette among experienced users.
Dawkins et al. 2012	Desire to smoke Nicotine withdrawal symptoms	Randomized clinical study of 86 e-cigarette-naïve smokers Three conditions: White Super™ e-cigarette (18 mg nicotine); White Super™ e-cigarette (0 mg nicotine); just holding the e-cigarette	Compared with just holding the e-cigarette, the e-cigarette both with and without nicotine reduced desire to smoke and some aspects of nicotine withdrawal symptoms.
Etter 2014a (early results reported by Etter and Bullen 2011b)	Saliva cotinine	Clinical study of 71 experienced e-cigarette users	Saliva cotinine levels were similar to those observed in smokers and higher than those usually observed in NRT users. Despite this, e-cigarettes are likely less addictive than conventional cigarettes because they deliver nicotine more slowly.

Citation	Endpoints	Study Design and Subjects	Authors' Conclusions
Farsalinos et al. 2013d	Vaping topography	Clinical study (randomized cross-over) 80 volunteers (35 experienced smokers and 45 experienced vapers) were videotaped using regular and e-cigarettes (Epsilon, Nobacco®) to examine differences in puff, inhalation and exhalation duration, as well as nicotine delivery	Inhalation duration was lower and puff duration was longer in experienced vapers, confirming that there is a learning curve in e-cigarette use. Puff number and duration were highly correlated with e-liquid consumption. To deliver a nicotine concentration similar to that of 1 tobacco cigarette, liquids with a nicotine concentration of 20-24 mg/mL should be used.
Farsalinos et al. 2014a	Plasma nicotine Craving	Clinical study of 23 experienced e-cigarette users who used a first-generation device and a new generation device, each with an 18 mg/mL nicotine cartridge.	Nicotine levels and reduction in craving were significantly higher with the new-generation device. However, even the new generation e-cigarette did not deliver nicotine to the bloodstream as rapidly as smoking. Nicotine levels must be higher to improve their effectiveness.
Nides et al. 2014	Plasma nicotine Withdrawal and craving	Clinical study of 25 smokers who were not interested in quitting were instructed how to use the NJOY® King Bold e-cigarette with 26 mg nicotine and given a 10-day supply	After 5 min using the e-cigarette, blood nicotine increased by a mean of 3.5 ng/mL and craving was reduced by 55%.
Vansickel et al. 2010 (early results reported by Eissenberg 2010)	Plasma nicotine Abstinence symptoms	Clinical study of 32 smokers Four conditions: usual cigarette; sham cigarette (unlit); NJOY® NPRO e-cigarette (18 mg nicotine); Hydro™ e-cigarette (16 mg nicotine)	Despite delivering no measurable nicotine, both e-cigarettes suppressed tobacco abstinence symptoms.
Vansickel and Eissenberg 2013	Nicotine delivery	Clinical study of 8 experienced e-cigarette users who used their preferred devices and nicotine cartridges	Plasma nicotine increased significantly within 5 min of the first puff and abstinence symptoms decreased. E-cigarettes can provide nicotine levels comparable to those obtained with cigarette smoking. User experience and device characteristics influence nicotine delivery and other effects.

Citation	Endpoints	Study Design and Subjects	Authors' Conclusions
Vansickel et al. 2012	Plasma nicotine Subjective effects Abuse liability	Clinical study of 20 smokers Subjects first use the Vapor King® e-cigarette. In 3 later sessions, they made choices between e-cigarette use and varying amounts of money; e-cigarette use and varying amounts of own cigarette use; or own cigarette use and varying amounts of money	The e-cigarette suppressed abstinence symptoms and gave reliable nicotine delivery, but had lower abuse potential than tobacco cigarettes.

Appendix 13 – Studies of Electronic Cigarettes for Smoking Reduction and Cessation

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
RANDOMIZED CONTROLLED TRIALS (n=3)				
Bullen et al. 2013b	Smoking reduction and cessation	Randomized controlled superiority trial (6 months) 657 smokers who wanted to quit were assigned to a 16 mg nicotine Elusion® e-cigarette, a 0 mg nicotine Elusion® e-cigarette, or a 21 mg nicotine patch for 12 weeks Low intensity behavioral support was provided by voluntary telephone counseling	At 6 months, verified abstinence was 7.3% with nicotine e-cigarettes, 5.8% with patches and 4.1% with placebo e-cigarettes. The risk difference for nicotine e-cigarettes vs patches was 1.51 (95% CI: -2.49-5.51) and for nicotine e-cigarettes vs placebo e-cigarettes was 3.16 (95% CI: -2.29-8.61). 57% of the nicotine e-cigarette users reduced their cigarettes per day by at least half at 6 months, which was significantly more than in the other 2 groups. There was insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes.	E-cigarettes, with or without nicotine, were modestly effective in helping smokers to quit, with similar achievement of abstinence as with nicotine patches.
Caponnetto et al. 2013a	Smoking reduction and cessation	Prospective, double-blind randomized controlled trial (12 months) (ECLAT) 300 smokers who did not intend to quit were assigned to the Categoria® e-cigarette with: 7.2 mg nicotine cartridges; 7.2 mg nicotine cartridges (6 weeks) followed by 5.4 mg nicotine cartridges (6 weeks); or no-nicotine cartridges No emphasis was placed on smoking cessation and after 12 weeks subjects could continue with their e-cigarette if they wished.	Number of cigarettes per day decreased significantly in all three groups ($p<0.001$ compared to baseline), with no consistent differences between study groups. Overall smoking reduction (>50% fewer cigarettes/day) was 22.3% at week 12 and 10.3% at week 52. Overall abstinence (not even a puff since the previous study visit) was 10.7% at week 12 and 8.7% at week 52.	In smokers not intending to quit, the use of e-cigarettes, with or without nicotine, decreased cigarette consumption and elicited enduring tobacco abstinence.

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Caponnetto et al. 2013b	Smoking reduction and cessation	Prospective 12-month pilot study (note that a randomized controlled trial is planned; see Caponnetto et al. 2014) 14 schizophrenic smokers who did not intend to quit were given the Categoria® e-cigarette; they attended 6 visits during the year at which smoking reduction and abstinence were encouraged.	At week 52, 2 subjects had achieved sustained smoking abstinence and another 7 had reduced the number of cigarettes smoked per day by half. There was no negative impact on schizophrenic symptoms.	Use of e-cigarettes substantially decreased cigarette consumption without causing significant side effects in chronic schizophrenic patients who did not intend to quit smoking.
INTERVENTIONAL STUDIES (n=3)				
Nides et al. 2014	Smoking reduction and cessation	Open-label, noncomparative 1-week pilot study 25 smokers not interested in quitting were instructed how to use the NJOY® King e-cigarette and provided with a 1-week supply	Mean daily cigarette smoking decreased in 89% of subjects. Mean reduction in cigarettes/day was 39%. 32% of subjects reduced smoking by 50% or more.	Use of the e-cigarette resulted in significant smoking reduction during a 1-week trial.
Polosa et al. 2013b (6-month data reported by Polosa et al. 2011)	Smoking reduction and cessation	2-year prospective observational study 40 smokers not intending to quit underwent a 6-month intervention period in which they were given the Categoria® e-cigarette and monitored. No cartridges were provided after 6 months.	At 24 months, 17 subjects were lost to follow-up. 11 of 40 subjects (27.5%) had a sustained 50% reduction in number of cigarettes/day. 5 of 40 (12.5%) achieved total smoking abstinence (not a puff for 30 days, objectively verified). 5 subjects stopped using the e-cigarette and stayed quit, while 3 relapsed to smoking.	Long-term e-cigarette use can decrease smoking substantially in smokers unwilling to quit and is well tolerated.

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Wagener et al. 2013	Readiness and confidence to quit smoking Smoking reduction	1-week pilot study 20 smokers not interested in quitting were instructed how to use e-cigarettes (3 brands) and provided with a 1-week supply	These unmotivated smokers reported a significant increase confidence to quit smoking and overall readiness to quit smoking. There was a significant reduction (44%) in regular cigarettes smoked per day from baseline.	E-cigarette experimentation and 1 week of ad lib use increased readiness and confidence to quit smoking and reduced cigarette smoking.
OBSERVATIONAL EPIDEMIOLOGY STUDIES (n=9)				
Adkison et al. 2013	Smoking reduction and cessation	Longitudinal study Subjects were 5,939 current and former smokers in The International Tobacco Control Four-Survey (US, Canada, UK, Australia). Data were collected at baseline (wave 7) and 1 year later (wave 8).	7.6% had ever tried e-cigarettes and 2.9% were current users. Current e-cigarette users were more likely than non-users to have reduced the number of cigarettes smoked per day ($p<0.05$) between waves. Users reduced from 20.1 to 16.3 cigarettes per day; nonusers reduced from 16.9 to 15.0 cigarettes per day. E-cigarette users were not more likely to quit smoking than non-users ($p=0.52$).	Current use of e-cigarettes was associated with a greater reduction in cigarettes per day, but users were not more likely to quit smoking. Because trial of e-cigarettes was associated with nondaily smoking and a desire to quit smoking, e-cigarettes may have the potential to serve as a cessation aid.
Brown et al. 2014b	Abstinence	Cross-sectional survey Subjects were a representative sample of the English population; there were 5,863 adults who had smoked in the past 12 months and made at least 1 quit attempt with e-cigarettes (n=464), NRT (n=1,922), or no aid (n=3,477)	E-cigarette users were more likely to report abstinence than either those who used NRT bought over the counter (OR=1.63, 95% CI:1.17-2.27) or no aid (OR=1.61 (95% CI:1.19-2.18) (these are fully adjusted odds ratios).	Among smokers trying to quit without professional support, those who used e-cigarettes were more likely to report abstinence than those who used licensed NRT bought over the counter or no aid. The difference persisted after adjusting for a range of smoker characteristics such as nicotine dependence.

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Brown et al. 2014a	Quit attempts	Cross-sectional survey Subjects were a national sample of 3,538 current 579 recent ex-smokers in Great Britain	Among current smokers, use of e-cigarettes was associated with having a past-year quit attempt (OR=2.82; 95% CI:2.38-3.34).	E-cigarette users appear to have attempted to quit in the past year.
Choi and Forster 2014a	Smoking reduction and cessation	Longitudinal study A cohort of 1,476 US Midwestern adults (mean age 24.1) was recruited and followed for 1 year	11% of smokers who used e-cigarettes ≥1 day in the past 30 days at baseline quit smoking at follow-up, whereas 17% of smokers who never used e-cigarettes quit smoking (OR=0.93, 95% CI:0.19-4.63, p=0.93; n=346). Change in average number of cigarettes per day from baseline to follow-up was almost identical for smokers who smoked e-cigarettes ≥1 day in the past 30 days at baseline (0.0) and those who never used e-cigarettes (-0.2). The difference was 0.2, 95% CI:-3.72-4.18, p=0.91. Both analyses were adjusted for demographics and baseline cigarette consumption.	Longitudinal data show no benefits of e-cigarette use on quitting or cutting down on conventional cigarettes.
Grana et al. 2014	Smoking reduction and cessation	Longitudinal study Online survey of a national sample of 949 current US smokers who provided information about e-cigarette use at baseline and 1 year later	E-cigarette use at baseline (n=88) was not significantly associated with greater intention to quit smoking (p=0.09), with self-reported quitting 1 year later (OR=0.71, 95% CI:0.35-1.46), or with a significant change in tobacco cigarette consumption (p=0.25). The low numbers of e-cigarette users may have limited the statistical power to detect a significant relationship between e-cigarette use and smoking cessation.	E-cigarette use by smokers was not followed by greater rates of quitting or by reduction in cigarette smoking 1 year later.

Citation	Endpoints	Study Design and Subjects	Findings	Authors' Conclusions
Pokhrel et al. 2013	Motivation to quit, quitting self-efficacy, quit duration	Cross-sectional survey Subjects were the 1,567 daily smokers in a multiethnic population in Hawaii	202 (13%) reported using e-cigarettes to quit smoking. E-cigarette users were significantly more motivated to quit, had significantly longer recent quit durations and were significantly more likely to have used FDA-approved smoking cessation products in the past than those who did not use e-cigarettes.	Smokers who used e-cigarettes were serious about wanting to quit.
Popova and Ling 2013	Smoking cessation	Cross-sectional survey Nationally representative probability-based sample of 1,836 current or recently former smokers	20.1% of subjects had used e-cigarettes. Use of e-cigarettes was significantly associated with having made an unsuccessful quit attempt (OR=1.78; 95% CI:1.25-2.53).	Alternative tobacco products are attractive to smokers who want to quit, but this study does not indicate that they promote cessation.
Regan et al. 2013	Smoking cessation	Cross-sectional survey Subjects were 10,328 US adults who responded to a mail-in survey (sampled to yield a demographic distribution similar to the US population)	2.7% had tried e-cigarettes in 2010. Among current smokers, those who had tried e-cigarettes did not differ significantly from those who had never tried them in their plans to quit smoking or their attempts to quit in the past year ($p \geq 0.05$).	Current smokers who had tried e-cigarettes did not say they planned to quit smoking more often than smokers who had never tried them.
Vickerman et al. 2013	Smoking cessation	Longitudinal study Subjects were 2,758 callers to tobacco quit lines in 6 states; data were collected 7 months after they received intervention from the quit line program.	30.9% of callers seeking cessation services had ever used e-cigarettes, most commonly to quit or replace use of other tobacco products. However, e-cigarette users were significantly less likely to be abstinent from cigarettes for 30 days at 7 months than those who had never tried e-cigarettes.	The relationship between callers seeking cessation services and e-cigarette use could be explained by confounding variables. Users had multiple previous quit attempts and were exposed to other tobacco users at work and home, so they may have had more difficulty quitting.

Appendix 14 – Estimates of Electronic Cigarette Use by Adolescent Never-Smokers (n=8)

Short Citation	Prevalence of Use by Never-Smokers	Population
Action on Smoking and Health 2013b, 2014	**1%** who had never smoked have tried e-cigarettes "once or twice" **0%** report continued use of e-cigarettes	Survey of 2,178 young people (11-18) in Great Britain (2013)
Choi and Forster 2013	**2.9%** of baseline never-smokers had ever used e-cigarettes at 1 year of follow-up	US longitudinal study of 1,379 young adults (mean age 24.1) (2010-2011)
Corey et al. 2013	**9.3%** of students who had tried an e-cigarette at least once in 2012 had never smoked tobacco cigarettes	US National Youth Tobacco Survey of students (number of students not reported) grades 6-12 (2012)
Douptcheva et al. 2013	**0.4%** of never-smokers had ever used an e-cigarette **0%** of never-smokers used e-cigarettes daily	Longitudinal study of 5,081 young Swiss men; (42% were under age 21, 58% were over age 21); 1,362 were never-smokers (2010-2013)
Dutra and Glantz 2014	In 2011: **1.5%** of never-smokers had ever tried e-cigarettes **0.5%** of never-smokers had used e-cigarettes in past 30 days In 2012: **4.1%** of never-smokers had ever tried e-cigarettes **1.0%** of never-smokers had used e-cigarettes in past 30 days	US National Youth Tobacco Survey students in grades 6-12 (17,353 students in 2011; 22,529 students in 2012)
Goniewicz and Zielinska-Danch 2012	**3.2%** of never-smokers had ever tried e-cigarettes **1.4%** had tried e-cigarettes in the past 30 days.	Survey of 20,240 Polish high school/university students (2010-2011)
Lee et al. 2013	**1.4%** initiated nicotine use with e-cigarettes	Online survey of 75,643 Korean adolescents age 13-18 (2011)
Pokhrel et al. 2014	**16%** of never-smokers had ever used e-cigarettes[114]	Online survey of 307 college students (mean age 23.5) (2013)
Sutfin et al. 2013	**12%** of students who had ever used e-cigarettes had never smoked a tobacco cigarette	Survey of 4,444 US college students; 216 students (mean age 2.5) had ever used an e-cigarette (2009)

[114] Discrepancy in paper; methods section says 18.4% of never-smokers ever used e-cigarettes, but results section says 16%.