



July 11, 2016

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

Re: Docket No. FDA-2015-D-2496, Draft Guidance on Premarket Tobacco Product Applications for Electronic Delivery Systems

Ladies and Gentlemen:

The undersigned organizations hereby submit these comments in the above-designated docket on FDA’s Draft Guidance on Premarket Tobacco Product Applications (PMTA) for Electronic Nicotine Delivery Systems (“ENDS”).

The process FDA develops to evaluate applications for premarket applications for ENDS products is of exceptional importance to the public health. As FDA noted in the Deeming Rule, issued concurrently with this Draft Guidance, ENDS products have the potential to benefit the public health if they enable users of combusted tobacco products, who cannot or will not quit smoking, to switch completely to using ENDS, or ideally, if they serve as an interim step toward complete cessation of nicotine products. However, ENDS products have the potential to harm public health if they enable adolescents or young adults to initiate tobacco use, if they influence smokers who otherwise would quit to use multiple tobacco products, or not quit, or if they entice former smokers to begin using nicotine again. These concerns are far from hypothetical: numerous national surveys show that the percentage of adolescents using e-cigarettes has grown rapidly and now exceeds the percentage of adolescents using cigarettes,¹ while national surveys of adults and youth show that the vast majority of current e-cigarette users are also current smokers.²

The PMTA pathway is particularly important for ENDS products. FDA notes that many ENDS products currently on the market were introduced long after either the 2007 date, or even after the Tobacco Control Act was enacted, and do not appear to be substantially equivalent to any product then on the market. Thus, for some unknown percentage of ENDS products, the

¹ U.S. Centers for Disease Control and Prevention (CDC), “Tobacco Use Among Middle and High School Students — United States, 2011-2015,” *Morbidity and Mortality Weekly Report (MMWR)* 65(14):361-367, April 14, 2016, <http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6514a1.pdf>

² CDC, “Electronic Cigarette Use Among Middle and High School Students — United States, 2011 – 2012,” *MMWR*, 62(35), September 6, 2013; King, BA, et al., “Trends in Awareness and Use of E-cigarettes Among US Adults, 2010-2013,” *Nicotine and Tobacco Research*, September 2014.

manufacturer may need to file a PMTA under section 910.³ The Draft Guidance is intended to facilitate the application and decision process for these ENDS products. The Draft Guidance should identify and reflect all the concerns FDA believes must be addressed by such applications, the data FDA believes is relevant to the resolution of those concerns, the methods for ensuring that data provided in the applications are reliable enough to inform FDA's decision, and a framework for evaluating such applications.

In general, the Draft Guidance has done a creditable job of identifying these concerns and data and informing manufacturers not only of the data they must provide, but also of the reasons why such data are relevant to FDA's decision-making process. These comments will seek to identify data relevant to FDA's consideration of such applications that have not been identified in the Draft Guidance and recommend clarification of the Guidance to improve the quality and relevance of the data provided. These comments will also make suggestions regarding the framework FDA should apply in considering such applications and further steps FDA should take between now and the end of the compliance period to ensure that its consideration of the applications it receives will most effectively protect the public health.

As the Draft Guidance accurately notes, applications for flavored ENDS products raise more difficult issues than applications for non-flavored or tobacco-flavored products, both with respect to considerations of individual harm and to population-level effects. With respect to individual harm, as the Draft Guidance and as the portion of the FDA proposed rule that was deleted by OMB concluded, research demonstrates that some flavorings have unacceptably high levels of harmful constituents. With respect to population-level effects, as FDA has itself noted, FDA's own research confirms that flavored ENDS products are particularly attractive to adolescents and thus present an increased risk of youth initiation. For these reasons, we present specific suggestions for FDA's review of applications for flavored products both with respect to individual level effects and population-level effects.

I. Establishing a Framework for Evaluation

Because the purpose of a PMTA is to enable FDA to determine whether granting an application would be appropriate for the protection of the public health, it is important to establish an analytical framework for evaluation of the data presented in an application. Consideration of the framework for evaluation is necessary in order to understand the kinds of evidence that FDA will need in evaluating the applications.

A. As FDA recognizes, the burden of proving every element of the public health standard is on the manufacturer.

Section 910 directs FDA to deny any application for a new tobacco product unless the manufacturer demonstrates that the marketing of the product is appropriate for the protection of the public health, measured both by the effect of the product on individual health and the population-level effect resulting from its marketing. This statutory language and Draft Guidance

³ It is important to note, however, that after the first wave of new product applications for ENDS products is granted, manufacturers of ENDS products may be able to use the Substantial Equivalence or Exemption from Substantial Equivalence pathways using the products for which PMTA applications have been granted as predicate products.

make it clear that the manufacturer is responsible for proving that the grant of an application is appropriate for the protection of the public health. The burden of proof applies to every element necessary to make the showing. In the absence of sufficient data to enable FDA to conclude that granting the application would be appropriate for the protection of the public health, the statute directs FDA to deny the application.

B. As FDA has already concluded, the public health standard requires proof of both individual health effects and effects on health at the population level

The determination that the marketing of a product is appropriate for the protection of the public health requires FDA to consider evidence about two different but related areas of concern: the effects of the product on individual health and the population-level effects of granting the application. The first set of concerns seeks to ensure that the products themselves minimize the risk to users and to non-users in the proximity of the aerosol. Evidence about the effects of the product on individual health consists primarily of (1) evidence concerning the levels of constituents in the product or produced by the product, in the form and manner that a person uses the product, that affect the health of the individual user and those potentially affected by such use (i.e., non-users exposed to the aerosol); and (2) evidence about the health effects of exposure to such constituents. Thus, this Guidance appropriately addresses a broad set of concerns designed to meet this objective: elimination of toxins; ensuring that the product is manufactured consistently according to specifications; assessing user topography, frequency of use, trends of use over time; evaluation of leachable constituents, humectants, physiochemical changes of the mixture due to temperature, wattage and/or voltage changes; studies of potential human exposure, particle size and deposition; ensuring that the product does not explode, etc.⁴

The second set of concerns seeks to ensure that no product will be marketed unless the benefits of having the product available are likely to outweigh the harms. There is a potential net benefit if smokers, who cannot or will not quit smoking, switch completely to a product that FDA has determined to be less hazardous and if that product as marketed will not (a) cause more non-users to start, (b) cause former smokers to relapse, or (c) result in dual use and thereby discourage smokers from quitting. The potential for significant harm is especially acute with respect to products that are particularly attractive to children, such as many flavored products, and to products marketed in ways that appeal to children. FDA has emphasized the importance of the population impact in its Draft Guidance, but should do even more to specify the evidence that will be required to support an application for such products with particular emphasis on these population-level effects.

C. Relationship between grant of PMTA applications and the marketing of other products and on other pathways to market.

In evaluating PMTA applications, FDA should take into account that the grant of an application could have implications for other products as well. Thus, decisions made in the review of individual applications should be based on principles FDA is prepared to apply to other applications.

⁴ Draft Guidance at 23-35.

The grant of an application will create a potential predicate product that may permit manufacturers to bring other products to market through the substantial equivalence or exemption to substantial equivalence pathways. Indeed, it is possible that many manufacturers will seek to market ENDS products through these pathways after FDA has taken action on the first wave of PMTA applications. In evaluating PMTA applications, FDA should therefore consider the precedential effect of its decision on other products as well.

II. Evidence About the Effect of Granting an Application on Individual Health

A. Levels of harmful or potentially harmful constituents in the product or produced by the product.

With respect to ENDS products, as FDA correctly notes in the Draft Guidance, the level of harmful and potentially harmful constituents as set forth in the Draft Guidance should be compared not only to the levels of such constituents in combusted tobacco products but also—and importantly—to the level of such constituents in other comparable ENDS products. No application should be granted for an ENDS product that contains or delivers harmful or potentially harmful constituents, other than nicotine, at a level higher than the level delivered by other comparable ENDS products or at even lower levels that could be reached by the application of achievable manufacturing processes. By requiring comparison of the subject product to other ENDS products the draft guidance acknowledges that this principle should govern the review of such applications. This principle should be explicitly stated in the final guidance.

B. Protection of the public health requires proof that the manufacturer can and will manufacture products consistently to specification and in accordance with accepted product quality standards.

It is important for the manufacturer to demonstrate that it can and will produce the product consistently with the same levels of nicotine and other harmful or potentially harmful constituents. Numerous studies have demonstrated that many ENDS products contain nicotine at far different levels than the level stated on the label and that different batches of the same product may offer greatly varying levels of nicotine.⁵ It is essential that a product that purports to contain a given level of nicotine stated on its label actually contain that level in every batch manufactured. We support the conclusion in the Draft Guidance that requires a manufacturer to demonstrate an ability to manufacture products consistently to specifications—both with respect to the content and the delivery to the consumer of nicotine and all other harmful or potentially harmful constituents. It is both reasonable and essential that such products be manufactured consistently to specification.

⁵ Buettner-Schmidt, K, Miller, DR, & Balasubramanian, N, “Electronic Cigarette Refill Liquids: Child-Resistant Packaging, Nicotine Content, and Sales to Minors,” *Journal of Pediatric Nursing* 31(4):373-9, July-August 2016. Cheng, T, “Chemical evaluation of electronic cigarettes,” *Tobacco Control* 23:ii11-ii17, 2014. Lisko, JG, et al., “Chemical Composition and Evaluation of Nicotine, Tobacco Alkaloids, pH, and Selected Flavors in E-Cigarette Cartridges and Refill Solutions,” *Nicotine & Tobacco Research* 17(10):1270-8, October 2015. Davis B, et al., “Nicotine Concentrations in Electronic Cigarette Refill and Do-It-Yourself Fluids,” *Nicotine & Tobacco Research* 17(2):134-41, February 2015. Salt Lake City Health Department, *Analysis of Nicotine Content in E-Liquid Samples*, December 2014.

The procedure endorsed in the deeming rule for master files provides a cost-efficient, non-burdensome mechanism for responsible manufacturers to be able to provide their customers with products that contain levels of nicotine, flavorings and harmful or potentially harmful constituents that have been reviewed by the FDA and that remains consistent from one batch to another.

As the Draft Guidance correctly notes, the many components of the devices that deliver e-liquids also impact the delivery of nicotine, different flavorings and other substances and FDA must consider information concerning each component in determining what the consumer actually receives and in ensuring that what the consumer receives is consistent from product to product. For example, it has been demonstrated that heating elements that reach higher temperatures deliver a higher dose of nicotine and impact the composition of the other substances taken in by the user.⁶ Thus, establishment of effective performance requirements for each component of the device used to deliver e-liquid is essential, as the FDA has proposed in the Draft Guidance.

Finally, PMTA review should also assess other potential risks arising from the failure by manufacturers to apply consistent and sufficient performance requirements, including such hazards as exploding batteries, leakage of e-liquids from ENDS devices, leaching of compounds from materials used to construct the devices into the e-liquids, etc.⁷

C. Some flavorings increase health risks to individual users.

As FDA itself has noted, the use of flavorings in e-cigarette products introduces the potential for increasing the level of harmful or potentially harmful constituents. Some flavors that are used in e-cigarette products currently on the market have been shown to contain harmful or potentially harmful substances. The degree to which the flavoring increases the level of harmful or potentially harmful constituents in the product should be a key factor in FDA's overall evaluation of the product, irrespective of any effect that flavoring may have on product appeal.

In the version of the deeming rule approved by FDA and submitted to OMB, FDA recognized that some chemical flavorings in newly deemed products contain toxic compounds.⁸ As FDA noted, "these chemicals can be dangerous to those exposed through inhalation and some are, therefore, subject to workplace limits." It cited a recent study that tested 159 e-liquids with sweet flavors such as toffee, chocolate and caramel and found that 74 percent of the samples

⁶ Talih, S, et al., "Effects of User Puff Topography, Device Voltage, and Liquid Nicotine Concentration on Electronic Cigarette Nicotine Yield: Measurements and Model Predictions," *Nicotine & Tobacco Research* 17(2):150-7, February 2015. Brown, CJ & Cheng, JM, "Electronic cigarettes: product characterization and design considerations," *Tobacco Control* 23:ii4-ii10, 2014.

⁷ See Comments of Campaign for Tobacco-Free Kids in Docket No. FDA-2014-N-1936, Electronic Cigarettes and the Public Health Workshop (July 2, 2015), at 30-31.

⁸ See Deeming Final Rule Redline Changes in Docket No. FDA-2014-N-0189-83193, Deeming Tobacco Products to be Subject to the 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 Required Warning Statements for Tobacco Products (May 27, 2016), <https://www.regulations.gov/document?D=FDA-2014-N-0189-83193>, at 180-181.

contained diacetyl or acetyl propionyl, both of which pose known inhalation risks.⁹ Nearly half of the liquids that tested positive could expose users to levels that exceed recommended workplace limits for breathing such chemicals.

FDA also cited another study analyzing thirty e-cigarette liquids and finding that many flavors, including cotton candy and bubble gum, contained aldehydes, a class of chemicals that can cause respiratory irritation, airway constriction and other effects.¹⁰ Two such flavors, dark chocolate and wild cherry, would expose e-cigarette users to more than twice the recommended workplace safety limit for the aldehydes vanillin and benzaldehyde. In addition, it cited still another study finding that several cinnamon-flavored e-cigarettes contained a chemical, cinnamaldehyde that is highly toxic to human cells in laboratory tests.¹¹

Moreover, testimony submitted to FDA at its workshop on e-cigarettes further demonstrated the dangers of toxicants and carcinogens present in flavorings used in e-cigarettes and noted high levels of such chemicals in many such products. Dr. Jessica Barrington-Trimis testified that “the potential toxicity for different flavoring components and the potential respiratory toxicity is quite high.”¹² One example is the chemical diacetyl, used to give food a buttery or creamy flavor. High doses of diacetyl, deemed safe for ingestion by the Flavor and Extract Managers Association (FEMA), have been shown to cause severe and irreversible obstructive lung disease when inhaled by workers exposed to particulate aerosolized flavorings containing diacetyl.¹³

In one study of 125 e-liquids manufactured by seven European manufacturers, benzaldehyde was found in 70 percent of the products and its concentration in aerosol generated from cherry-flavored samples was significantly higher than in products of other flavors. Exposure to benzaldehyde vapors has been shown to cause eye pain, conjunctiva redness, burning sensations in the nose and throat, cough and breathing difficulty.¹⁴

Numerous other recent studies, all of them published in the past six months, have found high levels of toxicants and carcinogens in large numbers of e-cigarette flavorings and have concluded that inhalation of such chemicals at the levels present in these products could have adverse health consequences.¹⁵

⁹ Deeming Final Rule Redline Changes at 181. See also Farsalinos, KE, “Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins,” *Nicotine & Tobacco Research*, 17(2): 168-174, 2015.

¹⁰ Deeming Final Rule Redline Changes at 181. See also Tierney, PA, et al., “Flavor chemicals in electronic cigarette liquids,” *Tobacco Control*, published online first April 15, 2015.

¹¹ Deeming Final Rule Redline Changes at 181. See also Behar, RZ, et al., “Identification of toxicants in cinnamon-flavored electronic cigarette refill liquids,” *Toxicology in vitro*, 28(2): 198-208, March 2014.

¹² Barrington-Tremis, JL, *Considerations Regarding the Impact of Flavorings*, Presentation at the FDA “Electronic Cigarettes and the Public Health: A Public Workshop,” March 9, 2015.

¹³ Barrington-Tremis, JL, Samet, JM, & McConnell, R, “Flavorings in Electronic Cigarettes: An Unrecognized Respiratory Health Hazard?,” *Journal of the American Medical Association*, doi:10.1001/jama.2014. 14830, published online November 10, 2014.

¹⁴ Goniewicz, M, *Toxicants in E-Cigarette Refill Solutions and Vapor*, Presentation at the FDA “Electronic Cigarettes and the Public Health: A Public Workshop,” December 10, 2014.

¹⁵ Sherwood, CL & Boitano, S, “Airway epithelial cell exposure to distinct e-cigarette liquid flavorings reveals toxicity thresholds and activation of CFTR by the chocolate flavoring 2,5-dimethylpyrazine,” *Respiratory Research*, 17, 2016; Allen, JG, et al., “Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes,” *Environmental Health Perspectives*, published online December 8, 2015; Kosnider, L, et al., “Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde,” *BMJ Thorax*,

The Guidance correctly notes that flavorings and ingredients approved for ingestion and use on the GRAS list have not been shown to be safe when inhaled in an ENDS. FDA must require that any flavoring, ingredient or additive to be used in an ENDS be tested for safety when used as part of an ENDS device that is the same as the product for which approval is sought. The proposed Guidance correctly recognizes the importance of this type of testing, but should provide additional information about the type of tests that it will require

D. Testing for Harmful and Potentially Harmful Components

Section VI.H.1 of the Draft Guidance addresses product analysis and accurately identifies the components, ingredients and additives of ENDS products that should be analyzed in support of an application. However, it is important for FDA to address methods of analysis to prevent some constituents from being missed or underreported because their levels were lower than those that detected by methods chosen by the manufacturer. The guidance should require the use of methods for HPHC characterization and quantitation that should include, at a minimum, state of the art liquid chromatography-tandem mass spectrometry, gas chromatography, tandem mass spectrometry, high resolution mass spectrometry, and related analytical chemistry techniques.

III. Population-Level Effects

A. General framework for evaluating population-level effects.

The draft guidelines properly acknowledge that the Tobacco Control Act requires that new product applications for ENDS products must address not only the effect of the application on individual health but also the population-level effects of the marketing of the product. Performing such an analysis involves an evaluation of the effects marketing a given product will have on consumer usage of all tobacco products.

The Tobacco Control Act specifies the factors to be considered in evaluating the population level effects of granting an application:

The finding as to whether the marketing of a tobacco product for which an application has been submitted is appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account

- (A) The increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- (B) The increased or decreased likelihood that those who do not use tobacco products will start using such products.

published online first January 28, 2016; Lerner, CA, et al., "E-Cigarette Aerosols Trigger Mitochondrial Stress Associated with Mitophagy in Lung Cells," *American Journal of Respiratory and Critical Care Medicine*, Vol. 193, Meeting Abstracts, 2016; Rowell, TR, et al., "Select E-Cigarette Flavors Alter Calcium Signaling, Cell Viability and Proliferation in Lung Epithelia," *American Journal of Respiratory and Critical Care Medicine*, Vol. 193, Meeting Abstracts, 2016.

The grant of an application to market an ENDS product has the potential to benefit the public health only if it results in existing users of tobacco products, who would not otherwise have quit, ceasing the use of all combusted tobacco products completely as a result of switching to the new product. Ideally, ENDS would serve as an interim step toward complete cessation of nicotine products.

There are several ways in which the marketing of an ENDS product could harm the public health. These possible detriments to the public health are listed on page 23, items (4)-(8) and in the bullet points on pages 35-36 of the draft guidance.

In order to demonstrate that the net benefits to the public health of granting the application outweigh the net detriments, FDA is correct in requiring a manufacturer to present evidence evaluating the likelihood of each of the outcomes, as well as evidence that the product as it is proposed to be marketed won't appeal to or attract large numbers of non-users, discourage smokers from quitting or increase the number of former smokers who relapse.

B. The demonstration of net benefits should be product-specific.

Whether or not ENDS products as a category, properly regulated and thoughtfully marketed, confer net benefits on the public health, does not mean that an application to market any specific ENDS product should be granted. Each product application should stand on its own. Therefore, a successful application for a particular product should demonstrate that granting the application would produce an incremental increase in net benefits compared to the net benefits that would occur if the application were denied. The guidance should make explicit the requirement for such a showing as a condition of granting the application.

C. As a category, flavored ENDS products are more likely to have harmful population-level effects on public health than are unflavored ENDS products.

One potential risk to the public health from the marketing of ENDS products is that youth and young adults who would not otherwise have started using tobacco products will initiate use with ENDS. Indeed, the massive increase in youth usage of e-cigarettes since 2011 underscores the significance of this concern.

The availability of flavored ENDS products and the aggressive marketing of these products to children fueled this increase. The version of the final deeming rule that was submitted by FDA to the Office of Management and Budget included a detailed discussion of the effects of flavored ENDS products on the public health, and specifically the effect of flavored ENDS products on youth initiation. That draft included the following findings.

FDA noted a nearly 800 percent increase in current e-cigarette usage among high school students between 2011 and 2014. More recently released data demonstrates a ten-fold increase since 2011, with 16% of high school students reporting current e-cigarette use.¹⁶ FDA concluded that the presence of flavored e-cigarettes had contributed to this increase. FDA found that "it is

¹⁶ CDC, "Tobacco Use Among Middle and High School Students — United States, 2011-2015," *Morbidity and Mortality Weekly Report (MMWR)* 65(14):361-367, April 14, 2016, <http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6514a1.pdf>.

more likely that a tobacco product with a characterizing flavor would appeal to youth and young adults than a product without a characterizing flavor.”¹⁷ FDA found that flavoring makes e-cigarette products easier to use and increases their appeal among new users, most notably among young people. The National Youth Tobacco Survey, cited by FDA, found that an estimated 1.58 million middle and high school students reported using flavored e-cigarettes during the past 30 days.¹⁸ Among the PATH youth cohort in 2013-2014, 81 percent of ever e-cigarette users reported that their first product was flavored and 85.3 percent reported using a flavored e-cigarette product in the past 30 days. 81.5 percent of current youth e-cigarette users stated that they used e-cigarettes because they “come in flavors I like.”¹⁹ FDA also cited evidence from cross-sectional studies suggesting that flavored e-cigarette use is popular among youth.²⁰ FDA took note of “the dramatic rise in youth and young adult use of flavored e-cigarettes.”

Moreover, FDA concluded that it was likely that youth e-cigarette users are not using e-cigarettes as a method to quit smoking. Rather, FDA cited a study showing that ninth graders having ever used e-cigarettes at the baseline assessment were approximately 2.7 times more likely than non-e-cigarette users to have started smoking combusted tobacco products 6 to 12 months later.²¹

Referencing a published study, FDA concluded that focus group data suggests that removing flavors from tobacco products may reduce young adults’ intentions to try these products and subsequently use them.²²

Moreover, FDA concluded on the basis of recent studies that “youth are particularly attracted to flavored ENDS products.” The final rule transmitted by FDA to OMB cites the statement by Lorillard Tobacco Company on its website that “kids may be particularly vulnerable to trying e-cigarettes due to an abundance of fun flavors such as cherry, vanilla, piña colada and berry.”²³

Nothing in the Final Rule as published casts doubt on the validity of any of the conclusions about the effect of flavors on youth usage of e-cigarettes in the rule transmitted to OMB. According to the Regulatory Impact Analysis, the benefits of the extended compliance period were extended to flavored e-cigarettes because of the potential impact on vape shops of a rule that would have required them to stop selling flavored products within 90 days of the

¹⁷ Deeming Final Rule Redline Changes at 168.

¹⁸ Deeming Final Rule Redline Changes at 171. See also CDC, “Flavored Tobacco Product Use Among Middle and High School Students—United States, 2014,” *MMWR*, 64(38): 1066-1070, October 2, 2015, <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6438a2.htm>.

¹⁹ Ambrose, BK, et al., “Flavored tobacco product use aged 12-17 years, 2013-2014,” *Journal of the American Medical Association*, 314(15): 1871-1873, 2015.

²⁰ Deeming Final Rule Redline Changes at 180. See also, Krishnan-Sarin, S, et al., “E-cigarette use among high school and middle school adolescents in Connecticut,” *Nicotine & Tobacco Research*, 17(7): 810-818, 2015.

²¹ Deeming Final Rule Redline Changes at 173. See also Leventhal, AM, et al., “Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence,” *Journal of the American Medical Association*, 314(7): 700-707, 2015.

²² Deeming Final Rule Redline Changes at 176. See also Choi, K, et al., “Young Adults’ Favorable Perceptions of Snus, Dissolvable Tobacco Products, and Electronic Cigarettes: Findings from a Focus Group Study,” *American Journal of Public Health*, 102(11): 2088-2093, 2012.

²³ Deeming Final Rule Redline Changes at 179. See also Lorillard, What you need to know about e-cigarettes – infographic. 2014; <http://www.realparentsrealanswers.com/what-you-need-to-know-about-e-cigarettes-infographic/>. Accessed August 6, 2014.

effective date of the rule and because of “emerging evidence” that some adults may be using these products to transition away from combusted tobacco use. (Redline Regulatory Impact Analysis, pp. 142-45) The validity of FDA’s analysis of the impact of flavors on youth was not cast into doubt.

These conclusions have important implications for FDA’s consideration of new product applications for flavored e-cigarette products. As a category, flavored ENDS products present a greater risk of increasing youth initiation. The existence of such strong evidence that flavored e-cigarette products have detrimental impacts on public health means that any manufacturer that wishes to market a flavored ENDS carries a heavy burden to demonstrate that the particular flavored product for which the manufacturer is seeking approval a) does not appeal to youth, and b) does contribute in a meaningful and measurable way to assisting a smoker to switch completely from a combusted tobacco product to an ENDS; and c) that the evidence provides a sound scientific basis for FDA to conclude that the approval of the application will provide a significant net benefit to public health. The question presented to FDA must be whether the applicant has shown that granting the application for the specific flavored product produces benefits in excess of the risks of harm.

D. The cost-benefit analysis under Section 910 concerns only public health impacts.

Under the Tobacco Control Act, FDA’s analysis of costs and benefits is limited to costs and benefits to the public health. To the extent that granting an application to market an ENDS product is expected to increase the number of smokers who quit, there is a benefit to the public health.

Recreational use of ENDS products by those who are not smokers trying to quit does not produce any benefit to the public health. Making ENDS products attractive for uses other than smoking cessation produces no benefit to the public health and should therefore not be considered in FDA’s analysis.

E. Use of master files and public dockets for uniquely identified compounds provides a thoughtful cost-effective way for manufacturers to obtain review and for FDA to establish standards that will improve consistency and better protect the public

The application process described in the Draft Guidance includes the potential for an applicant to reference a master file (p. 46), consisting of data submitted by the manufacturer of a component wherever possible to reduce the research burden on manufacturers and increase the efficiency of PMTA preparation. Encouraging the use of such procedures is likely to result in greater consistency of products on the market and greater standardization of the products that are marketed. Although some comments submitted to FDA regarding the deeming rule criticized the proposed deeming rule for encouraging product standardization, in fact such standardization should be a positive development for public health. Use of master files will facilitate such standardization and should be encouraged.

Similarly, FDA's announced intention to open public dockets (p. 46) for uniquely identified compounds likely to be used in ENDS products should help encourage the establishment of product quality standards and standardized product characteristics.

- F. Manufacturers submitting applications for products that have already been on the market should be required to present studies of consumer perception and consumer behavior with respect to the product.

The large majority of products for which applications will be filed are already on the market and will remain on the market during the compliance period. Thus, manufacturers have an opportunity to obtain and provide evidence of consumer perception and consumer behavior based on data concerning existing customers. Significant evidence of how consumers make decisions about product usage may well be drawn from consumers who are actually using the product. A manufacturer's inability to present evidence concerning actual usage of a product that has actually been on the market should raise significant questions about the population-level effects of its marketing. Such an inability would also raise questions about the ability of the manufacturer to perform satisfactory post-market studies of the actual usage of the product by consumers. The guidance should specify the elements that would make studies of product usage by existing customers reliable enough to be considered in evaluating the application.

- G. FDA should require submission of all advertising and marketing plans and all advertising and marketing materials for the product utilized prior to the application.

Consumer behavior is heavily influenced by advertising and marketing. Products advertised to be attractive to children will be used by children. The Draft Guidance recommends that applicants submit marketing plans as part of their applications. Given the importance of advertising and marketing in consumer decision-making, this recommendation should be a requirement. No application should be granted unless and until the advertising and marketing plans for the product have been reviewed.

Moreover, the grant of an application should be conditional on the manufacturer's adherence to the advertising and marketing plan submitted in order to ensure that the product, once permitted to be marketed, is not marketed to children. The sad history of the promotion of cigarettes to children demonstrates how effectively marketing plans can target young people. In many cases, examining the marketing materials may make it obvious that a product is being marketed to a youth audience or to another vulnerable sector of the market. Research shows that current e-cigarette marketing practices attract youth. The 2014 National Youth Tobacco Survey found that 68.9% of middle and high school students—18.3 million youth—had been exposed to e-cigarette advertisements from at least one source.²⁴ Another recent study found that 82 percent of 12-17 year olds and 88 percent of 18-21 year olds reported seeing e-cigarette advertising in 2015.²⁵ The investment in e-cigarette marketing has been coupled with an increase in use among youth and young adults. A 2016 study in *Pediatrics*, analyzing 2014 YTS data, found that exposure to e-cigarette advertising is associated with current e-cigarette use among youth and that greater exposure to e-cigarette advertising is associated with higher odds of use.²⁶

Moreover, it is not only the prospective advertising and promotion of the product that is relevant. The way the product has been advertised and promoted since its introduction to the market is also relevant to consumer perceptions and development of the existing customer base. A product that has been extensively advertised and promoted to children in prior years is likely to present a high risk of encouraging youth initiation in the future. Manufacturers should be required to submit as part of the application all advertising and promotional materials for the product since its introduction on the market as part of the application. Requiring provision of all such materials may give FDA insights into the marketing strategies of manufacturers that would not otherwise be apparent.

H. Importance of Post-Market Studies and Review

The grant of any application should be accompanied by a requirement to do post-market studies regarding the actual effects of the product on the public health.

No matter how careful FDA is in evaluating new product applications, the process depends on predictions about consumer behavior that may or may not turn out to be accurate. Given this inherent limitation, it is particularly important to require post-market surveillance to ensure that the presence of products on the market actually has the effect predicted in the application. FDA commonly requires post-market surveillance and reporting for drugs. For example, such surveillance and reporting was required when the manufacturer of nicotine gum was permitted to sell gum with mint flavor to ensure that the presence of a characterizing flavor did not increase the abuse potential of the product.²⁷

²⁴ CDC, Vital Signs: Exposure to Electronic Cigarette Advertising Among Middle School and High School Students—United States, 2014,” *Morbidity and Mortality Weekly Report*, 64(52): 1403-1408, January 8, 2016.

²⁵ Truth Initiative, *Vaporized: Youth and Young Adult Exposure to E-Cigarette Marketing*, November 2015, <http://truthinitiative.org/sites/default/files/VAPORIZED%20-%20FINAL%20VERSION.pdf>.

²⁶ Singh, T, et al., “Exposure to Advertisements and Electronic Cigarette Use Among US Middle and High School Students,” *Pediatrics*, published online April 25, 2016.

²⁷ When the application was initially submitted the sponsor was issued a Non-Approvable letter dated October 8, 1996 and a revised application, accompanied by results from a randomized clinical trial and a large amount of other information was subsequently approved in December, 1998. See http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/18-612s025_nicorette_admindocs.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/18-612025_Nicorette_medr_P1.pdf.

Ensuring that the design of post-market studies is appropriate is also an important element in FDA's consideration. Such post-market studies should be conducted in accordance with an established protocol to ensure that accurate results are obtained. FDA should consider the recommendations of the Institute of Medicine of the National Academies for post-market studies involving modified risk tobacco products as a model for developing appropriate study design for post-market study of new ENDS products.²⁸

IV. General issues applicable to both individual and population-level studies.

- A. Bridging of data should be accepted only where specific evidence clearly demonstrates that evidence submitted for one product is adequate to support an application for another.

The Draft Guidance states that in certain circumstances bridging of data from one product to another may be permitted. The example given in the Draft Guidance involves products that are identical except for nicotine content. The Draft Guidance properly states that manufacturers submitting evidence from bridging studies should provide the rationale and justification to support bridging. FDA's review of any application relying on the bridging of data from one product to another should include a critical examination of the rationale and justification submitted. Uncertainty about the validity of using data regarding one product to support an application for another product should be resolved by requiring evidence directly related to both products.

Moreover, as noted in Part I.C. above, the grant of a PMTA application makes it possible for manufacturers to use the product as a predicate product for a later substantial equivalence application or exemption from substantial equivalence. The potential availability of these pathways lessens the need for FDA to grant PMTA applications that rely on bridging data.

- B. Studies should be designed to meet scientific standards.

Each subject area specified in items i-viii on pages 36 through 38 of the draft guidance identifies a valid concern. It would be helpful for the final Guidance to include a more detailed description of the kinds of study designs that FDA regards as most appropriate for each such subject area and the kinds of evidence it would find persuasive.

V. FDA should design a procedure for considering applications that is transparent and that permits members of the public to understand the basis for FDA's decisions.

Members of the public have a right to know the criteria FDA is applying in evaluating applications for new products and the basis for its decisions regarding such applications. Neither the prior history of FDA's handling of substantial equivalence applications for products currently regulated by FDA nor the procedures proposed in the draft guidance for meetings between FDA and manufacturers provides a basis for expecting that FDA's decision-making will be properly

²⁸ Institute of Medicine. 2012. *Scientific Standards for Studies on Modified Risk Tobacco Products*. Washington, DC: The National Academies Press.

transparent. With regard to substantial equivalence applications, FDA has refused to provide even the most basic information and the information it has released with regard to applications when they are finally resolved has been inadequate to permit the public to understand the criteria being applied.

The procedure proposed in the Draft Guidance calls for private meetings between FDA and manufacturers. This procedure creates a legitimate concern that criteria for evaluating applications will be developed behind closed doors in meetings between FDA and manufacturers with no public participation and with no knowledge by members of the public about what criteria have been adopted and how they are being applied. FDA should adopt a procedure that provides the public with reasonable access to sufficient information to understand the criteria FDA is applying in evaluating the applications.

Moreover, the notice-and-comment rulemaking being used by FDA in this docket for development of guidance should be supplemented by public sessions at which issues can be explored in depth in discussions between responsible agency officials and experts in relevant scientific disciplines. In addition, FDA should consider seeking input from the Tobacco Products Scientific Advisory Committee on the Draft Guidance. TPSAC members have extensive experience in the relevant scientific disciplines and could provide important perspectives that would improve the quality of the guidance.

Respectfully submitted,

American Heart Association
American Lung Association
Campaign for Tobacco-Free Kids