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August 8, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
ATTN: Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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

Dear Dr. Hamburg:

Legacy is pleased to submit the following comments in response to the Food and Drug Administration's (FDA) Notice of Proposed Rulemaking (NPRM) on Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act).

The Tobacco Control Act gave FDA automatic jurisdiction over cigarettes, roll-your-own tobacco, and smokeless tobacco. It also gave FDA authority to regulate all other tobacco products, *but only* after issuing regulations deeming them as part of FDA's jurisdiction. Alarmingly, it has taken FDA five years to take this first step. During this time, and continuing into the present, broad categories of tobacco products have remained unregulated, presenting serious risks to the public health. It is essential that FDA move expeditiously to finalize this rule to fulfill its charge to protect the public health from these addictive and, in many cases, deadly products.

In these comments, Legacy urges the FDA to issue a deeming regulation, no later than a year from the date of the issuance of the NPRM, that, at a minimum: (1) extends its jurisdiction to ALL tobacco products including premium cigars and accessories; (2) requires warnings labels on packaging and advertising as proposed; (3) adopts the youth access proposals in the NPRM and expands them to ban all non-face-to-face sales or, at the least, require age verification for all Internet and other non-face-to-face sales; and (4) extends the youth

marketing restrictions currently in place for cigarettes and smokeless tobacco to all tobacco products.

We also provide information responsive to numerous, although not all, questions presented in the NPRM on other critically important issues, including flavored tobacco products, the continuum of harm, background on e-cigarettes and the need for specific product standards. Disturbingly, no regulations have been proposed on any these issues. We strongly encourage FDA to promptly commence regulatory proceedings to, at a minimum, ban all flavored tobacco products and issue basic safety product standards for e-cigarettes and other newly deemed products. This should be done as quickly as possible in order to protect the public health.

Consistent with Legacy's areas of expertise, our comments focus on the presentation of current, detailed scientific evidence which definitively demonstrate that the deeming rule and other recommended actions will satisfy the statutory public health standard: these regulatory proposals will provide benefits not only to individual users but, on a population-wide basis, will drive down tobacco use prevalence and related disease, principally by decreasing initiation with a specific focus on youth.[1] Areas of particular concern include findings on the relationships between use and initiation, progression to use or dual use, cessation, addictiveness, and health effects for three of the major categories of products that would be covered by the proposed rule.

Legacy has signed on to joint comments submitted by a number of leading public health organizations. While we agree with the broad goals of these comments, there are some areas where Legacy takes a slightly different approach to addressing the same issues.

The proposed rule is an important, if long overdue, first step and we look forward to continuing to work with FDA to ensure appropriate regulation of all tobacco and tobacco-derived nicotine products to reduce the death and disease associated with these products.

LEGACY
FOR LONGER HEALTHIER LIVES

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FDA must act expeditiously to enact the essential provisions of the deeming regulation –that is, to bring all products meeting the definition of "tobacco product" in the Tobacco Control Act under its authority. This first and necessary step to protect public health from the disease and death associated with tobacco is long overdue. FDA must act as soon as possible – and no later than one year after the publication of the proposed rule.

SECTION 2: FDA MUST REGULATE ALL TOBACCO PRODUCTS THAT MEET THE DEFINITION OF "TOBACCO PRODUCT" IN THE TOBACCO CONTROL ACT – INCLUDING PREMIUM CIGARS AND ACCESSORIES.

I. FDA MUST REGULATE ALL CIGAR PRODUCTS INCLUDING PREMIUM CIGARS.

First, cigars, including "premium" cigars, are a combustible tobacco product and therefore contain and produce carcinogenic compounds and other compounds that have serious negative effects on the health of the user.[2-5] In addition, secondhand smoke from cigars contains these same dangerous compounds, which have been causally linked to heart disease and lung cancer among non-smokers exposed to the tobacco smoke.[2] Regardless of whether used only occasionally or regularly, the data is clear: these "premium" cigars increase health risks to the users and bystanders. Second, there is no public health benefit, and there are numerous public health harms, in allowing one tobacco product on the market that would be exempt from a federal minimum age of purchase, vending machine bans in non-adult-only facilities, or other common sense regulations to keep these products out of the hands of youth. Third, the tobacco industry has a long, well-documented history of adapting their products to avoid regulation.[6] Finally, while there are some cigar smokers who have never smoked cigarettes, many cigar smokers are also current or former cigarette smokers.[2] This increases health risks by increasing and/or prolonging users' exposure to the deadly constituents found in combustible tobacco. Further, those who smoke cigarettes are more likely to inhale the cigar smoke,[7-10] significantly increasing the risk of disease and death. Exempting any category of cigars from FDA jurisdiction is directly inimical to the public health.

II. FDA MUST REGULATE OTHER TOBACCO PRODUCTS, INCLUDING E-CIGARETTES AND HOOKAH.

Legacy believes that the science and sound policy strongly supports coverage of ALL tobacco products, to the full extent that the term is defined in the Tobacco Control Act. In this section, we provide specific information strongly supporting FDA's assertion of authority over two rapidly expanding tobacco products not currently subject to FDA jurisdiction – e-cigarettes and hookah.

A. E-cigarettes

E-cigarettes are heterogeneous products intended to deliver nicotine using liquid nicotine that is vaporized and inhaled by users.[11] These products vary in quality (and therefore safety), size and efficiency of nicotine delivery.[12] Since they have been on the market for less than 10 years, their long-term health effects are unclear. Yet, in this completely unregulated environment, e-cigarettes have exploded onto the market. They come in a vast array of flavors, with inconsistent delivery of nicotine,

and very little known about what other ingredients are in the products. Further, these products continue to change and evolve,[13] unfettered by any regulations, making it difficult to know what exactly is in these products and how they impact public health.[12,14-17] That said, there is some hope that e-cigarettes, which by all accounts are less harmful to individual health than traditional cigarettes, could be a game-changing product that helps people move off deadly combustible tobacco to a less harmful nicotine product. Many questions must be answered before that is confirmed however. Regardless of these questions, one thing is clear: e-cigarettes must come under FDA regulation to ensure that any potential individual and public health benefit is realized and that public health harms are minimized.

B. Hookah

Hookah smoking is a centuries-old form of tobacco use also known as waterpipe, narghile, shisha, goza, and hubble-bubble.[18] Hookah is often smoked in group settings or at commercial establishments such as hookah bars,[19-21] and comes in a variety of fruit and candy flavors.[21-23] Hookah use has significant health effects, is highly addictive, and has disturbing ramifications for broader tobacco use initiation.[24] Despite these risks, hookah is widely perceived as less harmful [20-22,25] and less addictive [20,21,25] than cigarettes and has experienced a surge in prevalence in the U.S., particularly among adolescent and young adult populations.[26-28] The rapid increase in hookah use, especially among young people, as well as the significant health risks that hookah poses make it imperative that hookah tobacco is regulated by FDA.

III. FDA MUST REGULATE ACCESSORIES.

Legacy urges FDA to assert its authority to the full extent permitted by the statute, *including* accessories. Contrary to the NPRM's conclusory assertion that "because accessories are not expected to be used in the consumption of a tobacco product, we expect that accessories will not have a significant impact on the public health",[29] this proposed exclusion presents a real and serious threat to public safety and health. Examples of items that would be classified as accessories – and therefore exempt from regulation – include e-cigarette cartridges, cartomizers, tanks, bottles of nicotine-containing liquid, batteries, battery housings, chargers, and hookah charcoals. The demonstrated public health risks presented by items that could quite possibly be characterized as accessories under FDA's proposed, ill-defined and overbroad exclusion are real and substantial. We note that the exclusion for accessories was included at the OMB review stage. We believe that the views of the FDA – the agency with public health expertise – should be respected in this regard and accessories should be covered under the final rule.

SECTION 3: FDA MUST AGGRESIVELY APPLY OTHER REGULATORY MEASURES TO ALL TOBACCO PRODUCTS.

I. FDA MUST ENSURE APPLICATION OF ALL SELF-EXECUTING SECTIONS OF THE TOBACCO CONTROL ACT TO ALL TOBACCO PRODUCTS.

We recommend that the background discussion to the final deeming rule include a fuller list, in one place, of the provisions that will apply to the newly deemed products. These include, at least: Adulterated tobacco products;[30] Misbranded tobacco products;[31] Submission of health information to the Secretary, including but not limited to the required promulgation of the list of harmful and potentially harmful constituents;[32] Annual registration and product listing;[33] General provisions respecting control of tobacco products;[1] Tobacco product standards, other than the provisions

specifically regarding cigarettes;[34] Notifications and other remedies;[35] Records and Reports on tobacco products;[36] Application for review of certain tobacco products, including but not limited to premarket review and substantial equivalence requirements;[37] Modified risk tobacco products;[38] and Labeling, recordkeeping, records inspection.[39]

II. FDA MUST ADOPT APPROPRIATE WARNING LABELS FOR ALL TOBACCO PRODUCTS.

Legacy supports the proposed warnings based on clear evidence that large, prominently placed, and strong warnings provide significant public health benefits. Research has shown that such warning labels increase awareness and understanding of health effects and disease risk among users and non-users, encourage users' motivation and attempts to quit – and stay off tobacco,[40] and discourage uptake of tobacco.[40-43] We encourage FDA to continue to develop warnings about the health effects of tobacco use, encouraging tobacco users to quit, and non-users to refrain from starting in the first place.

Legacy strongly supports the warning labels for cigars included in the proposed rule.

The evidence is clear that the health effects of cigars are not well understood by the public. The larger sized warnings proposed for cigar packaging and advertisements will ensure that consumers will actually see the warnings and the critically important information will register with them. Legacy also encourages FDA to also adopt the fifth FTC cigar warning, WARNING: Tobacco Use Increases the Risk of Infertility, Stillbirth And Low Birth Weight. This is especially important in light of data showing that females are using cigars – little filtered cigars in particular – at relatively high rates.

Legacy strongly supports requiring warning labels for all tobacco products including the requirement that all tobacco products carry an addictiveness warning.

Given low knowledge of harm and addictiveness of non-cigarette tobacco products, this is of particular importance for products like hookah that do not currently carry any health warnings. Studies of non-cigarette products, including hookah, show that lower perceptions of harm and addictiveness of these products facilitate use among young adults.[44-46] Strong warnings regarding addictiveness of all tobacco products will help reduce trial and use in vulnerable populations.

III. FDA MUST BROADEN ITS YOUTH MARKETING RESTRICTIONS.

Legacy strongly supports the NPRM's proposals to establish 18 years of age as the uniform, national minimum age for the purchase of all covered tobacco products; require that retailers verify age by means of photographic identification; and prohibit most sales via vending machines and other electronic or mechanical devices.[47] However, to be effective, these access restrictions must be expanded to require that all tobacco sales be face-to-face or, at the very least, institute enforceable age-verification requirements for non-face-to-face sales.

The record is crystal clear: the tobacco epidemic is driven and sustained by youth uptake of tobacco use.[6] It is essential that efforts to curb tobacco use assure both that young people are not able to purchase tobacco products and that they are not targets of tobacco product marketing and promotion. The NPRM takes an important first step on the access question by establishing a uniform minimum age of 18 for the purchase of all tobacco products and requiring photo IDs for retail sales. However, it not only fails to require that all sales be face-to-face, it inexplicably fails to require any age verification requirements or enforcement mechanisms for Internet sales, thus leaving a loophole many young people will exploit to purchase tobacco products. While we strongly support the establishment of a federal minimum age of purchase for all tobacco products, as well as a ban on vending machine sales,

those provisions do not go nearly far enough to protect youth from these addictive and deadly products. It is essential that the final rule require face-to-face sales of all tobacco products or, at the least, include enforceable age verification requirements for Internet sales.

Legacy urges FDA to extend all of the applicable youth marketing/promotion provisions of the 1996 Final Rule to *all* tobacco products, adjusting as necessary for different types of products.
Without explanation, the NPRM does not include key provisions from the 1996 Rule which limit the marketing and promotion of tobacco products to youth. Without further regulatory action, these provisions will continue to apply only to cigarettes and smokeless tobacco. Given the powerful record establishing the extensive marketing of all tobacco products to youth as well as the effectiveness of such marketing, it is essential for FDA to include firm, actionable prohibitions against marketing to youth in the final deeming rule. The alternative is, quite simply, to squander an extremely important opportunity to protect our young people.

IV. FDA MUST REDUCE ITS PROPOSED COMPLIANCE GRACE PERIOD FROM 24 TO 12 MOTNHS AND MUST PRIORITIZE REVIEW OF APPLICATIONS FOR PRODUCTS ALREADY ON THE MARKET.

The proposed rule appropriately recognizes that there will be a practical problem with regard to the timing of compliance obligations for some products that will newly come under its jurisdiction once the proposed rule is finalized. However, Legacy strongly agrees with our public health colleagues that the proposed compliance grace period is far too long and should be reduced to 12 months. FDA should also ensure that applications for products submitted during the compliance grace period (and therefore applications for which products are already on the market) would get first priority for review over product applications that have not yet entered the market. Additionally, a condition of this compliance grace period should be that manufacturers agree to youth marketing restrictions, ingredient reporting, and quality controls that would ensure consistent delivery of nicotine and other constituents. This would go a long way to protecting the public health for products that have not yet been fully reviewed by FDA.

SECTION 4: LEGACY RESPONSES TO VARIOUS QUESTIONS POSED IN THE PROPOSED RULE, BUT NOT ASSOCIATED WITH A REGULATORY PROPOSAL

I. FDA SHOULD ACT PROMPTLY TO REQUIRE A BAN ON ALL FLAVORINGS IN TOBACCO PRODUCTS.

As a result of the Tobacco Control Act, FDA banned flavored cigarettes, except for menthol in 2009. Since then, Legacy has led the fight to ban menthol in cigarettes. Further, we have strongly supported the banning of all flavors from all tobacco products, given significant scientific evidence that flavored tobacco is preferred and used by the youngest tobacco users in the U.S. and abroad – youth and young adults. We are deeply disappointed that FDA did not issue any regulations to protect youth by banning all flavored tobacco products in the proposed rule. Legacy strongly urges FDA to move expeditiously to initiate regulatory action to institute such a ban.

II. RESPONSES TO QUESTIONS REGARDING THE CONTINUUM OF HARM

In the proposed rule, FDA acknowledged that no tobacco product is entirely safe, but that some products pose less harm to the individual than others. Legacy agrees that a continuum of harm of tobacco products exists, with combustible tobacco products at the most harmful end of the continuum

and FDA-approved nicotine replacement therapies (NRT) at the least harmful end. Legacy believes that the optimal tobacco control strategy is to achieve a society free of all nicotine and tobacco use (total abstinence). We recognize however, that some users will not be able or willing to stop using tobacco products altogether. Harm reduction, a strategy we endorse if properly implemented, adopts a secondary priority of moving those users to less-harmful non-combustible tobacco products while eliminating combustible product use entirely. This is feasible only if alternative, demonstrably lower harm, non-combustible products that can deliver nicotine are available. Regulations can play an important role in achieving this goal. Under the principle of harm reduction, each product must be regulated based both on its potential impact on individual health and the health of the public at large. FDA's deeming rule represents the first, highly critical, phase in determining how nicotine products, other than products currently regulated under either FDA's tobacco or pharmaceutical authority, will be designed, marketed and sold to consumers. Legacy strongly supports the comprehensive regulation of nicotine by the FDA across all of its divisions, particularly CTP and CDER, to ensure that FDA uses all of the tools at its disposal to communicate with the public regarding minimizing tobacco-related harm. Finally, and critically, any regulatory regime, including one that takes a harm reduction approach, must place heightened focus on the issues of youth initiation. A new generation of tobacco users – of any tobacco products -- is NOT an acceptable result. Legacy strongly urges the development of independent post-market surveillance systems to meet these goals and ensure success of FDA tobacco regulation.

SECTION 1: IN ORDER TO PROTECT THE PUBLIC HEALTH, FDA MUST PROMPTLY ISSUE A FINAL REGULATION ASSERTING JURISDICTION OVER *ALL* TOBACCO PRODUCTS, INCLUDING ALL CIGARS AND ACCESSORIES WITHIN ONE YEAR OF THE PROPOSED RULE'S PUBLICATION AND SOONER IF POSSIBLE.

FDA must act expeditiously to enact the essential provisions of the deeming regulation – that is, to bring all products meeting the definition of "tobacco product" in the Tobacco Control Act under its authority. This first and necessary step to protect public health from the disease and death associated with tobacco is long overdue. FDA must act as soon as possible – and no later than April 25, 2015, one year after the publication of the proposed rule.

In the absence of this regulation, and under the current state affairs that is now extending into its sixth year following the enactment of the Tobacco Control Act, FDA is powerless to protect the public from the risks presented by a wide range of tobacco products, all of which are addictive and all of which carry risks to their users. Without the deeming rule, all types of cigars, including little cigars and cigarillos, hookah and e-cigarettes, are on the market, broadly appealing to youth, [48] [49] -- and unregulated. FDA has no authority to limit youth access to or ban youth marketing of these products; it has no authority to require warning labels or to obtain information about product ingredients; it cannot even require the most basic product standards, for example, that receptacles containing nicotine liquid for use in e-cigarettes be child-proof. This situation is untenable and must not be permitted to continue.

Legacy, along with our public health partners, has signed on to letters to the Secretary of the Department of Health and Human Services (HHS) and to the Director of the Office on Management and Budget (OMB), urging the finalizing of the deeming portion of the rule within one year of the publication of the proposed rule, that is April 25, 2015. We have also signed on to a joint submission to this docket that also reiterates that the final rule must be issued no later than April 25, 2015. We incorporate by reference those letters and comments here. We make no apologies for the repetition of this point – we cannot state strongly or often enough the importance of FDA asserting jurisdiction over all tobacco products *now*. In the meantime, lives are at stake.

SECTION 2: FDA MUST REGULATE ALL PRODUCTS MEETING THE DEFINITION OF "TOBACCO PRODUCT" IN THE TOBACCO CONTROL ACT, INCLUDING PREMIUM CIGARS AND ACCESSORIES.

Legacy strongly believes FDA must regulate all products that meet the definition of "tobacco product" in the Tobacco Control Act. This is the only way to fulfill FDA's charge to protect public health. Tobacco products have gone unregulated for too long. There is no public health benefit. The current regulatory landscape where some tobacco products are regulated and others are not significantly undercuts FDA's ability to protect public health from the scourge of tobacco.

Protection of the public health is FDA's number one priority for all its products. When developing the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), Congress recognized the inappropriateness of the "safe and effective" standard by which FDA evaluates drugs, since tobacco causes disease and death when used as intended. Thus, Congress established a new public health standard by which tobacco regulation must be guided. We have discussed at length the public health standards in other submissions – including that found in our comments to Docket no. FDA-2013-N-0521.[50] Congress purposely made the standard broad, in order to not only protect individual health, but also to take into account the

overall population health. As such, FDA must consider not only the likelihood of risks and/or benefits of a product on the individual but also the likelihood of risks and/or benefits on the population as a whole – including users and non-users of the product.[1,51]

We have conducted systematic reviews of the evidence on cigars and e-cigarettes, as well as a detailed literature review on hookah. We provide a summary of the review for each product below. As a result of these reviews, we conclude that FDA regulation of each of these products is consistent with the public health standard. We include the full review for each of these products in Appendices A, B, and C.

I. FDA MUST REGULATE ALL CIGAR PRODUCTS INCLUDING PREMIUM CIGARS.

Legacy strongly encourages FDA to regulate all cigar products, including premium cigars. The proposed rule offers two options for regulating cigar products. The first option brings all cigar products under FDA's authority. But FDA has also put forward a second option that would carve out so-called "premium" cigars from FDA's authority altogether.[52] Legacy notes that this two option approach was inserted by the Office of Information and Regulatory Affairs (OIRA) at OMB. We urge OMB to defer to FDA's expertise and revert to the original proposal: to bring all cigars under FDA's authority including so-called "premium" cigars in addition to little cigars and cigarillos.

Regular cigar use has been estimated to cause 9,000 premature deaths in 2010 in the United States, and as a result of these lives cut short, cost approximately $22.9 billion.[53] These figures likely underestimate the total costs and number of deaths associated with cigar smoking, as this study does not estimate any of the deaths and costs associated with less frequent cigar use. Further, many cigar types come in a wide variety of flavors, many of which are enticing to youth and young adults. Some premium cigars are flavored, though the proposed rule does try to carve those that are not flavored out from FDA regulation.

The proposed rule defines "premium cigar" as a cigar that:

- Is wrapped in whole tobacco leaf;
- Contains a 100% leaf tobacco binder;
- Contains primarily long filler tobacco;
- Is made by combining manually the wrapper, filler and binder;
- Has no filter, tip, or non-tobacco mouthpiece and is capped by hand;
- Has a retail price (after any discounts or coupons) of no less than $10 per cigar (adjusted, as necessary, every 2 years, effective July 1st, to account for any increases in the price of tobacco products since the last price adjustment);
- Does not have a characterizing flavor other than tobacco; and
- Weighs more than 6 pounds per 1000 units.[54]

This definition was developed by OMB in an apparent effort to exempt such products from FDA's authority. We note that it is not based on or consistent with other definitions and would exist only for the purposes of exempting these products from FDA jurisdiction. It, for example, diverges from the Tax Code's approach which breaks cigars into two categories for the purpose of excise taxes: "small or little cigars" which are the same size as cigarettes (3 pounds per thousand sticks), and "large cigars" that cover every other type of cigar that is larger than 3 pounds per thousand sticks. It also ignores the wide variability in "cigar" products on the market; the category includes cigars that are just barely larger than cigarettes that are very similar to cigarettes with spongy filters; cigarillos, that sometimes have a wood or plastic tip; and a wide range of

traditional cigars –often referred to as "premium cigars" that range in price from $1 to more than $25 per cigar.[55]

Exempting any category of cigars from FDA jurisdiction is directly inimical to the public health. First, as highlighted in detail below, cigars, including "premium" cigars, are a combustible tobacco product and therefore contain and produce carcinogenic compounds and other compounds that have serious negative effects on the health of the user.[2-5] In addition, secondhand smoke from cigars contains these same dangerous compounds, which have been causally linked to heart disease and lung cancer among non-smokers exposed to the tobacco smoke.[2] Regardless of whether used only occasionally or regularly, the data is clear: these "premium" cigars increase health risks to the users and bystanders.

Second, there is no public health benefit, and numerous public health harms, in allowing one tobacco product on the market that would be exempt from a federal minimum age of purchase, vending machine bans in non-adult-only facilities, or other common sense regulations to keep these products out of the hands of youth. Supporters of the option to exempt premium cigars (Option 2) argue that these products are not used by youth and therefore pose no public health threat. However, data shows that at least some youth and young adults do use these products. For example, we looked at premium cigar brands that, as noted in a recent paper published in *Tobacco Control,* current youth and young adult cigar smokers indicated is their usual brand.[56] We then checked three different cigar retail websites to determine the retail price of these brands, which would indicate whether some of these brands would be exempted from regulation, as proposed in Option 2.[57-59] At least three of the brands (Cohiba, Montecristo, and Arturo Fuente) had at least one cigar – and in the case of Cohiba, several – that retailed for $10 or more per stick, thus meeting the definition of premium cigar in the proposed rule. Further, exempting "premium" cigars from FDA authority prevents FDA from issuing any product standards that have the potential to reduce the death and disease caused by these products.

Third, the tobacco industry has a long, well-documented history of adapting their products to avoid regulation.[6] This manipulation to avoid regulation continues, as exemplified as recently as 2009, when several little cigar brands increased their weight slightly in order to qualify as "large cigars" under the tax code. This gave them preferential tax treatment, making their products significantly cheaper.[55,60] Also in 2009, when the flavor ban on cigarettes went into effect, manufacturers of clove *cigarettes* simply turned their products into clove *cigars*.[61-63] Based on these actions, we have every reason to anticipate that, should FDA exempt certain products from their jurisdiction, the industry will simply modify their products to fit definitions of the unregulated products.

Finally, while there are some cigar smokers who have never smoked cigarettes , many cigar smokers are also current or former cigarette smokers.[2] This increases health risks by increasing and/or prolonging users' exposure to the deadly constituents found in combustible tobacco. Further, those who smoke cigarettes are more likely to inhale the cigar smoke,[7-10] significantly increasing the risk of disease and death.

Nothing prevents FDA from regulating different products differently based on public health impact. Proponents of Option 2 behave as if regulation of premium cigars constitutes a ban on these products. This is not the case. While there is no question that there is sufficient data to conclude that premium cigars should be subject to FDA jurisdiction, it may be that different cigar products pose different degrees of harm to public health, and to youth in particular. Should that prove true – though the data is not clear at this

point – there is no reason why FDA cannot issue an appropriate level of regulation for those products. Nonetheless, there are common sense regulations that should apply to all tobacco products, including manufacturer registration, reporting of ingredient lists, health impacts, and harmful and potentially harmful constituents, adulterated or misbranded products, prohibition on "light" or "low tar" labels or other claims for modified risk unless FDA issues a marketing order for such statements, among others. Further, there is no reason why a federal minimum age of purchase or restrictions on marketing to youth should apply to some tobacco products and not others. No tobacco product should be easily accessible to or marketed to youth.

Below we provide the supporting evidence that regulating all cigar products meets the public health standard. As we discussed above, cigars are not a homogenous product type, and the definition proposed for "premium cigar" is not based on any scientific data. Despite the wide range of cigar products, data on cigars does not differentiate between the different types of cigar products. Further, studies have shown that there is significant confusion about the various cigar products, leading to under-reporting and underestimations of cigar use.[64,65] Some studies have suggested providing brand names in population surveys as one way to reduce any confusion among products.[66] More recent surveys have begun to give brand name examples and/or use photos of the products to help respondents differentiate between the products.[66] The data we provide below reports on cigars as a general category, unless otherwise indicated. Regardless of the type of cigar, the evidence is clear: all cigar products pose significant health risks to both users and non-users, are used by youth and young adults, as well as other sub-populations, are addictive and are often used in conjunction with other tobacco products.

Cigars contain high levels of harmful constituents which pose serious health risks. In general, cigar smoke is similar to cigarette smoke, however, cigars have higher levels of: tobacco-specific nitrosamines (TSNAs);[5] NNK;[5] carbon monoxide (CO);[67] ammonia;[68] and tar.[68] As a result, cigar smoking poses serious health effects – even in those who don't use cigars on a daily basis. A large body of evidence shows that cigar smoking is causally associated with higher risk of oral, esophageal, laryngeal, and lung cancer.[2,3,53,69] Cigar smokers have a marked increase in risk for Chronic Obstructive Pulmonary Disease (COPD)[70], and cigar smokers experience higher mortality from COPD than do non-smokers.[71] Those who smoke cigars have a higher risk of fatal and non-fatal stroke than non-smokers, with the highest risk of stroke seen in dual users of cigars and cigarettes.[72] Cigar smokers, including those who reported they did not inhale, have shown significantly higher stomach cancer mortality than those who did not use tobacco.[73] For those who smoke cigars heavily, and for those who inhale, cigar use causes an increased risk of heart disease.[72]

Proponents of Option 2 claim that premium cigar users smoke them only infrequently, and therefore they have no risk of these diseases. However, one study found an increased risk in head and neck cancers for those who do not smoke cigarettes, but are ever cigar users.[74] Further, many studies found that while the risk for these diseases increases with the number of cigars used and the intensity of inhalation, disease risk still exists with any use.[2,74]

Even when not inhaled, cigars pose significant health risks to users. Some cigar smokers claim that they do not inhale, however, cigar smokers do inhale some amount of smoke -- even when they do not intend to inhale.[7] Regardless of how much inhalation actually takes place, studies show that because cigar smoke dissolves more easily in saliva than cigarette smoke cigar users absorb smoke (and nicotine) from cigars even when they report no inhalation.[70,75] It is important to note that those who smoke cigarettes or used to

smoke cigarettes are more likely to inhale cigar smoke.[2,7-9,76,77] Those who inhale cigar smoke are much more likely to absorb high levels of nicotine,[78] and experience a higher incidence of the health effects associated with cigar smoking,[2,79] including the risk of death.[3]

Secondhand cigar smoke is also dangerous. Secondhand cigar smoke contains higher concentrations of toxic and carcinogenic compounds than cigarette smoke and is a major source of fine-particle and carbon monoxide indoor air pollution.[2,3] One study suggests that "even normal breathing in a cigar smoke-filled room could result in substantial nicotine exposure to any person in the room."[78] Another study concluded that a non-smoker exposed to smoke during smoking of a cigar receives a much higher exposure to carbon monoxide (CO), respirable suspended particles, and particle-bound polycyclic aromatic hydrocarbons than would likely occur for a single cigarette.[67] Large/premium cigars in particular have more tobacco, nicotine, nitrosamines and higher levels of nitrogen oxides, ammonia, carbon monoxides, and tar than cigarettes.[68] There is a large body of evidence on how these components impact the health of not only the smoker, but to non-users exposed to the smoke.[80]

Not only do all cigar types pose health risks, data shows that consumption of cigars is rising, and prevalence has remained frustratingly flat, particularly among youth and young adults, even while cigarette consumption and prevalence have decreased. Overall consumption of cigars has risen from 2000-2011 while cigarette consumption declined in the same time.[53,81] In particular, large cigar consumption increased every year from 2000 to 2011, with large jumps in 2009 after the tax increase on all tobacco products, and especially on little cigars, went into effect and cigar companies increased slightly the weight of their little cigar products in order to be taxed as large cigars.[53,82] Further, numerous national surveys have shown no decline in cigar use prevalence, even while cigarette smoking prevalence has decreased. The 2012 National Survey on Drug Use and Health (NSDUH), showed that rates of current cigar use among 12-17 year-olds have remained similar from 2002-2012, while current cigarette use rates declined in those same years.[48] Moreover, a recent national survey showed that current cigar smoking among youth was higher than youth cigarette smoking in eight states and cigar use rates were similar to that of cigarette use rates in an additional two states.[83] In terms of the different types of cigars, data shows that while significant numbers of cigar smokers use cigarillos and other mass market cigars (61.8%), as well as little filtered cigars (18.4%), a significant proportion also usually smoke premium cigars (19.9%).[81]

Importantly for the public health, data shows that some subpopulations use cigars at higher rates than others including young adults, minorities and females. Young adults in particular have a higher prevalence of cigar smoking than other age groups. High rates of young adult cigar use have been a trend for several years.[84,85] In terms of the specific cigar products, the 2012-2013 National Adult Tobacco Survey (NATS) found that a large majority (72.1%) of young adults (aged 18-29 in this study) listed cigarillos and other mass market cigars as their usual cigar with premium cigars the next most popular (15.1%) and finally, little filtered cigars (12.8%).[81] Further, a recent study by Legacy researchers reported that in the Legacy Young Adult Cohort in 2013, ever cigar use was reported by 37.9% of the entire cohort. In the 18-24 age group of cigar users, 58.1% had ever used little cigars and cigarillos, 44.0% had used both little cigars and large cigars and 29.9% had used large cigars only.[86] In a follow up study of that same cohort over three waves from July 2011 to July 2012, found that ever large cigar use among 18-24 year olds increased by 10.2% and little cigar, cigarillo and bidi use increased by 9.1%.[87] While large cigars were not defined by brand name or description in this study, the survey did give brand-specific examples of little cigars and cigarillos, so respondents were less likely to confuse the various cigar products.

Cigars – particularly little cigars and cigarillos - are gaining traction in minority populations. The 2012 National Youth Tobacco Survey (NYTS) found current cigar use more than doubled among non-Hispanic black high school students from 2009 to 2011-2012 and found that high school males smoke cigars at twice the rate of high school females.[26] That same study showed that in 2012, among both middle and high school students, black, non-Hispanic as well as Hispanic students smoked cigars at higher rates than white non-Hispanic students.[26] In contrast, the 2013 YRBSS found that white, non-Hispanic; black, non-Hispanic and Hispanic youth used cigars at similar rates.[83] While the 2012 NSDUH found that lifetime and past year cigar use was higher among whites, past month cigar use was higher among blacks.[48] A Legacy study of young adults found that use of little cigars and cigarillos was significantly associated with being non-Hispanic black.[86] These findings are supported by other studies, including one online survey of college students in the southeastern U.S. which found that small cigar smokers were younger, more likely to be black than white or other, and attending a Historically Black College and University (HBCU) rather than a state university or technical school.[88] Another survey of adults in an inner city population in Hartford, Connecticut found that smoking of Black & Mild, a cigarillo brand, was more common among African Americans and Latinos than among white participants. [89]

In looking at gender differences, men were more likely to list premium cigars as their usual cigar, while little filtered cigars were the choice of more women than men.[81] Further, data suggests that female respondents are more attracted to cigarillos than to regular cigars. In one study, males were more likely to smoke cigars than females. However, the gender difference was larger for regular cigars than for cigarillos.[90] A recent study from Legacy showed that females were slightly more likely to have used a non-cigarette-combustible product (including cigars and hookah) than males.[87] Further, another Legacy study found that use of little cigars and cigarillos was significantly associated with being female.[86]

Cigars develop and sustain addiction. Because of their size, large/premium cigars contain significant amounts of tobacco, and therefore, large amounts of nicotine.[2] Inhalation of large/premium cigars increases nicotine delivery.[78] While most data suggests that cigar users do not use cigars every day or even every week, some studies do show that those who smoke less than daily still exhibit nicotine dependence. For example, studies showed that cigarillo smokers exhibit nicotine dependence.[91,92] A study using data from the 2012 NYTS found symptoms of tobacco dependence were still reported by cigar-only users even though a substantial majority reported use on 5 days or less in the past 30 days.[93]

Studies show that some youth smoke cigars, but not cigarettes.[93-95] This is concerning since this provides an additional source of nicotine exposure.[94] Exposure to nicotine in youth and young adulthood can lead to nicotine dependence and addiction – much more so than older adult exposure.[96-98]

That said, dual use or poly-use of cigars and other tobacco products is much more the norm. Poly-tobacco users have been shown to be more likely to report symptoms of nicotine dependence.[93] Concurrent use of cigars and other tobacco products increases exposure to nicotine and other harmful constituents, which also increases the risk of disease and causes higher mortality rates.[84] Further, those who smoke cigarettes are more likely to inhale cigar smoke, significantly increasing risk of disease.[8-10,77,99]

Polyuse of cigars with other tobacco products – especially cigarettes -- is widespread among both youth and adults. In fact nearly half of youth cigar smokers in one survey indicated they used multiple types of tobacco

products. Interestingly, a review of NYTS data from 1999-2009 revealed that while heavy and moderate cigarette smokers saw a decrease in cigar use, cigar use among light cigarette smokers increased over time.[100] The poly-tobacco use trend is found among adults as well. The 2012-2013 NATS found that 35.1% of adult premium cigar users, 58.3% of usual cigarillo and other mass market cigar smokers and 75.2% of usual little filtered cigars smokers all currently smoked cigarettes.[81] Several local or regional studies confirm these national survey findings as well, with young adult and/or youth users or both cigars and cigarettes ranging from 10.6% – 61.4%.[95,101-104] A study looking at TUS-CPS data from 1995 through 2002 showed that concurrent use of cigarettes and cigars increased in every socio-demographic category including race, education level, geographic location, income level, etc.[84] However, in other studies of nationally representative young adult populations, Whites were slightly more likely to use cigars and cigarettes than other races.[105] Finally, several studies show that cigar use is an indicator of use of other drugs, especially marijuana. This is particularly the case for little cigars and cigarillos.[85-88,102,103,106-109]

The little data on cigar cessation that exist shows that 48.4% of current youth cigar users intend to quit, and 48.0% of them reported making a past-year quit attempt. Among youth cigar users, prevalence of quit intentions among African Americans (62.5%) was significantly higher than whites (43.0%).[110]

In sum, the data is incontrovertible that all cigars pose serious health effects, are used by youth and young adults, are used in some subpopulations in higher numbers, and are addictive. In order to protect public health from these products, FDA must regulate all cigar products, including premium cigars.

II. FDA MUST REGULATE ALL ELECTRONIC NICOTINE DELIVERY PRODUCTS, SUCH AS E-CIGARETTES, VAPE PENS, AND NICOTINE VAPORIZERS AND HOOKAH PRODUCTS.

We have addressed cigars separately given the NPRM's specific request for comment on the two options proposed for coverage. Not only does the science and sound policy mandate FDA jurisdiction over all cigars, it also strongly supports coverage of ALL tobacco products, to the full extent that the term is defined in the Tobacco Control Act. In this section, we provide specific information strongly supporting FDA's assertion of authority over two rapidly expanding tobacco products not currently subject to FDA jurisdiction – e-cigarettes and hookah.

A. E-CIGARETTES

Electronic nicotine delivery systems, commonly known as e-cigarettes, are a heterogeneous new product type that ranges from disposable products that look like plastic cigarettes to large, refillable tank systems. Similar devices are sometimes called e-hookah, vape pens, or personal vaporizers. Throughout this comment, we refer to all of these products as e-cigarettes. These products vary in quality (and therefore safety), size and efficiency of nicotine delivery.[12] Since they have been on the market for less than 10 years, their long-term health effects are unclear. Yet, in this completely unregulated environment, e-cigarettes have exploded onto the market. They come in a vast array of flavors, with inconsistent delivery of nicotine, and very little known about what other ingredients are in the products. While these products started independently of the cigarette manufacturers, the big tobacco companies have become major players in this new market. Moreover, reminiscent of the tactics used by the tobacco industry, the products themselves continue to change and evolve,[13] unfettered by any regulations, making it difficult to know what exactly is in these products and how they impact public health.[12,14-17]

That said, there is some hope that e-cigarettes, which by all accounts are less harmful to individual health than traditional cigarettes, could be a game-changing product that helps people move off of deadly combustible tobacco to a less harmful nicotine product.[111] However, significant questions remain with regard to the impact on the public health. We address some of these questions and the role e-cigarettes have the potential to play later in our comments. Regardless of these questions, one thing is clear: e-cigarettes must come under FDA regulation to ensure that any potential individual and public health benefit is realized and that public health harms are minimized.

Below we highlight the importance of FDA regulation due the fact that these products are not without risk and that youth and young adults are using these products.

While nicotine is addictive, its level of addictiveness can vary depending on its mode of delivery. For example, in cigarettes, nicotine is highly addictive. On the other hand, FDA-approved nicotine replacement therapies (NRTs) are minimally addictive and can be used in the long term. Studies suggest that the current generation of e-cigarettes is less addictive than combustible cigarettes and closer in profile to NRTs.[112,113] That said, studies show that e-cigarettes do indeed deliver nicotine, though delivery is dependent on the e-cigarette device and liquid type, as well as the rate at which the nicotine is delivered and the user's experience with e-cigarette use.[114-118] Three clinical laboratory reports among experienced e-cigarette users indicated e-cigarette use reliably increased plasma nicotine but at levels and speeds much lower than those achieved from a conventional cigarette.[117-119] E-cigarettes show signs of inducing dependence, reliably decreasing adverse symptoms related to tobacco abstinence (e.g., urges to smoke, irritability)[16,114-117,120,121] and increases ratings of satisfaction/pleasantness.[114-116,119,122]

Mainstream vapor from e-cigarettes also contains measurable levels of nicotine.[123,124] Studies show that e-cigarette vapor emits nicotine and particulate matter into the air, but at lower levels than combustible cigarettes.[123-130] In the one study we found on secondhand vapor, cotinine levels of non-smokers exposed to e-cigarette vapor were significantly higher than at baseline.[131,132] Nicotine causes birth defects during pregnancy and affects the developing brain, so there is particular concern in terms of exposing bystanders, including youth and pregnant women to nicotine in the air.[127]

In addition to nicotine, there are other constituents in e-cigarette liquids that pose health risks. Available data suggests that e-cigarette vapor is less harmful than cigarette smoke, though e-cigarette vapor is not simply water vapor, as is sometimes advertised.[133] Potentially harmful constituents have been identified in some e-cigarette liquid and vapor, including nitrosamines, heavy metals and carbonyls, though these constituents are found in lower levels than in cigarette smoke.[113,124,126,127,130,134-136]

Further, there is considerable data about adverse events from e-cigarette use. E-cigarettes contain nicotine which, in high doses, is poisonous and can cause death when mishandled, ingested or absorbed through the skin.[137-142] While most common events include mouth and throat irritation,[16,116,117,143-145] nausea,[116,143] headache,[143,144] and dry cough,[143,144] U.S. poison centers reported that calls regarding nicotine exposure from e-cigarettes dramatically increased from one in September 2010 to 215 in 2014.[139] More than half of those calls involved children 5 years and younger. A serious poisoning of a 10-month old infant has also been reported.[146] The 2012 annual report from the National Poison Data System (NPDS) documented 427 single exposures to e-cigarettes. Of these exposures, 83 had no outcome, 102 were deemed to have a minor outcome, 18 had a moderate outcome, 1 had a major outcome and 1 was a death. In comparison, the

report documented 5,700 single exposures to cigarettes. Of these exposures, 1,854 had no outcome, 998 had a minor outcome, 68 had a moderate outcome, 2 had a major outcome and 1 was a death.[147]

As stated earlier, the long-term effects of e-cigarette use remain unknown. What little is known regarding the health effects of e-cigarettes is that they are significantly less harmful than cigarettes, but beyond that more research is needed.

Despite this lack of knowledge on the health effects of e-cigarettes, ever use and current use of e-cigarettes is growing in all age groups. Indeed, e-cigarettes are suddenly everywhere. Some financial analysts estimate that U.S. sales of e-cigarettes are estimated to surpass $10 billion by 2017.[148] This is reflected by national surveys showing increases in ever use of e-cigarettes. In just one year (2011 to 2012), ever e-cigarette use in youth and young adults (18-34) doubled - from 3.3% to 6.8%[49] and from 5.0% to 10.3%,[87] respectively. In adults overall, ever e-cigarette use nearly doubled, from 3.3% in 2010 to 6.2% in 2011.[149] In terms of subpopulations, in looking at middle school students, significant increases in ever e-cigarette use were seen among females, males, and Hispanics.[26] Among high school students, increases in ever e-cigarette use were seen in females, males, non-Hispanic whites and Hispanics.[26]

Current e-cigarette use has also increased. From 2011-2012 among youth in grades 6-12, current e-cigarette use increased from 1.1% to 2.1%.[49] In adults, current e-cigarette use has increased from 1.2% in 2010[150] to 1.9% in 2012.[151] Existing national studies demonstrate rapid increases in ever use and current use of e-cigarettes in the U.S. They do not, however, demonstrate an age gradient in e-cigarette use and at present, data suggests that youth, young adults, and adults, overall, have a similarly low prevalence of current e-cigarette use at about 2%[49,151], with young adults more likely to report e-cigarette trial compared to older adults.[152]

Existing research on co-use of e-cigarettes and more traditional tobacco products is cross-sectional and highlights that the majority of e-cigarette use – in all age groups – occurs among current cigarette smokers and that dual use of combustible cigarettes and e-cigarettes is high.[87,153,154] More than three quarters (76.3%) of youth current e-cigarette users were also cigarette smokers.[49] Further, according to one study, current youth smokers are 58 times more likely to try an e-cigarette than non-smokers.[155] Among young adults, one study of college students showed that current daily smokers, current non-daily smokers, and former smokers were more likely to ever use e-cigarettes than non-smokers.[156] Among U.S. adults in 2012, 28.1% of dual tobacco product users reported using e-cigarettes and another tobacco product.[153] Only 0.4% of adults reported using e-cigarettes exclusively[153] and only 0.6% of youth had ever tried an e-cigarette but were never smokers of combustible cigarettes (i.e., 6.8% ever e-cigarette users, of whom 9.3% had never smoked a conventional cigarette).[49] While studies of youth have advanced the notion that use of e-cigarettes may encourage cigarette use,[157] exploration of alternate hypotheses must also be considered.[111,158,159] As noted by Niaura et al., "It is equally plausible that use of combustible cigarettes leads to use of e-cigarettes, because they are perceived as a less harmful alternative for smokers who are addicted to nicotine. The cross-sectional survey data do not prove that this is the process that explains the association, but they are just as consistent with it…"[159] Additionally, there is very limited evidence from longitudinal observational studies to determine how e-cigarette use influences other patterns of tobacco use[87] and this is further complicated by the low population prevalence of e-cigarette use and limitations of the selected nature of the populations studied in observational studies.

Dual use or poly-tobacco use is of concern because it could delay or prevent cessation of combustible tobacco products, and may exacerbate the health effects from the various tobacco products. For example, studies show that non-daily and daily cigarette smokers try e-cigarettes more than former and never smokers[160], and that former smokers are more likely to be established e-cigarette users compared to daily smokers.[161-163] The flip side of that is that it is possible that some are using both combustible and non-combustible products to gradually reduce their use of combustible products, in an effort to move off of those products completely, or to stave off cravings to smoke in former smokers. Indeed, two randomized controlled trials to date show that e-cigarettes are effective in helping some adult smokers to quit or reduce their cigarette consumption.[144,164] This could be positive for public health, and we discuss this in more detail later in our comments. Regardless, that is all the more reason that these products need to be regulated – to help ensure that any possible health benefit is maximized, but also to prevent or reduce public health harms.

B. HOOKAH

Hookah smoking is a centuries-old form of tobacco use also known as waterpipe, narghile, shisha, goza, and hubble-bubble.[18] Hookah is often smoked in group settings or at commercial establishments such as hookah bars,[19-21] and comes in a variety of fruit and candy flavors.[21-23] Hookah use has significant health effects, is highly addictive, and has disturbing ramifications for broader tobacco use initiation.[24]

Hookah use is associated with significant nicotine and toxicant exposure including carbon monoxide, tobacco-specific nitrosamines, and polycyclic aromatic hydrocarbons.[23,165-167] Hookah smoke exposes users to many of the same toxicants found in cigarette smoke,[168,169] and may place users at risk for many of the same diseases as cigarette smokers, including a greater risk of lung cancer and respiratory illness[24,170-172] as well as low birth weight,[24] periodontal disease,[24] and coronary artery disease.[173] Secondhand hookah smoke exposure also poses risks to users and non-users, including extremely high levels of particulate matter in hookah cafes (i.e., indoor smoking venues).[174-176]

Further, hookah smokers are exposed to significant levels of nicotine during typical use, which may be a catalyst to nicotine dependence and progression to regular tobacco use. The volume of smoke inhaled during a typical hookah session can be the equivalent of more than 100 cigarettes,[177,178] and lead to peak nicotine exposure levels similar to those observed during cigarette smoking.[23,166] Daily use of hookah can lead to a nicotine absorption equivalent to approximately 10 cigarettes/day.[179] Thus, nicotine dependence characteristics are observed in some hookah users. For example, hookah is associated with suppressing cravings to smoke and anxiousness,[23,165,180] with one study showing that hookah suppressed withdrawal symptoms comparably to cigarettes.[180]

Despite these risks, hookah is widely perceived as less harmful [20-22,25] and less addictive[20,21,25] than cigarettes and has experienced a surge in prevalence in the U.S., particularly among adolescent and young adult populations.[26-28] In 2011, the NYTS first included questions about hookah. From 2011 to 2012 among high school students, hookah use rose from 4.1% to 5.4%.[181] Among young adults, the Legacy Young Adult Cohort Study found that 17% of 18-34 year olds in the U.S. had ever used hookah, and 8% were current users.[105]

In addition, dual use of hookah and other combustible tobacco products is extremely high. Dual use of cigarettes and hookah is one of the most common tobacco use profiles found in young adults (18-24),[19,182,183] with 59%-75% of hookah users also using cigarettes and/or cigars.[28,183] As with other products, especially combustible tobacco products, dual use presents great concerns for individual health, as it increases exposure to nicotine and other harmful constituents, and may exacerbate disease risk associated with both products.[181]

Finally, studies show that hookah users have a high degree of confidence that they can quit anytime, with a low desire to quit.[20,21] Perceptions that hookah is not as harmful and addictive as cigarettes may also contribute to a low desire to quit.[184]

The rapid increase in hookah use, especially among young people, as well as the significant health risks that hookah poses make it imperative that hookah tobacco is regulated by FDA. This will allow consumers to learn more about the health risks of the product, and learn what is in the product, both of which may deter non-users from starting and encourage current users to quit.

III. FDA MUST REGULATE ACCESSORIES.

The statute defines "tobacco product" as "any product made or derived from tobacco that is intended for human consumption, *including any component, part, or accessory of a tobacco product* (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)"[185] (emphasis added). With the possible—and very significant – exception of premium cigars, see discussion beginning on page 10 taking the view that *all* cigars should be covered, the NPRM proposes to extend FDA's jurisdiction to all products and categories meeting the definition of tobacco product under 201(rr) of the FDCA *except* for one: "accessories of such other tobacco products".[52]

Legacy urges FDA to assert its authority to the full extent permitted by the statute, *including* accessories. Contrary to the NPRM's conclusory assertion that "because accessories are not expected to be used in the consumption of a tobacco product, we expect that accessories will not have a significant impact on the public health",[29] this proposed exclusion presents a real and serious threat to public safety and health. This is exacerbated by the vague and imprecise explanation offered for what would constitute an accessory[29], suggesting that an item is an accessory – and therefore exempt from regulation – if it is not part of a "finished" tobacco product or "used in consumption" or for "storage". There are a burgeoning number of items on the market that are associated with tobacco products, in particular, e-cigarettes and hookah. Some of these items could well be considered accessories within the meaning of the NPRM despite the fact that they present real, documented dangers to safety and health. It is essential that FDA have the tools to regulate these products to address these risks.

E-cigarette "refill" containers offer a prime example of "storage" products that are likely not part of a "finished" tobacco product or "used in consumption" – but are part and parcel of a documented public health risk. These receptacles contain the nicotine liquid (at various concentrations) increasingly used by "vapers" to mix their own custom solutions and/or refill the cartridges or tanks directly connected to their e-cigarettes. As explained by Davis et al., "EC cartridges, cartomizers, and tanks, which hold the fluid, can be refilled from drip bottles of refill fluid that are readily available over the Internet, in EC retail shops, and in malls."[186] Another recent study documents that substantial percentages of e-cigarette users use these refill

containers, finding that seventy-two percent of participants used a 'tank' system which enables users to mix their own "liquid" from which they refill cartridges.[16]

The risks presented by the nicotine liquid found in these containers are well-established as demonstrated by clear scientific evidence concerning the toxicity of nicotine[142] and growing numbers of anecdotal reports and records of poison control center calls.[139] Tragically, these dangers are growing most rapidly for children under five years of age. The Centers for Disease Control and Prevention recently issued a major report on this subject and found that e-cigarettes accounted for an increasing proportion of combined monthly e-cigarette and cigarette exposure calls, increasing from 0.3% in September 2010 to 41.7% in February 2014 and over half of e-cigarette exposures were among persons aged 0 - 5 years (51.1%).[139] Reports indicated the poisoning of a ten-month old baby by e-cigarette refill liquid and noted that lack of regulatory oversight has resulted in inconsistent labeling, insufficient or nonexistent child protective packaging, and product design and flavoring that may encourage children to explore and ingest these products.[146,187,188]

Even assuming that the solutions contained in these receptacles would be covered, it would be nothing short of a travesty if FDA willingly walked away from the authority to require common sense safety standards for the receptacles themselves. These include, at a minimum, that they be child-proof, spill-proof and leak-proof and comply with standardized labeling requirements to assure that consumers have notice of what is actually contained in these receptacles and the risks that are presented. But that could well be the practical result of the FDA's proposal to exclude accessories.

A second example is presented by the batteries, battery housings and chargers used in connection with e-cigarettes. Anecdotal reports are accumulating concerning the risk of explosions, fire, and overheating from e-cigarettes either during regular use or during charging.[189-191] Again, the FDA's ability to require common-sense safety standards is essential without the self-inflicted burden of first having to parse imprecise and confusing definitional requirements and then run the risk of having to justify its conclusions in a regulatory or other legal proceeding.

Health and safety risks are also presented by hookah-related items which could well be viewed as "accessories" under the NPRM. For example, the NPRM suggests that flavored hookah charcoals would not be excluded as an accessory[192], presumably because the flavoring finds its way into the smoke that is inhaled. But irrespective of flavoring, hookah charcoal accounts for a significant source of toxicants in hookah smoke and should be subject to regulation – regardless of whether it is part of a "finished" tobacco product or "used in consumption". One study demonstrated that the high yields of carbon monoxide (CO) and polycyclic aromatic hydrocarbons (PAHs) in mainstream [hookah] smoke mainly derive from the charcoal… the charcoal is itself an important toxicant source for [hookah] users and those in their company.[193] Hookah charcoal burners and holders the NPRM would exclude from coverage[29] could also affect hookah emissions. The foil used in connection with hookah presents a second example. The NPRM is silent on the treatment of foil, although it would exclude foil cutters.[29] But studies show that foil is heated to the same extent as the charcoal and thereby could present a burning danger.[168]

Our concerns are underscored by the NPRM's failure to propose a regulatory definition for "accessories" and the vague and imprecise language in the commentary as to the line between accessories, which would not be covered, and parts and components, which would be subject to FDA regulation. "Finished product", "used in consumption", and used for "storage" are not terms of art and no definition is even suggested. The

lists of examples provide no assistance in generalizing the "analysis" to other unique items. In addition, as discussed earlier, the proffered list would exclude at least certain items which should be subject to regulation. At best, this will result in uncertainty and confusion for consumers, retailers and manufacturers as to what items are accessories and therefore excluded from coverage. It could also well have the perverse effect of encouraging litigation over what is covered and/or efforts by manufacturers and retailers to manipulate items in order to avoid coverage.

We have considered FDA's invitation to offer our own definition of "accessories". However, we do not view a "better" definition as the answer. To begin with, in light of the constantly morphing numbers and types of items that are marketed in some connection with tobacco products, any definition – even if one could be developed to take into consideration this exceedingly broad range of products -- would soon be outdated. Moreover, FDA's stated – but purely hypothetical and unsupported -- concern that in the absence of an exclusion for accessories, extraneous items such as carrying cases and humidors would be somehow swept under its jurisdiction is unpersuasive. Congress cannot reasonably be understood to have intended to authorize FDA regulation of items so unrelated to the public health risks presented by tobacco products – indeed, to tobacco use itself – and with no record of posing any independent danger. There is certainly nothing in the language of the Act or the legislative history to suggest otherwise.

Not only is FDA's approach based on a misreading of the statute, the demonstrated public health risks presented by items that could quite possibly be characterized as accessories under FDA's proposed, ill-defined and overbroad exclusion are real and substantial. We note that the exclusion for accessories was included at the OMB review stage. We believe that the views of the FDA – the agency with public health expertise – should be respected in this regard and accessories should be covered under the final rule.

SECTION 3: FDA MUST AGGRESSIVELY APPLY OTHER REGULATORY MEASURES TO ALL TOBACCO PRODUCTS.

I. FDA MUST ENSURE APPLICATION OF ALL SELF-EXECUTING SECTIONS OF THE TOBACCO ACT TO ALL TOBACCO PRODUCTS.

One of the most important results of the final deeming rule will be the automatic application of numerous provisions already in the Tobacco Control Act to the newly covered tobacco products. This will directly – and substantially – benefit the public health for many of the same reasons that the current applicability of these provisions to cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco already benefits the public health.

Since the application of these provisions will be self-executing upon the adoption of the final deeming rule, specific regulatory language applying each provision to the newly covered products is not called for. The NPRM's discussion of this point in the background materials, amplified by examples, constitutes the appropriate approach.[192] We recognize, however, that some provisions in the Act are specific to cigarettes and/or smokeless tobacco and therefore will not apply to newly deemed products. As a result, for the sake of clarity and the avoidance of confusion, we recommend that the background discussion to the final deeming rule include a fuller list, in one place, of the provisions that will apply to the newly deemed products. These include, at least: Adulterated tobacco products[30]; Misbranded tobacco products[31]; Submission of health information to the Secretary, including but not limited to the required promulgation of the list of harmful and potentially harmful constituents[32]; Annual registration and product listing[33]; General

provisions respecting control of tobacco products[1]; Tobacco product standards, other than the provisions specifically regarding cigarettes[34]; Notifications and other remedies[35]; Records and Reports on tobacco products[36]; Application for review of certain tobacco products, including but not limited to premarket review and substantial equivalence requirements[37]; Modified risk tobacco products[38]; and Labeling, recordkeeping, and records inspection[39].

We do not see a need to specify the more general and procedural provisions which would also apply, such as the definitional section[194], FDA authority[195], and Regulation requirements[196], etc., but would certainly have no objection if FDA chose to take this route.

II. FDA MUST ADOPT APPROPRIATE WARNING LABELS FOR ALL TOBACCO PRODUCTS.

Legacy supports the requirement in the proposed rule for an addictiveness warning label on all newly-deemed products, as well as additional warning labels for cigar products brought under FDA's authority. Warning labels should be applied to all tobacco products to reduce misperceptions about the harms and addictiveness of tobacco products, particularly those which have not previously carried health warning labels. Large, prominently placed, and strong warnings provide significant public health benefits. Research has shown that such warning labels influence increased awareness and understanding of health effects and disease risk among users and non-users, encourage users' motivation and attempts to quit – and stay off tobacco,[40,197] and discourage uptake of tobacco.[40-43] In fact, one 2008 study in the United Kingdom reported that nearly 90% of youth non-smokers indicated that health warnings had discouraged initiation.[198] This may also apply to young adults as well. Unpublished data from Legacy found that little cigar and cigarillo users, hookah users and non-users closed to smoking were more than twice as likely to report that new graphic health warning labels would make them think about not smoking. This study suggests that the extension of prominent health warning labels to other tobacco products, including cigars and hookah, may also serve as a preventive measure.

Many studies emphasize that the larger size and more prominent location of warning labels plays a critical role in these outcomes. Indeed, a 2011 review of health warning studies concluded, "Youth and adults are more likely to recall larger warnings, rate larger warnings as having greater impact, and often equate the size of the warning with the magnitude of the risk." That paper went on to say, "the findings suggest that small text warnings are associated with low levels of awareness and poor recall."[41] For this reason, the Framework Convention on Tobacco Control (FCTC) requires rotating health warnings that cover at least 30% of the front and back of cigarette packages. The Tobacco Control Act required smokeless tobacco warning labels to take up 30% of the packages, as well as advertisements. The proposed rule correctly extends this requirement to all newly-deemed tobacco products.

However, recent data released by FDA indicates that health warnings in cigarettes and smokeless tobacco are not, by themselves, necessarily noticed by youth, nor do they effectively stimulate thoughts about health risks – especially in current cigarette and smokeless tobacco users.[199] This confirms data that warning labels need to be relevant, and frequently updated to ensure that youth see them and that the messages are heeded. We encourage FDA to continue to develop warnings that correct misperceptions about the health effects of tobacco products, encourage tobacco users to quit, and non-users to refrain from starting in the first place.

A. THE PROPOSED CIGAR WARNING LABELS

In 2001, the Federal Trade Commission (FTC) established five cigar warnings based on data from the National Cancer Institute Monograph on Cigars.[200,201] FDA has proposed requiring four of these five warnings on all cigars that fall under its jurisdiction. While the health effects of cigars are well established (as demonstrated elsewhere in our comments), they are not well-known by the public. Below we discuss the need for warning labels for cigars in general, as well as the appropriateness of the specific warnings in the proposed rule.

Numerous articles in the scientific literature highlight the need for education on the health effects of cigars.[68,101,106,184,202-211] Several of these articles indicate that cigar users significantly underestimate the health risks of cigars,[3,106] while others indicate that respondents either did not know whether or not cigars were more or less harmful than cigarettes or perceived cigars to be less harmful than cigarettes.[68,101,203,205,208-210,212] Still other studies show that some respondents did not know that cigars contain tobacco or nicotine.[89,207] In particular, this misperception of the health effects of cigars was shown to be higher in specific demographic groups[101] – young adults[89,106,184,208] and black youth, in particular.[89,101,209]

Strong, clear warning labels describing the health risks associated with cigar use can help dispel some of the misperceptions of the health impact of all cigars. Some studies indicate that this lack of knowledge could be a predictor for initiating cigar smoking.[205,209] An unpublished study produced by Legacy indicates that including graphic health warning labels on other tobacco products, including little cigars and cigarillos, may prevent initiation. This is confirmed by an additional study of graphic warning labels for cigars.[211] We encourage FDA to study the possibility of graphic warning labels for cigars in the future.

In the meantime, we strongly support the warning labels for cigars included in the proposed rule. As noted above, the rule adopts four of the five warnings for cigars established by the FTC. Those warnings include:
WARNING: Cigar Smoking Can Cause Cancers of the Mouth and Throat, Even If You Do Not Inhale.
WARNING: Cigar Smoking Can Cause Lung Cancer and Heart Disease
WARNING: Cigars Are Not a Safe Alternative to Cigarettes
WARNING: Tobacco Smoke Increases the Risk of Lung Cancer and Disease

In Appendix A we provide a systematic review of the science around the health effects of cigars. Appendix A provides significant evidence that these statements are factual. Further, the six largest cigar companies agreed to these warnings, indicating that the companies themselves do not dispute the truth of these statements.

Further, we encourage FDA to include the fifth FTC warning as part of the final rule. The text of that warning is WARNING: Tobacco Use Increases the Risk of Infertility, Stillbirth And Low Birth Weight. This warning is based on data related to cigarette smoke. Given that cigarette smoke is very similar to cigar smoke, and in many cases, cigar smoke is more dangerous than cigarette smoke, it is a logical conclusion that this warning is appropriate for cigars. This is especially important in light of the data above, showing that females are using cigars – little filtered cigars in particular – at relatively high rates.

The evidence is clear that the true health effects of cigars are not known well enough by the public and these warnings provide factual health information to consumers in a larger format that helps ensure that they are seen by consumers, and non-consumers, and that the information registers with them.

B. THE PROPOSED "NICOTINE IS ADDICTIVE" WARNING

Legacy strongly supports the application of warning labels to all tobacco products and the requirement that all tobacco products carry an addictiveness warning. Given low knowledge of harm and addictiveness of non-cigarette tobacco products, this is of particular importance for products that do not currently carry any health warnings. Studies of non-cigarette products, including hookah, show lower perceptions of harm and addictiveness of these products facilitate use among young adults. Strong warnings regarding the addictiveness of all tobacco products may reduce trial and use in vulnerable populations. Further, tobacco users are more likely than non-users to believe that the government evaluates each type of tobacco product for safety, including the proposed deemed products.[213]

In the proposed rule, FDA would require the following warning on all tobacco products that contain nicotine: ''*WARNING:* This product contains nicotine derived from tobacco. Nicotine is an addictive chemical.''[214] To facilitate improved education regarding product-specific risks, we recommend that the addictiveness warning be modified to be aligned with the corrective statements recently issued by Judge Kessler[215] and be specific to the product on which it is applied, as illustrated below:

- Cigarettes: "Cigarette smoking is addictive. Nicotine is the addictive chemical in cigarettes."
- Cigars: "Cigar smoking is addictive. Nicotine is the addictive chemical in cigars."
- Hookah: "Hookah smoking is addictive. Nicotine is the addictive chemical in hookah tobacco."
- E-cigarettes: "E-cigarettes contain nicotine. Nicotine is addictive."

A recent study on the impact of the proposed corrective statements to smokers indicates that they provide novel information and that novelty was associated with greater relevance of the message and motivation to quit.[216] Another recent study showed that pairing some educational ads with snus ads reduced favorable attitudes and intention to use snus.[217] The federal proceedings and results of these recent studies reinforce the idea that providing fact-based messages about the potential harms of nicotine exposure and tobacco use can impact intentions and behavior.

III. FDA MUST INCLUDE THE PROPOSED YOUTH ACCESS RESTRICTIONS, BUT ALSO BROADEN THEM TO INCLUDE YOUTH MARKETING RESTRICTIONS.

The record is crystal clear: the tobacco epidemic is driven and sustained by youth uptake of tobacco use.[6] Nearly 90% of adult smokers in the United States began smoking by 18 years of age.[61] In 2012, the prevalence of current tobacco product use among middle and high school students was 6.7% and 23.3%, respectively.[26] The tobacco industry has a history of targeting youth in its marketing efforts. In 1984, a tobacco company called younger adult smokers "replacement smokers" and brainstormed targeting potential smokers in school bathrooms, playgrounds, YMCAs, and city parks.[218,219] In 2006, the U.S. District Court for the District of Columbia found that the industry:

> …intentionally marketed to young people under the age of twenty-one in order to recruit 'replacement smokers' and to ensure the economic future of the tobacco industry… [and] admitted that stimulating youth smoking initiation and retaining and increasing their share of the youth market is crucial to the success of their businesses…and for that reason create marketing campaigns designed to increase youth consumption.[6]

In its 1994 report, the Institute of Medicine concluded that "tobacco advertising and promotion undoubtedly contribute to the multiple and convergent psychological influences that lead children and youths to begin using these products and to become addicted to them."[220] Evidence indicates that there is a causal relationship between advertising and promotional efforts of the tobacco companies and the initiation and progression of tobacco use among young people.[61] As a result, it is essential that efforts to curb tobacco use assure both that young people are not able to purchase tobacco products and that they are not targets of tobacco product marketing and promotion. The NPRM takes an important first step on the access question by establishing a uniform minimum age of 18 for the purchase of all tobacco products and requiring photo IDs for retail sales. However, it not only fails to require that all sales be face-to-face, it inexplicably fails to require any enforcement mechanisms for Internet sales, thus leaving a loophole many young people will exploit to purchase tobacco products. Just as inexplicably, and despite the clear template offered by the 1996 Final Rule, now codified at *21 U.S. Code § 387a–1*, the NPRM includes only the barest limitations on youth-directed marketing and promotion. While we strongly support the establishment of a federal minimum age of purchase for all tobacco products, as well as a ban on vending machine sales, those provisions do not go nearly far enough to protect youth from these addictive and deadly products. It is essential that the final rule require only face-to-face sales of all tobacco products or, at the least create enforceable age verification requirements for Internet sales, and apply all of the applicable provisions in the 1996 Final Rule to marketing and promotions for all tobacco products.

A. Youth Access

Legacy strongly supports the NPRM's proposals to establish 18 years of age as the uniform, national minimum age for the purchase of all covered tobacco products; require that retailers verify age by means of photographic identification; and prohibit most sales via vending machines and other electronic or mechanical devices.[47] These are proven-effective mechanisms for keeping minors from purchasing tobacco products.

Along with many of our colleagues in public health, we believe that a key element of preventing youth access to tobacco products is to require that all sales be face-to-face. Studies have found that minors were able to successfully purchase tobacco products on the Internet with no effective age verification.[221,222] We note with concern that this is completely lacking from the NPRM and urge FDA to include such a requirement in the final rule. We are also deeply concerned that the NPRM does not – at the very least— take the essential step of requiring age verification for purchases of tobacco products in settings where the buyer is not in the physical presence of the seller when the purchase is made. This principally includes Internet and phone sales, although given the rapid developments in technology, these types of sales could certainly expand to other platforms.

In fact, despite a direct statutory mandate, FDA has yet to issue regulations to establish age verification requirements for the Internet and other non-face-to-face purchase of ANY tobacco products. The Tobacco Control Act required FDA, within 18 months of the date of the enactment, to "promulgate regulations regarding the sale and distribution of tobacco products that occur through means other than a direct, face-to-face exchange between a retailer and a consumer in order to prevent the sale and distribution of tobacco products to individuals who have not attained the minimum age established by applicable law for the purchase of such products, *including requirements for age verification*"[223] (emphasis added). This time

period expired in December, 2010. FDA issued an Advanced Notice of Proposed Rulemaking on this subject on September 9, 2011 but has taken no further action.[224] Legacy joined comments submitted in connection with that ANPRM which we incorporate herein by reference.[225]

Remarkably, the failure to address this issue in this regulation is not an oversight. The NPRM states "This prohibition on sales from electronic or mechanical devices is not intended to impact the sale of any tobacco product via the Internet."[226] But there is no explanation whatsoever for the decision to leave this obvious and gaping loophole which will permit widespread evasion of the youth access restrictions as they apply to all tobacco products, including cigarettes and smokeless tobacco as well as newly deemed products such as e-cigarettes, little cigars, and hookah tobacco.

This utter failure to comply with the clear statutory mandate is all the more puzzling since mechanisms for age verification for Internet sales – including for the purchase of tobacco products -- are well-established and readily available. Indeed, the Prevent All Cigarette Trafficking Act (PACT Act) offers an obvious and directly relevant model. The PACT Act requires age verification before a seller may sell or ship cigarettes or smokeless tobacco products to a buyer. Pursuant to 15 USCA § 376a (b)(4)(A)(iii), before accepting a sales order for such products, the seller must verify that the purchaser is of the required minimum age by: (1) obtaining the purchaser's full name, birth date, and residential address and (2) verifying the information through a commercially available database or aggregate of databases using data from government sources. We strongly urge the FDA to add these requirements to the final rule to fulfill its statutory mandate and assure that the youth access restrictions apply to all purchases of ALL tobacco products.

B. Youth Marketing

The sordid history of decades of concerted industry marketing and promotion of cigarettes to under-age youth, the extraordinary effectiveness of these efforts in driving youth initiation of tobacco use, and the industry's pious denials of what it was plainly doing, is set out in great detail in *U.S. v. Philip Morris USA, Inc., et al., No. 99-CV-02496GK (U.S. Dist. Ct., D.C.) (Final Opinion) (August 17, 2006)* at 561 – 692. The recent Surgeon General's Report (SGR) on tobacco use in youth and young adults provides yet more conclusive evidence that tobacco industry advertising and promotional activities cause youth and young adults to start smoking.[61,227-229]

Current law restricts youth marketing of cigarettes and smokeless.[230,231] However, it is just as important to extend these same restrictions to the marketing of *all* tobacco products to youth. We will offer, as a case in point, the growing evidence, much of which our own researchers have developed, of the concerted marketing of e-cigarettes to youth.

Recently, Legacy undertook two studies examining youth marketing of e-cigarettes and published a report entitled "Vaporized: E-cigarettes, advertising and youth," available for download on our website (http://legacyforhealth.org/content/download/4542/63436/version/1/file/LEG-Vaporized-E-cig_Report-May2014.pdf).[232] The first study surveyed youth and young adults using an online panel to measure their use and awareness of e-cigarettes and e-cigarette advertising. The second study analyzed media expenditure data to estimate whether e-cigarette advertising is reaching young people. Results of the first study indicated that awareness of e-cigarettes among young people in this study was nearly ubiquitous, ranging from 89% for 13-17 year olds to 94% for young adults aged 18-21. For current or ever traditional

cigarette smokers, awareness was even higher at over 95% among both youth and young adults. Similar levels of awareness held across racial and ethnic groups. Most respondents indicated they saw e-cigarette ads in the retail setting (convenience stores, supermarkets or gas stations) and our recent work highlights the penetrance of e-cigarette advertising in the point-of-sale environment.[233] There was also high awareness of television advertising of e-cigarettes, with 45% of 13-17 year olds reporting they saw TV ads always, most or some of the time. Additionally 43% of 13-17 year olds responded that they saw e-cigarette ads always, most or some of the time when they were online. The numbers were even higher for young adults.

The second study examined advertising expenditures and estimated audience exposure data for the 24 most popular brands of e-cigarettes from June to November of 2013 estimated by MediaCom, who obtained the data from paid subscriptions to proprietary data. This study highlights not only how much the e-cigarette industry spent on advertising overall, but also how much specific brands spent, on which channels they advertised, and who saw their ads. Overall, in that 6-month period, e-cigarette advertisers spent $39 million. Magazine advertising received the largest amount of money from that – 58%. National television advertising came in second at 19%. In that June to November 2013 timeframe, the three biggest-spending brand names were blu, NJOY and FIN – accounting for 86% of the overall spending. By far, blu spent the most at $22 million, with NJOY and FIN brands spending $5.6 million and $4.9 million respectively. VUSE, which was available only in Denver, CO as a test product during this time frame, spent $1.4 million.

VUSE's advertising expenditures are likely to rise as they roll out their product nationally[234] and Philip Morris recently announced that it will launch its e-cigarette brand, MarkTen, nationwide in the second quarter of 2014.[235] According to data from Legacy's second study in the "Vaporized" report,[232] blu, Lorillard's e-cigarette brand, spent approximately $50 million on advertising in 2013. Legacy commissioned additional analyses from MediaCom to estimate youth and young adult exposure to e-cigarette advertising in 2014. Based on blu's 2013 print and television advertising schedule, if VUSE (R.J. Reynolds' e-cigarette brand), blu and Mark Ten (Altria's e-cigarette brand) each spend approximately $50 million in 2014 and assuming all other advertisers spend the same amount in 2014 as they did in 2013, *an estimated 97% of youth and young adults aged 12-24 would be exposed to this advertising*. That is 22.4 million, or 92%, of 12-17 year olds, and 28.9 million, or 97%, of 18-24 year olds. These findings highlight the potential of Big Tobacco to drive the messages people see about these products and the rapidity with which youth and young adult exposure to these messages will occur if unrestricted.

Legacy researchers also conducted a randomized controlled trial to assess the impact of a brief exposure to e-cigarette ads on perceptions, curiosity, susceptibility, intention, and subsequent use of e-cigarettes in a national, longitudinal sample of 4,232 young adults aged 18-34 in January 2013 from GfK's KnowledgePanel®, of which 74% provided follow-up data at six months (manuscript in progress). Questions on e-cigarette perceptions, curiosity, susceptibility, and intention to use e-cigarettes were asked following ad exposure in the exposed group and in a similar location in the survey in the unexposed group; e-cigarette trial among never e-cigarette users was assessed at six-month follow-up. Post-stratification weights were used to offset any non-response or non-coverage bias and produce nationally representative estimates. Among the subgroup of young adults aged 18-24 who had never used cigarettes or e-cigarettes at baseline (weighted n = 891), exposure to the e-cigarette ads was associated with greater curiosity to try an e-cigarette compared to the control group (10.1% exposed vs. 3.6% unexposed; $p = 0.016$), greater susceptibility to use an e-cigarette (23.8% exposed vs. 14.5% unexposed; $p = 0.015$) and a greater likelihood

of e-cigarette trial at six-month follow-up (5.9% exposed vs. 1.5% unexposed; p = 0.03). Cigarette trial at six months was slightly higher among those exposed (11.4%) to the e-cigarette ads versus unexposed (6.9%), but the difference was not statistically significant (p = 0.14). Exploratory analyses supported that curiosity to try an e-cigarette fully mediated the relationship between study group and e-cigarette trial.

Legacy's research findings are consistent with a growing body of additional research**.** Other recent studies document rapid increases in promotional expenditures for e-cigarettes over the past three years[236,237] and advertising of e-cigarettes occurs predominantly through youth-oriented channels where marketing of other tobacco products is banned (e.g., television, sponsorships).[232,238] One study reported that on television alone, youth exposure to e-cigarette advertisements increased an estimated 256% from 2011 to 2013 and was primarily for blu e-cigarettes.[239] Specifically, blu was shown to be responsible for 81.7% of e-cigarette ads airing to youth aged 12-17 and 80.4% of those airing to young adults aged 18-24.[239] Some televised e-cigarette ads include celebrities and imagery of e-cigarette vapor that is indistinguishable from cigarette smoke.[239]

Expansion of 1996 Final Rule to Cover All Tobacco Products

One of the signature achievements of the Tobacco Control Act was the requirement that FDA promptly re-issue the regulations originally promulgated in 1996 ("1996 Final Rule").[240] The regulations were duly issued on March 19, 2010. The purpose of the 1996 Final Rule is "to establish restrictions on the sale, distribution, and use of cigarettes and smokeless tobacco in order to reduce the number of children and adolescents who use these products, and to reduce the life-threatening consequences associated with tobacco use."[241] Legacy strongly supports the NPRM's proposal to extend to all tobacco products several key provisions of the 1996 Final Rule which currently apply only to the purchase of cigarettes and smokeless tobacco, most notably the minimum purchase age of 18 and picture ID requirements. We also welcome the NPRM's observation that the prohibition of free sampling extends to all covered tobacco products – although it important to note that this is properly viewed as a clarification and not a new requirement since the 1996 Final Rule already prohibits manufacturers, distributors, or retailers from distributing or causing to be distributed "any free samples of cigarettes, smokeless tobacco, *or other tobacco products (as such term is defined in section 201 of the Federal Food, Drug, and Cosmetic Act)*" subject to certain provisions pertaining to adult only facilities.[242] (Emphasis added). Nonetheless, the language in the NPRM clears up any confusion on this point and also underscores the FDA's authority to enforce the ban for all tobacco products.[192,243]

But, without explanation – or the most basic logic -- the NPRM does not include other provisions from the 1996 Rule which limit the marketing and promotion of tobacco products to youth. Without further regulatory action, these provisions will continue to apply only to cigarettes and smokeless tobacco. We urge FDA to extend all of the youth marketing/promotion provisions of the 1996 Final Rule to *all* tobacco products, adjusting as necessary for different types of products, except for those provisions which were held invalid in *Discount Tobacco City & Lottery, Inc., v. U.S.,* 674 F. 3d 509 (6th Cir. 2012), *cert. denied sub nom*, *American Snuff Co., LLC v. U.S.*, 133 S. Ct. 1996 (2013). More specifically:

- A minimum package size should be established for little cigars and cigarillos, *see* §1140.16 (b) establishing a minimum cigarette package size of 20 cigarettes;
- The ban on the sale of unpackaged cigarettes in numbers smaller than the required minimum package and of cigarette or smokeless tobacco in amounts smaller than the smallest package

distributed by the manufacturer for individual consumer use should be extended to all tobacco products as appropriate, *see* §1140.14 (d);

- The ban on the use of non-tobacco product branding for cigarettes and smokeless tobacco, §1140.16 (a), upheld in *Discount Tobacco* at 541-542, should extend to all tobacco products, including premium cigars;
- The ban on cigarette or smokeless tobacco product branding of non-tobacco items, §1140.34(a), should be extended to all tobacco products, including premium cigars;
- The ban on cigarette and smokeless tobacco product branding of athletic, musical, artistic or other social or cultural events, §1140.34(c), upheld in *Discount Tobacco* at 543, should be extended to all tobacco products, including premium cigars.

Given the powerful record establishing the extensive marketing of all tobacco products to youth as well as the effectiveness of such marketing, it is essential for FDA to include firm, actionable prohibitions against marketing to youth in the final rule. The alternative is, quite simply, to squander an extremely important opportunity to protect our young people. Yet this is exactly the path that the NPRM would take.

This failure is all the more perplexing since the Tobacco Control Act provides a clear and straightforward roadmap for FDA to follow. First, FDA should extend the provisions in the re-promulgated 1996 Final Rule regarding marketing and promotion to all covered tobacco products. Second, FDA should immediately come into compliance with the statutory requirement that it issue regulations to address the promotion and marketing of tobacco products that are sold by means other than direct, face-to-face exchanges in order to protect individuals who have not attained the minimum age for the purchase of such products. Third, FDA should create an enforcement action plan for restricting advertising and promotion of the deemed products to youth as provided in the expansion of the 1996 Rule and the new regulations focused on non-face-to-face retail sales. Fourth, as we address later, FDA should move forward in a parallel proceeding to ban flavorings from tobacco products.

IV. FDA MUST REDUCE ITS PROPOSED COMPLIANCE GRACE PERIOD FROM 24 TO 12 MONTHS AND MUST PRIORITIZE REVIEW OF APPLICATIONS FOR PRODUCTS ALREADY ON THE MARKET.

The Tobacco Control Act established a definition of "new product" for which a new product pre-market application must be submitted and FDA must grant an order allowing the product to be marketed. Otherwise, such products were not allowed to be on the market. That definition is as follows:

> …'new tobacco product' means (A) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or (B) any modification (including a change in design, any component, any part, or any constituent, including smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.[37]

The proposed rule recognizes that the law presents a problem for some products that would come under its jurisdiction once the proposed rule is finalized. Specifically, there are products now on the market that were not on the market before the statutorily established date of February 15, 2007, and as such, should be removed from the market because FDA has not granted them an order allowing them to be on the market. To prevent a disruption of the market for these products, FDA proposed exercising its enforcement authority

by creating a compliance grace period during with FDA would not enforce its authority, and a product could stay on the market for 24 months after the finalization of this rule, as long as the manufacturer had submitted an application for substantial equivalence, substantial equivalence exemption or an application for premarket review of a new product.

We concur with our public health colleagues in the submission to this docket with regard to this section of the rule and incorporate that by reference. We strongly believe, for all the reasons outlined in that submission to the docket, that the proposed compliance grace period is far too long, and should be reduced to 12 months, instead of 24 months, after the finalization of this rule.

Additionally, we strongly agree with our public health colleagues that FDA must ensure that applications for products submitted during the compliance grace period (and therefore applications for which products are already on the market) would get first priority for review over product applications that have not yet entered the market. This is a departure from the procedure used for cigarettes and smokeless tobacco for the substantial equivalence process. However, we believe FDA was in error in prioritizing the review of applications for products that were not yet on the market over products that are on the market and being used without FDA review. With these newly deemed products, FDA simply cannot prolong their unregulated availability.

Finally, we further concur with our colleagues that a condition of this compliance grace period is that manufacturers agree to youth marketing restrictions, ingredient reporting, and quality controls that would ensure consistent delivery of nicotine and other constituents. This would go a long way to protecting the public health for products that have not yet been fully reviewed by FDA.

SECTION 4: LEGACY RESPONSES TO VARIOUS QUESTIONS POSED IN THE PROPOSED RULE, BUT NOT ASSOCIATED WITH A REGULATORY PROPOSAL AT THIS TIME

I. FDA MUST BAN FLAVORED TOBACCO PRODUCTS AS SOON AS POSSIBLE.

As a result of the Tobacco Control Act, FDA banned flavored cigarettes, except for menthol in 2009. Since then, Legacy has led the fight to ban menthol cigarettes. Further, we have strongly advocated for the banning of all flavors from all tobacco products. We are deeply disappointed that FDA did not issue any regulations to protect youth by banning flavored tobacco products in the proposed rule.

Tobacco products such as smokeless tobacco, hookah, cigars and e-cigarettes all come in a wide range of flavors, most of which are directly appealing to youth. Examples (but by no means an exhaustive list) of flavored tobacco products include:

- Smokeless products: Berry, Cherry, Apple, Peach, Citrus, Wintergreen
- Cigar products: Strawberry, Blueberry, Grape, Peach, Cherry, Cream, Vanilla, Chocolate, Honey, Mango, Piña Colada, Tequila, Rum, Sour Apple, Watermelon
- Hookah products: Chocolate, Cherry, Champagne, Cinnamon, Clove, Grape, Mango, Lemonade, Piña Colada, Pineapple, Watermelon, Raspberry, Cola, Irish Cream, Key Lime Pie, Peach, Root Beer, Hazelnut, Butter Scotch, Chai
- E-cigarette products: Peppermint Party, Piña Colada, Very Vanilla, Cherry Crush, Peach Passion, Bazooka Joe Bubble Gum, Cotton Candy, Mojito, Chocolate, Mango, Strawberry, Gummy Bear, Peanut Butter

Candy makers know what appeals to kids. In just one example, a package of Jelly Belly's "Kids Mix – 20 flavors kids love!" included flavors such as Berry Blue, Blueberry, Bubble Gum, Buttered Popcorn, Chocolate Pudding, Cotton Candy, Green Apple, Lemon, Lemon Lime, Orange Sherbet, Peach, Raspberry, Red Apple, Sour Apple, Sour Cherry, Strawberry, Toasted Marshmallow, Tutti-Frutti, Very Cherry, Watermelon – many of the exact flavors found in tobacco products.[244] While that is just one anecdotal example, a recent study confirms that the chemical-specific flavor sensory cues associated with fruit flavors in candy are the same as those found in tobacco products.[245] The tobacco industry has long shown that it also knows what appeals to youth. One tobacco company's so-called tobacco prevention website, "Real Parents, Real Answers" even acknowledges that kids like flavors when it states, "kids may be particularly vulnerable to trying e-cigarettes due to an abundance of fun flavors such as cherry, vanilla, piña colada and berry."[246] Ironically, until a very recent merger and spin off of companies, this same company sold e-cigarettes in those very flavors.[247]

What's more, many of the products are often found in stores right next to the candy flavors they emulate. Due to the impact of nicotine on the developing brain, it is critical that FDA do all it can to prevent youth from ever using nicotine. One way to do that is to ban flavors in all tobacco products. Based on the public health standard, there is sufficient scientific evidence to do just that. We provide supporting evidence below.

National data show that more than 6% of U.S. youth in 2011 reporting using either flavored little cigars or flavored cigarettes.[248] Given that there were 25.1 million youth (aged 12-17) in 2011,[249] this means that nearly 1.6 million youths were flavored cigarette or little cigar users. Of studies that have examined the use of flavored tobacco products by age or by grade,[56,94,248,250-262] two national studies demonstrate that youth and young adult tobacco users are more likely to use flavored products than adults.[56,253] Three national studies also show that younger adults are more likely to use flavored tobacco products than older adults.[252,253,262] Three additional studies in adolescents, two of which were in national samples, show that flavored tobacco use is higher among high school students compared to middle school students[94,248,250] and this trend holds true across multiple flavored products, including little cigars,[248] cigarettes,[248] bidis,[250] and kreteks.[94,250] Data on youth and young adults from the National Survey on Drug Use and Health also document a high prevalence of flavored product use among youth and young adult smokers.[56,251] Data from the 2010-2011 National Survey on Drug Use and Health showed that a surprising 95% of young cigar smokers aged 12-17 and 89% of young adult cigar smokers aged 18-25 used a brand that makes flavored cigars.[56]

Qualitative data collected from adolescents and young adults supports the idea that the flavoring drives tobacco use in these populations[258,263,264] and early findings substantiate a potential mechanism linking experimentation with flavored tobacco products through progression to regular use in young tobacco users. In line with studies showing that youth menthol smokers report greater levels of nicotine dependence than youth non-menthol smokers,[265-269] one study of youth and young adults found that flavored tobacco use facilitates nicotine dependence among young smokers, despite low smoking frequency.[251] Furthermore, a recent study of middle and high school students reported that flavored cigarette users were more likely to be daily smokers than non-flavored cigarette users,[248] another possible pathway to dependence. Both increased frequency of tobacco use and nicotine dependence among young flavored tobacco users highlight the possible role of flavored tobacco products in facilitating regular use in youth and young adults.

Moreover, flavored tobacco use is correlated with dual use of other tobacco products. Cigarette smoking[261] and smokeless tobacco use[270] have been shown to be associated with a significant increase in kretek use, and among young adult tobacco users, use of any menthol product has been shown to be associated with a significant increase in any current non-menthol flavored tobacco use.[262]

There is limited research examining the effects of flavored tobacco use on tobacco cessation among adults,[16,256,271] but among youth, flavored tobacco use is correlated with lower quit intentions compared to non-flavored use.[248] Additionally, some evidence suggests that using flavored tobacco products poses direct health risks,[272-275] and causes increased or unique harm when compared to non-flavored tobacco use, including increased exposure to harmful chemicals[254,276,277] and co-use of tobacco and marijuana.[278]

In sum, the evidence shows that young age is associated with flavored tobacco use. This finding is consistent over time and has been replicated across multiple national datasets. Literature examining flavored tobacco use by age is consistent with the data on menthol cigarette use, as prevalence of menthol cigarette use is higher in youth than in young adults and adults,[279-282] and similar to menthol, early research indicates that flavored tobacco use contributes to the frequency of tobacco use[248] and nicotine dependence[251] in youth and young adults. Studies also indicate that dual use of flavored tobacco products and other tobacco products is common and that the prevalence of flavored tobacco use for some products is as high as 95% in youth tobacco users.[56] Flavored tobacco product use may also pose unique health risks by increasing exposure to harmful chemicals used as additives[254,276,277] or by facilitating other substance use, particularly marijuana.[278] As a result, it is very likely that a ban on flavored tobacco products would reduce nicotine dependence at the population level, largely through reductions in youth and young adult initiation of tobacco use.

II. Continuum of Harm

In the proposed rule, FDA acknowledged that no tobacco product is entirely safe, but that some products pose less harm to the individual than others. Legacy agrees that a continuum of harm of tobacco products exists, with combustible tobacco products at the most harmful end of the continuum and FDA-approved nicotine replacement therapies (NRT) at the least harmful end. As such Legacy endorses the principle of harm reduction.[283] Combustible tobacco creates an array of toxic compounds that, when inhaled, increases harmful exposure to these toxicants thereby increasing risk for disease. On the other hand, nicotine by itself, in normal doses and in non-pregnant, healthy adults, presents much reduced health risks.

Legacy believes that the optimal tobacco control strategy is to achieve a society free of all nicotine and tobacco use (total abstinence). We recognize however, that some users will not be able or willing to stop using tobacco products altogether. Harm reduction, a strategy we support if properly implemented, adopts a secondary priority of moving those users to less-harmful non-combustible tobacco products while eliminating combustible product use entirely. This is feasible only if alternative, demonstrably lower harm, non-combustible products that can deliver nicotine are available. Regulations can play an important role in achieving this goal. Based on the 2014 Surgeon General's Report, Legacy urges FDA to consider combustible tobacco products – the most toxic tobacco products – as the primary comparator under both current and proposed regulatory policy when considering population-level harms. This can be implemented by monitoring total population prevalence of combustible tobacco use, including youth prevalence, and the population combustible product quit rate in pre-market and post-market surveillance. Regulatory actions

that maintain or speed current trends of reduction in combustible tobacco use should be viewed as beneficial, and those that reverse trends in combustible use should be identified as harmful.

Under the principle of harm reduction, each product must be regulated based both on its potential impact on individual health and the health of the public at large. This approach is reflected throughout this submission. The bar for identifying harm minimizing products must be rigorous but not set so high that it takes decades to create a marketplace where products that pose lower health risks can compete with, and hopefully assist in the ultimate demise of, combustible products. A system where it is easier to buy a cigarette than NRT therapy simply does not make sense.

FDA's deeming rule represents the first, highly critical, phase in determining how nicotine products, other than products currently regulated under either FDA's tobacco or pharmaceutical authority, will be designed, marketed and sold to consumers. If e-cigarettes (and other forms of refined nicotine) are carefully regulated, they have the potential to shift smokers permanently away from combustible products including cigarettes, cigars and hookah, to cleaner, less harmful forms of nicotine. As we note above, if we consider combustible tobacco use as the most toxic comparator, we can distinguish between different types of nicotine-containing products. Per Fiore et al.: "we need to communicate intelligently…[that] not all nicotine-containing products are equal, and the public health focus should be on eliminating combustible tobacco products, even if some people who give up combustibles will continue using FDA-approved medications, e-cigarettes, or smokeless tobacco products indefinitely."[284] The potential exists for products approved by CTP as modified risk products to assist current smokers with craving reduction, in combination with other nicotine replacement therapies and as part of a reduce-to-quit strategy in line with FDA's recent NRT labeling changes.[285] As such, Legacy strongly supports the comprehensive regulation of nicotine by the FDA across all of its divisions, particularly CTP and CDER, to ensure that FDA uses all of the tools at its disposal to communicate with the public regarding minimizing tobacco-related harm.

Finally, and critically, any regulatory regime, very much including one that takes a harm reduction approach, must place heightened focus on the issues of youth initiation. A new generation of tobacco users – of any tobacco products – is NOT an acceptable result. Indeed, this is a primary focus of Legacy's suggestions throughout this comment. Monitoring patterns of tobacco use, particularly among youth, through post-market surveillance is essential to ensuring that public health is not endangered by new modified risk tobacco products and that regulation is having its intended effect. In addition to providing FDA with the authority to remove products from the market if determined to be harmful to users or to the population at-large, these data will also support the public education campaigns to minimize misperceptions and maximize benefit of regulatory actions. Legacy strongly urges the development of independent post-market surveillance systems, beyond PATH alone, to meet these goals and ensure success of FDA tobacco regulation.

Currently, e-cigarettes and other products that deliver nicotine vapor are at the center of the debate around harm reduction. Our specific recommendations for regulations are included in the preceding sections of this comment. However, there is a continuing body of evidence being developed around these products and their effects on individual health and public health. In order to assist the FDA in considering these complex issues, we have prepared a systematic literature review of studies on e-cigarettes and smoking cessation and a synthesis of how the findings of these studies fit with the established literature on the use of nicotine replacement therapies (NRT) for cessation of combustible cigarettes, attached as Appendix F.

CONCLUSION

Legacy welcomes this first-step proposal to extend FDAs jurisdiction to other tobacco products. First and foremost, it is critical that FDA finalize a strong deeming rule by April 25, 2015, or sooner. The urgency for FDA moving forward to finalize a deeming regulation to regulate *all* products meeting the definition of tobacco product, including premium cigars and accessories, cannot be overstated. All tobacco products pose health risks and the only way to ensure protection of the public health is to bring them all under FDA's authority. Bringing these products under FDA's jurisdiction meets the public health standard established by the Tobacco Control Act. Thus, the status quo where some products are regulated and others are not simply undermines any efforts to protect the public from the disease and death associated with tobacco.

Further, there are other important regulatory measures FDA should finalize as well. First, FDA must educate the public about the disease risks, and of the addictiveness of tobacco products through proposed warning labels. Second, no tobacco product should be easily accessible to or marketed to youth. Therefore, Legacy strongly encourages FDA to broaden the proposed marketing and youth access restrictions. Third, FDA has proposed that it will not enforce regulations regarding new product applications or substantial equivalence applications for some products, most likely e-cigarettes, for a period of 24 months, leaving these products unregulated for that time. That is far too long and Legacy recommends shortening that period to 12 months, as FDA has originally proposed. Finally, FDA must ensure that all the automatically applicable provisions of the Tobacco Control Act be applied to all the products under its jurisdiction.

As requested in the NPRM, Legacy has provided significant information on the need for FDA to issue a ban on flavored tobacco products as soon as possible. Flavored products are used in higher numbers by youth, and entice them to try tobacco. As we have stated numerous times, nicotine is a highly addictive substance, especially in young, developing brains. Banning flavors in all tobacco products is a common sense measure to protect our youth from tobacco related death and disease. Appendix E provides a systematic review of literature on this topic.

Further, as also requested in the NPRM, Legacy has provided guidance to FDA on moving forward with a harm reduction strategy. While our first goal should be complete tobacco abstinence, if that is not possible, we encourage moving people from the most harmful products – combustible products – to less harmful products. Appendix F provides a systematic review of literature on e-cigarettes and the cessation of combustible cigarettes. Implementation of a harm reduction strategy, of course, must be done in the context of preventing youth from starting in the first place.

Legacy's goal is to help create the first tobacco free generation. FDA has the power through regulation to play a big role in achieving that. The proposed rule is a first step and we look forward to collaborating with FDA as we work to finish tobacco once and for all.

Sincerely,

Robin L. Koval
President and CEO

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APPENDIX A
SYSTEMATIC REVIEW OF STUDIES ON CIGARS

Note on Methods:
The findings below were compiled from a systematic review of all published scientific literature on cigars conducted via a PubMed search through June 9, 2014. The search strategy consisted of the following keywords: "cigar" OR "lcc" OR "cigarillo" AND ("tobacco" OR "smoking") NOT "mosaic virus" NOT "Bangladesh" NOT ("gene" OR "genes" OR "genetic") NOT "moxa" NOT "fermentation" NOT "lesion*". Studies that were not related to cigars, not in English, conducted outside of the United States or Canada, or related to genetics or tobacco farming were excluded.

Upon retrieval from PubMed, studies were catalogued based on title and abstract review to one or more of the following topic areas: 1) Product Features; 2) Health and Safety; 3) Consumer Perceptions; 4) Patterns of Use; 5) Marketing; 6) Sales; and 7) Policies. Reviews were catalogued separately and are not included in the detailed summary of study findings. For the purposes of this Appendix, the review below focuses on the patterns of use data, as well as the data on health effects of cigar use.

HEALTH EFFECTS

The health and economic burden in the United States of cigar smoking is large and could increase over time as consumption of cigars increases.

- A study estimating the mortality and economics costs from regular cigar use found that regular cigar smoking was responsible for approximately 9,000 premature deaths among adults aged 35 and older in the United States in 2010. These deaths represented almost 140,000 years of potential life lost, representing an average of 15.1 years of life lost per death. The loss of these years of life represented a monetary loss of $22.9 billion. Total premature mortality may be underestimated because deaths resulting from less frequent cigar smoking were not estimated.[1]

Cigar smoking poses serious health effects – even in those who don't use cigars on a daily basis.
Since the 1950s, evidence has shown causal associations with large/premium cigar smoking and several cancers, and other diseases.[2,3] In 1998, the National Cancer Institute released a monograph outlining, among other things, the health effects of large cigars.[2] Since the publication of that document, several additional studies show strong evidence of the health risks associated with cigars.

- Specifically, cigar smoking is associated with higher risk of oral, esophageal, laryngeal, and lung cancer.[1-4] One study found an increased risk in head and neck cancers for those who do not smoke cigarettes, but are ever cigar users.[5]
- Data on cigar smoking and pancreatic cancer are mixed. Some studies showed higher rates of pancreatic cancer for cigar smokers than for non-smokers, and at rates similar to cigarette smokers.[6-8] Others showed no association between cigar smokers and pancreatic cancer.[9,10]
- Cigar smokers have a marked increase in risk for COPD[11], and cigar smokers experience higher mortality from COPD than do non-smokers.[12]
- For those who smoke cigars heavily, and for those who inhale, cigar use causes an increased risk of heart disease.[13]
- Those who smoke cigars have a higher risk of fatal and non-fatal stroke than non-smokers, with the highest risk of stroke seen in dual users of cigars and cigarettes.[13]
- Cigar smokers are at higher risk of tooth loss than non-smokers.[14]

Proponents of Option 2 claim that premium cigar users smoke them only infrequently, and therefore they have no risk of these diseases. However, many studies found that while the risk for these diseases increases with the number of cigars used and the intensity of inhalation, disease risk still exists.[2,5]

Cigars contain high levels of harmful constituents.

- In general, cigar smoke is similar to cigarette smoke, however, cigars have higher levels of:
  - Tobacco-specific Nitrosamines (TSNAs)[6]
  - NNK[6]
  - Carbon monoxide (CO)[15]
  - Ammonia[16]
  - Tar[16]

Dual use of cigarettes and cigars promotes even more health risks than cigar use alone.

- Those who smoke cigarettes are more likely to inhale cigar smoke, significantly increasing risk of disease.[17-21]
- Concurrent use of cigars and other tobacco products increases exposure to nicotine and other harmful constituents, which also increases the risk of disease and causes higher mortality rates.[22]

Even when not inhaled, cigars pose significant health dangers to users.

- Most cigar smokers do inhale some amount of smoke and are unaware that they are doing it -- even among those who do not intend to inhale.[23]
- Regardless of how much inhalation actually takes place, studies show that because cigar smoke dissolves more easily in saliva than cigarette smoke and that cigar users absorb smoke (and nicotine) from cigars even when they report no inhalation.[11,24]
- In another study examining the effects of using various tobacco products on stomach cancer incidence, current male cigar smokers, including those who reported they did not inhale, had significantly higher stomach cancer mortality than those who did not use tobacco.[25]
- Clearly, inhaling cigar smoke poses much higher rates of risk than not inhaling, though, as noted above, significant risk is posed even without inhalation. It is important to note that those who smoke cigarettes or used to smoke cigarettes are more likely to inhale cigar smoke.[2,18-20,23,26] Those who inhale cigar smoke are much more likely to absorb high levels of nicotine[27] and experience a higher incidence of the health effects associated with cigar smoking,[2,28] including the risk of death.[3]

Secondhand cigar smoke contains dangerous compounds and chemicals that pose significant health problems.

- Secondhand cigar smoke is also dangerous, containing higher concentrations of toxic and carcinogenic compounds than cigarette smoke and is a major source of fine-particle and carbon monoxide indoor air pollution.[2,3] One study suggests that "even normal breathing in a cigar smoke-filled room could result in substantial nicotine exposure to any person in the room".[27] Another study concluded that a non-smoker exposed to smoke during smoking of a cigar receives a much higher exposure to carbon monoxide, respirable suspended particles, and particle-bound polycyclic aromatic hydrocarbons than would likely occur for a single cigarette.[15]
- Large/premium cigars in particular have more tobacco, nicotine, nitrosamines and higher levels of nitrogen oxides, ammonia, carbon monoxides, and tar than cigarettes.[16] There is a large body

of evidence on how these components impact health of not only the smoker, but to non-users exposed to the smoke.[29]

Cigar smokers are likely to experiment or be current users of other illicit drugs.

- Several studies show that cigar use is an indicator of use of other drugs, especially marijuana. This is particularly the case for little cigars and cigarillos.[30-39]

Smoking little cigars and cigarillos poses significant health risks to users.

- Because little cigars and cigarillos look so much like cigarettes, consumers are much more likely to inhale, leading to similar health risks as cigarette use. Young consumers usually inhale the smoke of Black & Mild cigars, unlike large cigar smoke.[40] Small cigar smoking is associated with smoke inhalation that leads to significant exposure to nicotine, CO, and presumably other components of tobacco smoke. Removing the inner paper liner (freaking) does not substantially reduce toxin exposure.[41]
- An experimental study of 16 Black & Mild smokers found that ten puffs from a Black & Mild cigarillo delivers considerable amounts of carbon monoxide. This carbon monoxide exposure likely poses significant health risks.[42]
- The mainstream smoke from cigarillos is not less toxic than the mainstream smoke from cigarettes.[43] One study examined the delivery of "tar," nicotine and CO per liter of smoke for different tobacco products. They found that the mean yields per liter of smoke were highest for small cigars followed by hand-rolled and manufactured cigarettes and were lowest for large cigars.[2]

While cigar health effects are well established, they are not well known among the public.

- Several studies show that cigar smokers are more likely to believe that cigars are less harmful and/or more natural than cigarettes.[16,30,44-49] Studies found that participants preferred little cigars and cigarillos to cigarettes for various reasons including taste, smell, a better "buzz," social purposes, status, and perceptions that smoking little cigars is less addictive and less harmful than smoking cigarettes.[30,40,44,50] One survey even found that 64% of youth respondents did not believe there was tobacco in Black & Mild cigars or reported that they did not know if there was or not.[30]
- Some older studies indicated that many former cigarette smokers were advised to switch to cigars or pipes instead, and subsequently mortality rates for pipe and cigar smokers who were former cigarette smokers were higher than those for pipe and cigar smokers who had never smoked cigarettes.[51,52]
- A study investigating the effects of graphic-enhanced web-based cigar smoking risk messages found that participants who viewed a cigar risk message with a graphic, as opposed to text only, were more likely to perceive cigar smoking risks at a level consistent with the scientific literature and were more likely to share the information with others.[53]

INITIATION (INCLUDING YOUTH AND YOUNG ADULT PREVALENCE)

The CDC has estimated that consumption of cigars has risen from 2001 – 2011.

- Consistent with prevalence data, consumption of cigars has risen from 2000-2011 while cigarette consumption declined in the same time.[1,54] Consumption rates of cigars and loose tobacco went from 3.4% in 2000 to 10.4% in 2011.[55]

- Large cigar consumption increased every year from 2000 to 2011, with especially large jumps in 2009 after the tax increase on all tobacco products, but especially little cigars, went into effect and cigar companies increased slightly the weight of their little cigar products in order to be taxed as large cigars.[1,55]

National Surveys show no decline in prevalence of cigar smoking in the overall population in recent years, even while cigarette smoking prevalence has decreased. Importantly, among some subpopulations, cigar prevalence appears to be increasing. Current cigar use is highest among young adults.

- Overall prevalence rates of current cigar use among those 12 and older is 5.2%.[56] The 2012 National Survey on Drug Use and Health (NSDUH), showed that rates of current cigar use among 12-17 year-olds have remained similar from 2002-2012, while current cigarette use rates declined in those same years.[56] Another survey of adults 18 and over, the 2012-2013 National Adult Tobacco Survey (NATS), found current cigar use rates of 5.8%.[57]
- Data from the 2012-2013 NATS indicates that 61.8% of adult cigar smokers usually use cigarillos and other mass market cigars, 19.9% usually smoke premium cigars, and 18.4% usually smoke little filtered cigars. Cigarillos and other mass market cigars were the usual cigar of most men and most women. Premium cigars were the usual cigar of 23.9% of men, and little filtered cigars were the choice of more women than men.[54]
- Prevalence rates of current cigar use among young adults (18-25) are higher than for other age groups,[56,57] ranging from 8.9%[57] to 10.7%.[56] Young adult prevalence rates of current cigar use were similar in 2012 to those of 2002[32,56] while cigarette smoking among this age group declined.[56] High rates of young adult cigar use have been a trend for several years.[22,32]
- The 2012-2013 NATS found that among adult cigar smokers who usually smoked premium cigars, 3.3% reported "every day" use, 25.6% reported "some day" use, and 71.2% reported use "rarely." Among adult usual smokers of cigarillos and other mass market cigars, 13.3% reported "every day" use, 23.0% reported "some day" use, and 63.8% reported use "rarely." Among adult usual smokers of little filtered cigars, 36.0% reported "every day" use, 21.5% reported "some day" use, and 42.5% reported use "rarely."[54]
- Among youth, two recent, separate national surveys (the 2013 Youth Risk Behavior Surveillance System and the 2012 National Youth Tobacco Survey) reported that 12.6% of high school students were current cigar smokers.[58,59] One of those surveys, the 2012 National Youth Tobacco Survey (NYTS), reported middle school current cigar use rates of 2.6%.[59] The 2012 NSDUH reported current cigar use among youth ages 12-17 at 5.2%.[56]
- The 2013 Youth Risk Behavior Surveillance System (YRBSS) showed that while among high school students current cigar smoking has declined since 1997, the decline has slowed since 2001 and no significant change occurred between 2011 and 2013.[58] While the decline in youth cigar rates has stagnated, youth cigarette rates continue to decline. In 2013, the YRBSS recorded the lowest-ever cigarette smoking rate since 1991, when that survey was first administered.[58]
- Among some sub-populations, cigar use has increased. The 2012 NYTS found current cigar use more than doubled among non-Hispanic black high school students from 2009 to 2011-2012 and found that high school males smoke cigars at twice the rate of high school females.[59] That same study showed that in 2012, among both middle and high school students, black, non-Hispanic as well as Hispanic students smoked cigars at higher rates than white non-Hispanic students.[59] In contrast, the 2013 YRBSS found that white, non-Hispanic; black, non-Hispanic and Hispanic youth used cigars at similar rates.[58] While the 2012 NSDUH found that lifetime and past year cigar use was higher among whites, past month cigar use was higher among blacks.[56] Finally, a

study reviewing data from 2002-2008 found that current cigar smoking among non-Hispanic whites increased in that time, as well as among Hispanics.[32]

State and local surveys confirm that high rates of young adults and youth are using cigars.

- One report showed that current cigar smoking among youth was higher than youth cigarette smoking in 8 states and cigar use rates were similar to that of cigarette use rates in an additional 2 states.[58]
- A 2003 survey of Massachusetts youth indicated subpopulations of cigar smokers, who do not smoke cigarettes, do exist. Interestingly, the subpopulations in this survey tended to be those with higher grade point averages and/or have parents with higher levels of education.[60]
- A study published in 2008 of young adult military recruits showed that 12.3% of them were current cigar users, and 51.3% were ever cigar users. Those recruits over the age of 20 were slightly less likely to have used a cigar than those younger than 20, though this was not statistically significant. As with others, this study did not differentiate between little cigars, cigarillos or large/premium cigars. However, interestingly, those with a family income of more than $70,000 per year were 1.35 times more likely to have used cigars as those with an annual family income of $25,000 or less.[61]

Data shows that young adults are using large/premium cigars.

- Data from the 2012-2013 NATS shows that an estimated 15.1% of young adults, aged 18 to 29 years, smoke premium cigars.[54]
- In 2013, researchers from Legacy reported that in the Legacy Young Adult Cohort, 29.9% of large cigar-only users were 18-24 years old; and 44% of those who used both little cigars and large cigars were 18-24 years old.[31] While large cigars were not specifically defined in this study, the survey did give brand-specific examples of little cigars and cigarillos, so respondents were less likely to confuse the various cigar products. This study also found that the average age of initiation for large cigar-only users was 16.43, while the average age of initiation for little cigar and cigarillo-only users was 16.18.[31]
- Another Legacy study following the Legacy Young Adult Cohort over three waves from July 2011 to July 2012 found that ever large cigar use among 18-24 year olds increased by 10.2% in that timeframe. Again, large cigars were not specifically defined in this study, but the survey gave brand-specific examples of little cigars and cigarillos, so respondents were less likely to confuse the products.[35]
- One study using Nielson scanner data and the 2010-2011 NSDUH data, found that 3.8% of 12-17 year old cigar smokers reported preferring a premium cigar brand. In addition, approximately 12% of 18-25 year old cigar smokers reported preferring a premium cigar brand.[62]

Little cigar and cigarillo use is particularly high among young adults and African Americans.

- The 2012-2013 NATS found that cigarillos and other mass market cigars were the usual cigar of 72.1% of young adults, aged 18-29 years) and little filtered cigars were the usual cigar of 12.8% of young adults. The same survey found that cigarillos and other mass market cigars were the usual cigar of 82.6% of African American adult cigar smokers.[54]
- 2012 data from Legacy's Young Adult Cohort Study, a nationally representative sample of young adults ages 18-34, found that 37.9% of young adults surveyed had ever smoked cigars. Of the cigar smokers, 21.5% had ever smoked only little cigars and cigarillos and 32.3% had ever smoked only large cigars. 46.2% were dual users of both. Use of little cigars and cigarillos was significantly associated with being female, being in the 18-24-year-old age group, non-Hispanic

black race/ethnicity, and daily use of marijuana. These estimates support studies showing increasingly higher prevalence of young adults smoking cigars.[31]

- In 2010, an online survey assessed small cigar use among college students in the southeastern United States. Current use was reported as follows: 12.1% smoked small cigars, 5.1% smoked cigarillos, 10.2% smoked little cigars, and 3.2% reported smoking both cigarillos and little cigars.[38] This study found that small cigar smokers were younger, more likely to be black than white or other, and attending an HBCU rather than a state university or technical school.[38]
- A survey of adults in an inner city population in Hartford, Connecticut found that smoking of Black & Milds was more common among African Americans and Latinos than among white participants. Black & Mild users were younger than the sample as a whole. Mean age of participants who reported using Black & Milds was 33 years, compared to 38 years for those who did not use them. Black & Mild users were less likely to be employed and more likely to report being homeless than non-users.[40]
- Data suggests that female respondents are more attracted to cigarillos than to regular cigars. In one study, male individuals were more likely to smoke cigars than female individuals. However, the gender difference was larger for regular cigars than for cigarillos.[63] A recent study from Legacy showed that females were slightly more likely to have used a non-cigarette-combustible product (including cigars and hookah) than males.[35]

Little cigar and cigarillo consumption, while variable, has increased significantly in the past 20 years.

- From 1993 -1998 large cigars were the fastest growing product. However, from 1993 to 2006, unit sales of cigarillos increased from 25% to 32% of the cigar market[64] and between 1998 – 2004, small cigars increased in consumption by 76%.[65] Small cigar consumption continued to increase until 2009.[55]
- In 2009, following the tax increase on all tobacco products, but especially little cigars, many little cigar companies have simply increased the weight of their products to receive a better tax rate.[66,67] As a result, large cigar consumption from 2008-2011 increased 126.3%.[55]

Prevalence of little cigar and cigarillo use is very likely underestimated.

- In the 2011 NYTS, students were asked about ever and current cigar, cigarillo, and little cigar smoking. In 2012, the instructions for the cigar section listed brand examples. Ever cigar smoking was higher in 2012 (27.8%) than 2011 (19.5%) among African American students overall. Current cigar smoking was much higher among African American females and students 17 years and older, in 2012 than 2011. For African American females, current cigar smoking was two times greater than that of white females in 2012, whereas the prevalence among these subpopulations was comparable in 2011. The 2011 and 2012 NSDUH did not list branded examples and similar changes among these subpopulations were not observed. The inclusion of brand examples in the 2012 NYTS improved measurement of cigar use and identified disparities in cigar use among subpopulations.[68]
- A 2008 nationally representative youth survey in Canada found that the prevalence of current cigarillo and little cigar use was higher than the prevalence of daily and occasional cigarette smoking, which suggests that the actual magnitude of tobacco use among youth in Canada may be largely underestimated.[69]
- In a Virginia survey of adolescents, 60% of respondents who reported current use of Black & Milds, a cigarillo brand, did not report current use of “cigars, cigarillos, or little cigars.” The rate of cigar use among this sample nearly doubled when rates were adjusted for this subgroup of respondents. Results revealed that misreporting was two to three times more likely among

older respondents than those aged 12 or younger, as well as two to three times more likely among African American adolescents than white adolescents. These findings suggest developmental and cultural factors may play a role in the interpretation of cigar use items on tobacco use surveillance measures.[70]

ADDICTIVENESS

Cigars develop and sustain addiction.

- Because of their size, large/premium cigars contain significant amounts of tobacco, and therefore, large amounts of nicotine.[2] Inhalation of large/premium cigars increases nicotine delivery.[27]
- Cigar smoke tends to have a higher pH than cigarette smoke, which increases the amount of free nicotine in the particulate and vapor phases of the smoke.[3] Further, the pH level of cigars varies greatly, but one study showed that if cigars, and their smoke, have high pH levels, then it is likely to deliver nicotine more quickly through the buccal mucosa. Thus, even when unlit, cigars can deliver nicotine into the body.[27] This same study suggested that because large/premium cigars are more alkaline, more nicotine could be absorbed through the buccal mucosa from that type of cigar than from cigarillos and little cigars – even if the smoke is not inhaled.[27]
- While most data suggests that premium cigar users do not use cigars every day or even every week, some studies do show that those who smoke less than daily still exhibit nicotine dependence. For example, one study showed that cigarillo smokers do exhibit nicotine dependence.[41,42] Further, another study of college students showed that non-daily smokers who were never daily cigarette smokers were more likely to use other tobacco products, especially cigars, which increases their nicotine exposure.[39]
- A study using data from the 2012 National Youth Tobacco Survey found that 6.7% of youth cigar-only users indicated they had strong cravings for a tobacco product during the past 30 days, compared to 42.6% of cigarette-only users and 32.2% of smokeless tobacco-only users. 2.3% of youth cigar-only users reported a strong desire to want to use tobacco during the past 30 days, compared with 18.5% of cigarette-only users and 12.7% of smokeless tobacco-only users. Additionally, 7.8% of youth cigar-only users reported feeling irritable or restless when not using tobacco for a while, compared to 35.9% of cigarette-only users and 21.9% of smokeless tobacco-only users. Symptoms of tobacco dependence were still reported by cigar-only users even though a substantial majority reported use on 5 days or less in the past 30 days.[71]
- In the same study using data from the 2012 National Youth Tobacco Survey, polytobacco users were more likely to report symptoms of nicotine dependence.[71]
- A study that examined the absorption of nicotine from small cigars labeled with 14C-nicotine found that the amount of nicotine delivered to the smoker's mouth during cigar smoking was greater than that during cigarette smoking, but the proportion retained by the subject was similar for cigars and cigarettes.[2]
- Ten puffs from a Black & Mild cigarillo deliver active doses of nicotine but do not suppress abstinence-induced withdrawal symptoms reliably. The nicotine delivery profile suggests that cigarillo smoking, especially in those who also smoke cigarettes, may promote nicotine/tobacco dependence. However, this area needs to be studied more closely.[42]
- Inhalation parameters have a dramatic effect on nicotine delivery. A study which examined the absorption of nicotine from non-inhaled cigar smoke found nicotine delivery to be slower than that observed following cigarette smoke inhalation.[2] There is evidence that tobacco companies

knew this well, and used it to their advantage. For example, RJ Reynolds' initial focus groups while product testing its little cigars noted that the product would probably be inhaled, much like cigarettes. Industry documents revealed the following: "Most men (and women) inhaled their first puffs of this new product. When asked why, they said it was because the product seemed like a cigarette in terms of its size and shape and because the filter suggested that it could be smoked just like a cigarette…many said they could not imagine giving up inhaling under any circumstances."[72]

While dual use is the norm, some youth smoke cigars but not cigarettes, which provides another pathway to nicotine addiction.

- Studies show that some youth smoke cigars, but not cigarettes.[14,60,71] This is concerning since this provides an additional source of nicotine exposure.[60] Exposure to nicotine in youth and young adulthood can lead to nicotine dependence and addiction – much more so than older adult exposure.[73-75]

PROGRESSION TO OTHER TOBACCO USE/DUAL USE

There are distinct patterns of dual use of different types of cigars as well as dual use of cigars and cigarettes. Additionally, several studies indicate that dual use of little cigars and cigarillos with cigarettes and other tobacco products is high.

- A nationally representative study of young adults reported that among 18-24 year olds, 23% smoked both cigarettes and cigars, and 26% were current cigarette and little cigar users.[76] Further study of the same cohort found 44% used both little cigars and large cigars.[31] A study using data from the 2012 National Youth Tobacco Survey found that 48.2% of youth cigar smokers used multiple types of tobacco products.[77] Another study using NSDUH data from 2001-2008 found that younger age of initiation of cigar use was associated with current use of cigarettes, marijuana, or blunts.[32] Further, a review of NYTS data from 1999-2009 revealed that heavy and moderate cigarette smokers saw a decrease in cigar use, though rates of current cigar use returned to 1999 levels by 2009 among heavy cigarette smokers. In the same timeframe, cigar use among light cigarette smokers increased over time.[78] The 2012-2013 NATS found that among adult usual smokers of premium cigars, 35.1% currently smoked cigarettes. 58.3% of adult usual cigarillo and other mass market cigar smokers currently smoked cigarettes and 75.2% of adult usual little filtered cigar smokers currently smoked cigarettes.[54]
- Several studies of local counties or regional colleges found high rates of current young adults and/or youth users of both cigars and cigarettes, ranging from 10.6% – 61.4%.[14,36,39,47,79] One study found that those who used both cigarettes and cigars, smoked cigars more often than cigar-only smokers.[14]
- Over half of cigar and little cigar (including cigarillo) users are also concurrent cigarette users, potentially increasing their exposure to tobacco and thereby increasing their risk for tobacco-related illnesses.[47] Black and low-income adult cigarette smokers are more likely to use other tobacco products, such as little cigars, and to be multiple product users.[47]
- In a 2010 online survey of college students in the southeastern United States, 72% of small cigar smokers reported concurrent cigarette use. Small cigar smokers reported more frequent use of alcohol and were also more likely to report current use of cigars, smokeless tobacco, hookah, and marijuana.[38]
- A 2008 nationally representative youth survey in Canada found that 5.4% of high school students reported currently smoking both cigars and cigarillos or little cigars. Current cigarillo or

little cigar smokers were likely to have ever smoked cigars (67.7%) and to have ever used flavored tobacco (81.2%).[69]

- One survey using a convenience sample of young adults and adults ages 19-29 in Canada found that 56% of respondents reported their primary reason for smoking cigarillos was the flavors and 30% reported it was to replace smoking cigarettes.[30]
- A study of military recruits found that cigarette smokers were more likely to smoke other forms of tobacco products, including cigars.[61]
- A study looking at TUS-CPS data from 1995 through 2002 showed that concurrent use of cigarettes and cigars increased in every socio-demographic category including race, education level, geographic location, income level, etc.[22] However, in other studies of nationally representative young adult populations, whites were slightly more likely to use cigars and cigarettes than other races.[76]

In youth, initiation with cigars facilitates greater dual use with cigarettes.

- One study examining use of tobacco in youth in a Midwestern county found that among youth who initiated smoking with cigars, 14.6% currently used cigarettes only, 12.2% currently used cigars only and 43.6% currently used both cigarettes and cigars. This was in contrast to those who initiated smoking with cigarettes where 17.4% currently used cigarettes only, 4.0% currently used cigars only, and 15.9% currently used both cigars and cigarettes.[14] Another study of youth in school districts across Massachusetts found that of those who smoked both cigarettes and cigars, 14.5% initiated cigars first, 55.4% initiated cigarettes first, and 30.1% began smoking both products at the same time.[60]

CESSATION

- Data from the 2012 National Youth Tobacco Survey indicates that 48.4% of youth cigar users intend to quit. Among youth cigar users, prevalence of quit intentions among African Americans (62.5%) was significantly higher than whites (43.0%). 54.4% of youth cigar users agreed that all tobacco products are dangerous while 33.0% disagreed. 48.0% of current youth cigar users reported making a past-year quit attempt.[77]
- Very little data exists on cigar cessation. As of 2005, no smoking cessation or tobacco prevention programs or literature focused on cigars.[16] This will need to change if we want to truly protect public health from these products.

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APPENDIX B
SYSTEMATIC REVIEW OF STUDIES ON E-CIGARETTES

E-cigarettes (or more accurately Electronic Nicotine Delivery Systems, or ENDS) have recently attracted considerable attention for several reasons. Compared to regular, combustible cigarettes they (1) deliver nicotine without combustion; (2) are thought to be less toxic; (3) can be used to reduce craving/withdrawal when one cannot smoke; (4) are less expensive; and (5) can possibly help one quit smoking/prevent relapse.

While there is great variability in the design and performance of e-cigarette products within and across brands, characterizing features include the use of a battery and a heating element that when activated deliver an aerosol mist from a solution containing tobacco-derived nicotine, flavorings and other ingredients. E-cigarettes typically fall into three categories: disposable "cigalike" products, rechargeable "cigalike" products, and larger rechargeable products (i.e., personal vaporizers, tank systems). As well as physical and performance-related differences, these categories of products differ in price, where they are typically sold, and the type of e-cigarette user that purchases them.

Rapid developments in manufacturing, marketing, and consumer domains related to e-cigarettes will warrant frequent re-evaluation, based on the state of the evolving science. The purpose of this document is to provide a current and comprehensive review of the published scientific literature on e-cigarettes related to five areas central to the public health standard: potential impact on 1) initiation; 2) progression to other tobacco products/dual use; 3) addictiveness; 4) cessation; and 5) health effects.

Notes on Methods:
The findings below were compiled from a systematic review of all published scientific literature on e-cigarettes conducted via a PubMed search through July 3, 2014. The search strategy consisted of the following keywords: "e-cigarette*" OR "electronic cigarette" OR "electronic cigarettes" OR "electronic nicotine delivery." Eligible studies were experimental studies, quasi-experimental studies, observational studies (including case control, cohort and cross sectional studies), case reports, case series, qualitative studies and mixed methods studies providing empirical data on e-cigarettes. Other sources were obtained by emailing experts and internal discussion of studies underway at Legacy.

Upon retrieval from PubMed, studies were catalogued based on title and abstract review to one or more of the following topic areas: 1) Product Features; 2) Health and safety; 3) Consumer perceptions; 4) Patterns of Use; 5) Marketing; 6) Sales; 7) Policies; and 8) Statements from public health organizations. Reviews were catalogued separately and are not included in the detailed summary of study findings; similarly, commentaries and editorials on e-cigarettes were not included in this review. For the purposes of these comments, the review below focuses on the patterns of use data, as well as the data on health effects of e-cigarette use or exposure.

HEALTH EFFECTS

There have been approximately 41 studies conducted to examine the impact of e-cigarettes on individuals' health and safety.[1-43]

Secondhand Vapor Exposure

Data is very limited on the impact of exposure to e-cigarette vapor on health, with one study indicating an increase in cotinine level, but no difference in lung function or complete blood count, following exposure to machine-generated vapor.[20,21]

- Several studies have been conducted measuring the constituents found in e-cigarette vapor generated by both machines and humans; however, only one study has examined the individual health effects of exposure to the vapor itself (not via inhalation).[20,21] To our knowledge, there have been no studies measuring biomarkers in bystanders, or non-vaping individuals exposed to e-cigarette vapor generated by humans, which could be qualitatively different than machine-generated vapor. In the one secondhand vapor study we identified, participants (N=15) were never-smokers naïve to e-cigarettes and were exposed to air polluted with e-cigarette vapor via an air pump for one hour in a chamber set to simulate a bar or restaurant environment.[20,21] Cotinine level was found to be significantly higher than baseline following both secondhand e-cigarette vapor and secondhand tobacco smoke exposure, with no significant difference between vapor and smoke. Following e-cigarette vapor exposure, there were no differences in lung function or complete blood count.

Physiologic Effects

Studies demonstrate modest increases in nicotine biomarkers after e-cigarette use and at much lower levels than for conventional cigarette use. E-cigarette use has no or minimal impact on other physiologic measures, with the impact being generally positive for cigarette smokers switching to e-cigarettes.

- Most studies found a modest to no increase in plasma nicotine [9,20,31,32,43] and saliva cotinine [6,14-16] levels after e-cigarette use. Few studies have examined cardiovascular measures associated with e-cigarette use, and findings are divided with respect to the impact of e-cigarette use on heart rate.[13,30-32,43,44] Among smokers, exhaled carbon monoxide (eCO) and nitric oxide (eNO) have been found to decrease after switching to e-cigarettes,[5,6,23] and various clinical studies have found no difference in eCO levels following e-cigarette experiments.[26,30,43] One study found that lung resistance and airway impedance increased after ad libitum use of an e-cigarette containing nicotine, but use of an e-cigarette with no nicotine has been shown to have no impact on lung function[33]; however, among asthmatic smokers, e-cigarettes have been shown to improve lung function and reduce symptom exacerbations.[38] A worldwide online survey in 2013 found that the majority (74.5%) of respondents who had initiated e-cigarette use reported better general physical status after initiation, with improvements seen mostly in former smokers.[19] The same survey found that 35.0-75.7% of respondents with chronic conditions (such as diabetes, coronary artery disease, and chronic obstructive pulmonary disorder) experienced improvements in their symptoms following e-cigarette initiation. 18.4% of respondents with lung disease stopped using medications after initiating e-cigarette use.[19]

Cognitive Effects

Few studies have been published on the cognitive effects of e-cigarette use, but these studies indicate a minimal but positive impact on cognitive measures.[10,11,19]

- Minimal research has been conducted on the cognitive effects of e-cigarette use. Performance on memory-related tests has been shown to be better among participants who used nicotine-containing e-cigarettes than those using nicotine-free e-cigarettes.[10,11] Among former and current smokers, a worldwide survey revealed that 32.1% of respondents reported an improvement in mood and 16.2% reported an improvement in memory.[19] One study did not find

a difference in cognitive ability (attention/speed of processing and visual-spatial scanning ability) after use of a nicotinic e-cigarette among e-cigarette naïve smokers.[11]

Adverse Events

FDA adverse event reports related to e-cigarettes have increased since 2008 and e-cigarettes represented the tobacco product with the highest number of adverse event reports from 2008 through early 2012.[8] Common adverse effects associated with e-cigarette use include complaints relating to the mouth and respiratory system.[2,5,22,45]

- There is adequate data on the adverse effects of e-cigarette use. Most common events include mouth and throat irritation,[2,5,6,9,12,43] nausea,[2,5] headache,[5,6] and dry cough.[5,6] The majority of survey respondents (94.5%) reported at least partially resolved adverse symptoms over time.[19] A study analyzing online e-cigarette forums revealed more negative than positive effects of e-cigarette use.[22] FDA Center for Tobacco Products reports that the proportion of tobacco product complaints that are e-cigarette related has increased from 1/8 in 2008 to 9/11 in the first quarter of 2012.[8]
- US poison centers reported that e-cigarette exposure calls per month have increased from one in September 2010 to 215 in February 2014, although they are still lower in number than cigarette exposure calls.[7] In 2010-2012, there were 35 cases of e-cigarette-related poisonings in California.[4]
- The 2012 annual report from the National Poison Data System (NPDS) documented 427 single exposures to e-cigarettes, 59 were deemed an adverse reaction and 107 were treated in a health care facility.[46] Of these exposures, 83 had no outcome, 102 were deemed to have a minor outcome, 18 had a moderate outcome, 1 had a major outcome and 1 was a death. Among the 11 exposures to nicotine liquid, 1 was deemed an adverse reaction and 5 were treated in a health care facility; there were 2 classified as no outcome, 3 as minor outcome, 2 as moderate outcome and 0 as major outcome or death. This compares to 5,700 exposures to cigarettes, of which 30 were considered adverse reactions and 860 treated in a health care facility. Of these, 1,854 were considered to have no outcome, 998 to have a minor outcome, 68 to have a moderate outcome, 2 to have a major outcome, and 1 was a death.

Cytotoxicity

Several experiments have measured cytotoxicity of liquid and vapor, revealing that particular flavors are more cytotoxic than others, but all are less cytotoxic than cigarette smoke extract.

- Particular e-cigarette flavors are more cytotoxic than others, but all are less cytotoxic than cigarette smoke extract.[18,25,37] Studies found that between 5-43% of e-cigarette flavors samples had a slight/moderate cytotoxic effect on human and mouse stem and myocardial cells and 3-10% of samples had a high cytotoxic effect.[1,18,25] The most common flavor found to be cytotoxic is cinnamon.[1,18,41] Vegetable glycerin and propylene glycol have be found to be non-cytotoxic at all concentrations for all cell types.[1] Research is mixed on whether nicotine levels are correlated with cytotoxicity.[1,18,37]

INITIATION (INCLUDING YOUTH AND YOUNG ADULT PREVALENCE)

National data demonstrates that ever use of e-cigarettes in the U.S. is increasing rapidly in all populations: youth, young adults, and adults.

- **Youth**: Data from the National Youth Tobacco Survey show that from 2011 to 2012, among all students in grades 6–12 in the U.S., ever e-cigarette use increased from 3.3% to 6.8%.[47]
- **Young adults**: Ever e-cigarette use has also increased in young adults in the U.S. since 2010,[48] with one study showing a doubling of ever e-cigarette use (5.0% to 10.3%) from 2011 to 2012 in U.S. young adults aged 18-34.[49]
- **Adults**: Ever use of e-cigarettes in adults aged 18 and over rose from 0.6% in 2009 to 2.7% in 2010.[50] In a different study, ever use almost doubled from 3.3% in 2010 to 6.2% in 2011.[48] Rates have continued to rise. Data from 2012 show ever use at 8.1% among all adults[51,52] and rates in 2012-13 show ever use at 14.1%.[53]
- Data from other countries shows similar increases in ever use. In Great Britain, ever use increased from 2.7% in 2010 to 6.7% in 2012.[54] Data from a representative sample from the EU and member nations in 2012 estimated that 29.3 million European adults had tried an e-cigarette.[55] Two nationally representative samples of middle and high school youth in Korea show that ever use increased from 0.5% in 2008[56] to 9.8% in 2011.[57]

Current use of e-cigarettes is also growing for all age groups.[47,53,54,58]

- Recent data from national studies indicates that the prevalence of current e-cigarette use among youth is 2.1-2.3%,[47,58] 1.9% among adults overall[53] and 2.4% among young adults aged 18-24.[53]
- **Youth:** During 2011–2012, among all students in grades 6–12 in the U.S., current e-cigarette use increased from 1.1% to 2.1%.[47] Among middle school students, significant increases were seen among females (0.4% to 0.8%), males (0.7% to 1.5%), and Hispanics (0.6% to 2.0%).[59] Among high school students, significant increases were seen among females (0.7% to 1.9%), males (2.3% to 3.7%), non-Hispanic whites (1.8% to 3.4%), and Hispanics (1.3% to 2.7%).[59] A survey of high school students (grades 9-12) in Connecticut and New York (n=1345) also showed an increase in past 30-day e-cigarette use from February 2010 (0.9%) to June 2011 (2.3%) (p=0.05).[58] Cross-sectional studies of youth from other countries find single prevalence current use estimates of 8.2% in high school students in Poland[60] and 4.7% of middle and high school students in South Korea.[57]
- **Young Adults:** In a nationally representative sample of 60,192 U.S. adults aged 18 and over conducted in 2012-13, the highest rates of every day or someday use of e-cigarettes was among young adults aged 18-24 (2.4%) and adults aged 25-44 (2.4%).[53] Among adults classified as using every day, somedays, or rarely, use of e-cigarettes was highest among 18-24 year olds (8.3%), compared to 4.2% among adults overall. These estimates are consistent with measures of past-30 day use of e-cigarettes, particularly 2011 findings from the Legacy Young Adult Cohort Study, which using a nationally representative sample of young adults aged 18-34, reported 7.0% past 30-day use of e-cigarettes among every day or someday use of cigarette or other tobacco products.[61] It is also an increase from a population-based, prospective cohort study in the Midwest which found that 1.2% of young adults were current users of e-cigarettes in 2010-2011.[62] Among young adults, college students may have been early adopters of e-cigarettes with a 2009 study of North Carolina college students showing 1.5% past 30-day use of e-cigarettes[63] and a 2010-11 study in Poland showing current use among university students at 5.9% in the past 30 days.[60]
- **Adults**: In a national sample of U.S. adults in 2010, 1.2% had used e-cigarettes in the past 30 days.[50] In 2012, a nationally representative online survey detailed current use at 1.4%.[52] A 2012-13 national survey found that 1.9% of adults noted that they currently use e-cigarettes every day or some days and 4.2% use e-cigarettes every day, somedays, or rarely.[53]

In the U.S., e-cigarette trial is high among young adults.

- A nationally representative online sample found an inverse relationship between ever use of e-cigarettes and age, with younger ages more likely to have tried e-cigarettes.[64] A Midwestern prospective cohort study found that 7.0% of young adults were ever users of e-cigarettes in 2010/2011 (n=2,624). Among this cohort, those aged 20-24 were 1.5 times more likely to have used e-cigarettes compared with those 25-28.[62] Earlier studies using categorical ages did not find a significant relationship between age and ever use.[48,50]
- These findings are consistent with patterns of e-cigarette use outside of the U.S. A representative survey across the European Union and its member countries in 2012 found that participant age was one of the strongest correlates of e-cigarette use. Respondents aged 15-24 were 3.3 times more likely to have ever used an e-cigarette compared with those over age 55.[55] A study from 2010-2011 of high school and university students in Poland (n=20,240) found 23.5% of students aged 15-19 and 19% of those aged 20-24 had ever used an e-cigarette.[60]

ADDICTIVENESS

E-cigarettes deliver nicotine, but more research is needed to determine whether the levels of nicotine delivered support the potential for nicotine dependence.

- At least 14 clinical studies have examined nicotine biomarkers resulting from e-cigarette use.[2,6,9,13-16,20,26,29-32,65] Acute examinations demonstrate that nicotine delivery is dependent on the e-cigarette device and liquid type, as well as the rate at which the nicotine is delivered and the user's experience with e-cigarette use (i.e., naïve or not naïve).[2,9,30,32,65] Addiction liability is a result of the rapid peak level that is still only found in combustible tobacco products. Three clinical laboratory reports among experienced e-cigarette users indicated 10 puffs of a nicotine-containing e-cigarette reliably increased plasma nicotine within 5-10 minutes but levels were all significantly lower and reached a peak more slowly than that achieved with 10 puffs from a conventional cigarette.[9,31,65] The profile was highly variable and resembled that of NRTs which engender none to minimal nicotine dependence.
    - Farsalinos et al.[65] measured plasma nicotine levels among experienced e-cigarette users after use of first- and new-generation devices (administered on two separate days in random order) compared to cigarettes (data from Vansickel et al.[30]). During the first five minutes, participants were instructed to take 10 puffs of the device and to use ad lib for the following 60 minutes. Plasma nicotine levels were significantly higher after use of the new-generation than the first-generation device at all time points (see Figure 1), with levels being 70% higher at 20 minutes. Peak blood levels were found after 65 minutes for e-cigarette use [15.75 ng/ml (SE 1.2) for first-generation and 23.47 ng/l (SE 1.94) for new-generation][65] and after five minutes for cigarette use [18.8 ng/ml (SD 11.8)].[30] At five minutes, levels were 3-fold lower for new-generation and 4-fold lower for first-generation devices than smoking one tobacco cigarette. At 35 minutes, levels were equal between the tobacco cigarette and the new-generation device, but levels were still 73% higher for the first-generation device.[30,65]

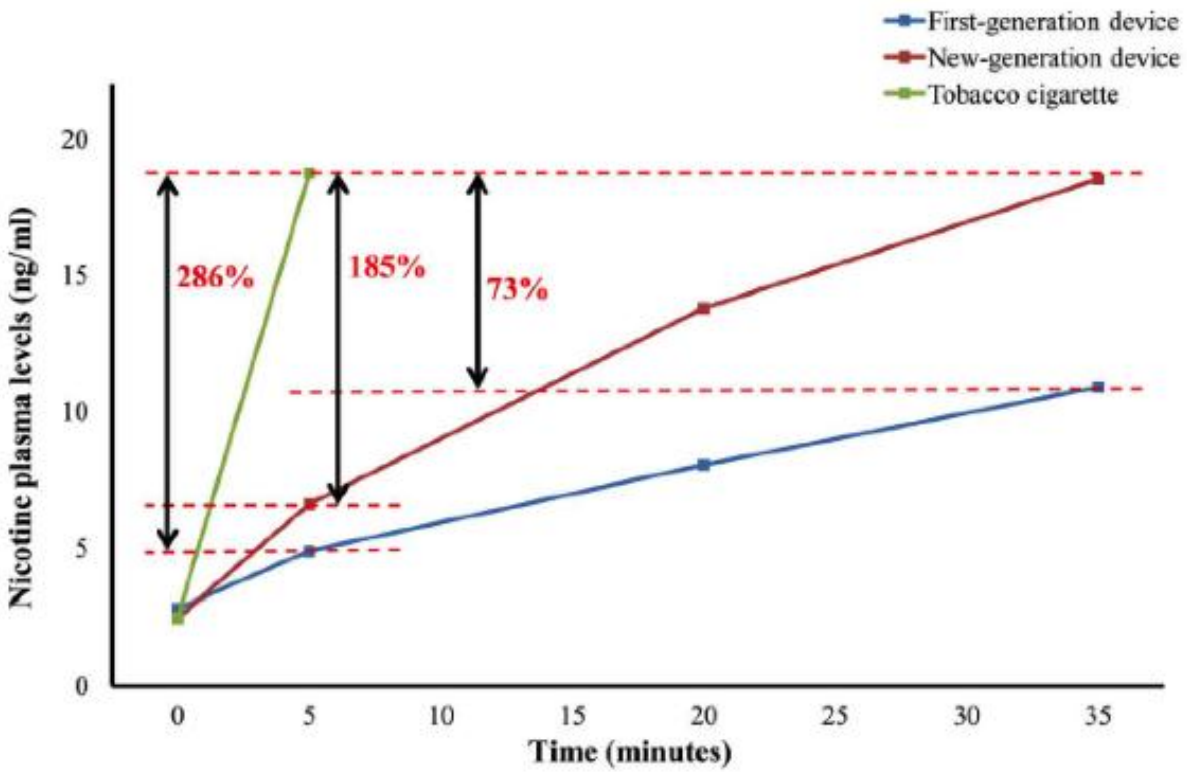

Figure 1. Comparison between tobacco cigarette and electronic cigarette devices in plasma nicotine levels.[65]

- Thirteen studies have examined the abuse liability and/or subjective effects of e-cigarette use.[2,6,9-13,16,29-32,34] These studies indicate e-cigarette use reliably decreases adverse symptoms related to tobacco abstinence (e.g., urges to smoke, irritability)[2,9-12,30,32] and increases ratings of satisfaction/pleasantness.[2,30-32,34] Among current cigarette smokers who had completed six 10-puff bouts with two types of e-cigarettes, results from a multiple choice procedure to determine the reinforcing efficacy of these products suggested that e-cigarettes were less reinforcing than own brand cigarettes.[32]

- Dependence is a major component of e-cigarettes' abuse liability. No well-validated scales of e-cigarette dependence are available, although at least one measure has been proposed.[66] Some characteristics to consider when determining e-cigarette dependence are as follows:[67]
    A. Total dose delivered
    B. Speed of uptake
    C. Amount of behavioral conditioning
    D. Social factors
    E. Taste and other sensations
    F. Adverse effects
    G. Price, availability, etc.

More research is needed to determine whether the levels of nicotine delivered support the potential for e-cigarettes to be sufficiently satisfying to displace combustible tobacco products and to determine what level of nicotine dependence may be acceptable at the population level.

- It is also unclear whether severity of dependence on a cleaner form of nicotine is of as much public health concern if the degree of addiction/dependence is de-coupled from the toxicity in combusted products (i.e., a delivery system that increases addiction liability, but with cleaner nicotine delivery). The net public health benefits versus harms would need to be determined by the degree to which a more addictive clean delivery system can successfully compete with combusted tobacco. That is, the benefits of a product with high addiction liability and with minimal harm (associated with clean nicotine) would outweigh harms associated with combusted tobacco if that product strongly encouraged complete switching away from combusted products. This would contrast with a lower addiction liability product that resulted not in complete switching but rather prolonged dual use (a public health benefit if the comparison is to lethal cigarettes and not to placebo or nothing).

Overall, e-cigarettes are associated with lower levels of nicotine exposure relative to cigarettes and bear some similarities to dependence-inducing tobacco products (e.g., cigarettes, smokeless tobacco) in terms of tobacco abstinence symptom suppression and positive subjective effects. To date, these data are inconclusive as to whether e-cigarettes do or do not support the potential for nicotine dependence/addiction.

PROGRESSION TO OTHER TOBACCO USE/DUAL USE

Across all age groups, the majority of ever and current e-cigarette users are current cigarette smokers.

- **Youth**: Data from the 2012 National Youth Tobacco Survey (NYTS) indicate that among ever e-cigarette users, 90.7% reported ever smoking conventional cigarettes and among current e-cigarette users, 76.3% reported current conventional cigarette smoking.[47] Additional analyses in the 2011 and 2012 National Youth Tobacco Survey showed that in 2011, 49.7% of current e-cigarette users were current smokers of conventional cigarettes and in 2012, 49.8% of current e-cigarette users were current cigarette smokers.[68] Current e-cigarette use was also associated with ever cigarette smoking (OR = 7.42; 95% CI, 5.63-9.79) and current cigarette smoking (OR = 7.88; 95%CI, 6.01-10.32). A study using only the 2011 NYTS data also showed that the odds of lifetime e-cigarette use were 58 times higher among current cigarette smokers (OR = 58.44, 95%CI: 34.71-98.39) compared to nonsmokers, controlling for age, gender, race/ethnicity, disposable income, living with a smoker and having a smoking friend.[69]
- **Young adults:** Among a sample of college students (n=4,444), current daily smokers (AOR=5.6; 95% CI 2.70, 11.60), current non-daily smokers (AOR=6.6; 95% CI 3.81, 11.2), and former smokers (AOR=5.7; 95% CI 3.37, 9.51) had higher odds of ever using e-cigarettes compared with non-smokers.[63]
- **Adults:** Increased use of e-cigarettes among current cigarette smokers has been documented in a number of national samples. One study using a consumer-based mail-in survey of U.S. adults in 2009 (n=10,587) and 2010 (n=10,328) found that current smokers and tobacco users were more likely than nonsmokers to have used e-cigarettes.[50] Similarly, a U.S. nationally representative cross-sectional survey conducted in 2010 among 2,649 participants aged 18 and older found that between 6.4% and 7.1% of current smokers have ever used an e-cigarette, compared to less than 1.0% of non-smokers.[64] A 2012 U.S. nationally representative survey of 10,041 adults aged 18 and older found that about 1% of never smokers had ever tried e-cigarettes, while over 32% of current smokers had used e-cigarettes.[52]
- Studies from other countries have documented similar findings. Across the European Union (n=26, 566), 20.3% of smokers, 4.4% of former smokers, and 1.1% of never smokers reported ever use of e-cigarettes in 2012. Smokers were 10 times more likely to have used e-cigarettes compared with non-smokers (AOR 10.63 95%CI 8.72, 12.95).[55] In Switzerland, one longitudinal

study among 5,081 young Swiss men found that among current smokers, 9.3% had used e-cigarettes, whereas among never smokers, 0.4% had used e-cigarettes.[70] One survey conducted with a cluster sample of 20,240 students at 176 nationally representative Polish high schools and universities between September 2010 and June 2011 found that current smokers were more likely to have used an e-cigarette in the last 30 days than nonsmokers (11.3% vs. 0.8%).[60] A South Korean nationally representative web-based survey of middle and high school students in 2011 found that current smokers were significantly more likely than never or former cigarette smokers to use e-cigarettes ($p<0.001$), and those who had smoked daily for the past 30 days had the highest rate of current e-cigarette use (50.8% vs. 0.6% of non-smokers) ($p<0.001$).[57]

Ever use among current smokers has grown substantially in the U.S. from around 9.8% in 2010 to 21.2% in 2011 to over 32% in 2012.[52,71]

- One national study of U.S. adults found that from 2010 (n=2,505) to 2011 (n=4,050), ever use of e-cigarettes increased among former smokers (2.5% to 7.4%) and among current smokers (9.8% to 21.2%).[71]
- A study of British adults found that in a survey of the general public, almost all of the growth in e-cigarette use came among current smokers. In this group, current use of e-cigarettes increased from 2.7% to 6.7% between 2010 and 2012. In this study, only 1.1% of former smokers and 0.1% of never smokers reported current e-cigarette use in 2012.[54]
- In cross-sectional studies of adult smokers and former smokers, ever use prevalence estimates differed substantially across study populations. In the U.S., in a broader U.S. sample of the ITC four country survey (n=6,110) 11% of respondents had ever used an e-cigarette,[72] while in Wave 8 of this study in 2010-11, 14.9% had done so (n=1,520).[73] In a separate national sample of smokers and former smokers (n=1,826), 20.1% had ever used e-cigarettes in 2011,[74] while in a sample of callers to 6 U.S. state quitlines in 2011-12, 31% reported using an e-cigarette.[75] Ever use estimates varied even more widely across non-U.S. samples with ever use among smokers and former smokers in 2010-11 at 2% in Australia, 4% in Canada, and 9.6% in the UK;[73] 26% in a convenience sample of smokers in Prague in 2011;[76] and 50% in a convenience sample of smokers in the Czech Republic.[77] In 2011-12, 7% of New Zealand current and former smokers reported purchase of an e-cigarette.[78]

E-cigarette trial has increased among non-daily smokers.

- A nationally representative, cross-sectional study of 3,240 adults in the U.S. in 2010 found that nondaily smokers (8.2%) and daily smokers (6.2%) were more likely to have ever used e-cigarettes compared with former smokers and never smokers.[79]
- One study conducted telephone interviews and web surveys among current and former smokers in four countries aged 18 and older from July 2010 to June 2011. Greater e-cigarette trial was reported among non-daily smokers.[73]

Greater e-cigarette use occurs among former rather than current cigarette smokers.

- A web-survey of current and former smokers (n=2136) found that more every day smokers (49.6%) had ever used e-cigarettes compared with some days smokers (43.6%) and former smokers (38.3%). However, former smokers had over three times the odds of being an established e-cigarette user (with over 50 lifetime uses) compared with current everyday smokers (AOR 3.24 95%CI 1.13, 9.30).[80]

- A longitudinal observational study of a convenience sample of adults aged 18 and over found that most e-cigarette users at baseline were former smokers (72%), and most were using e-cigarettes daily (76%).[81]
- In a U.S. national study, 11.5% of current smokers used e-cigarettes daily while 45.7% of recent former smokers used e-cigarettes daily.[52]

Dual use of e-cigarettes and other tobacco products, particularly cigarettes, is high.[49,82,83]

- Among U.S. adults in 2012, 10.6% of respondents reported being dual product tobacco users and 28.1% of dual users reported using e-cigarettes and another tobacco product. Only 0.4% of the adult population reported using e-cigarettes exclusively while 1.9% reported using e-cigarettes and cigarettes in combination.[82]
- A survey of high school students (grades 9-12) in Connecticut and New York (n=1345) showed an increase in dual use of cigarettes and e-cigarettes from February 2010 (0.8%) to June 2011 (1.9%) (p=0.03). The majority of e-cigarette users were dual users (87.5% in Wave 1, 82.8% in Wave 2, 83.9% in Wave 3).[58]
- In a nationally representative longitudinal study of young adults from 2011-2012, ever use of e-cigarettes rose from 5.0% at Wave 1 to 10.3% at Wave 3. However, most of this use was among dual or poly-tobacco users. Less than 1% of users at each wave used a non-combustible tobacco product exclusively.[49]
- In a sample of college students, ever use of e-cigarettes was associated with ever use of hookah in bivariate, but not multivariate analyses.[63]

Current evidence suggests a high level of dual (poly) use of e-cigarettes and cigarettes. More research is needed to understand the relationship between ever use and current use, extent of use of e-cigarettes (e.g., daily or occasional use), length of use of e-cigarettes over time and how these impact patterns of cigarette use.

Current use among ever users

- Studies among U.S. adults indicate that among ever users of e-cigarettes, current use of e-cigarettes ranged from 43% in 2010[50] to 18% in 2012.[52]
- In the U.S. in 2010-11, data showed that 6% of current or former smoking adults were current e-cigarette users and among those who had tried e-cigarettes, 37% were current e-cigarette users.[73]
- A nationally representative, cross-sectional study of 3,240 adults in the U.S. found that among those who had tried an e-cigarette, 19.7% were current users in 2010.[79]
- Among a nationally representative sample of adolescents in grades 6 to 12, of those who had tried e-cigarettes, 29.3% were currently using.[84]

Extent of Use

- A longitudinal observational study of a convenience sample of adults aged 18 and older found that at baseline most e-cigarette users were daily users (76%), and had been using for an average of three months. Of those, 98% of daily e-cigarette users at baseline were still using daily after one month and 89% after one year.[81]
- A web-based study of 179 e-cigarette users in Poland found that 98% of participants used e-cigarettes every day. A total of 25% reported that they were not smoking conventional cigarettes when they started using e-cigs.[85]

- A convenience sample of smokers (n=1,738) in the Czech Republic in 2012 found that 18.3% of smokers used e-cigarettes regularly and 14% used them daily.[77]

Length of Use

- One study conducted surveys among callers to six U.S. state quitlines from June 2011 through March 2012. Results indicated that among those who had tried an e-cigarette, 62% were short term (less than one month) users and 37% had used for less than a week.[75]
- In Britain, quantitative online surveys in 2010 and 2012 found that the proportion of smokers who had tried e-cigs but do not use them anymore increased between 2010 and 2012 (5.5% to 15.0%).[54]

CESSATION

To date, there have been no studies examining cessation of e-cigarettes, but there have been several studies on the use of e-cigarettes to quit smoking combustible cigarettes. A review of these studies is presented in Appendix F, focused on the continuum of harm and current evidence on the potential for e-cigarettes to serve as a harm reduction tool by inducing cessation of combustible cigarettes**.**

SUMMARY

Concerns about e-cigarette use largely focus on the potential for them to serve as a gateway to other tobacco products, particularly among youth, to delay or halt cessation altogether via prolonged dual use of e-cigarettes and cigarettes, or to induce relapse among former smokers. Existing studies demonstrate rapid increases in ever use and current use of e-cigarettes in the U.S. They do not, however, demonstrate an age gradient in e-cigarette use and at present, data suggests that youth and adults, overall, have a similarly low prevalence of current e-cigarette use,[47,53] with young adults (aged 18-24) exhibiting the highest levels of e-cigarette trial and current use. [53,64] It is also unknown whether e-cigarettes deliver sufficient nicotine to support nicotine dependence.

Existing research on co-use of e-cigarettes and more traditional tobacco products is cross-sectional and highlights that the majority of e-cigarette use – in all age groups – occurs among current cigarette smokers and that dual use of combustible cigarettes and e-cigarettes is high. Existing studies also highlight the possibility of greater e-cigarette trial among nondaily smokers and greater use among former cigarette smokers. While studies of youth have advanced the notion that use of e-cigarettes may encourage cigarette use,[68] exploration of alternate hypotheses must also be considered.[86-88] As noted by Niaura et al., "It is equally plausible that use of combustible cigarettes leads to use of e-cigarettes, because they are perceived as a less harmful alternative for smokers who are addicted to nicotine. The cross-sectional survey data do not prove that this is the process that explains the association, but they are just as consistent with it…"[88] Additionally, there is very limited evidence from the longitudinal observational studies to determine how e-cigarette use influences other patterns of tobacco use[49] and this is further complicated by the low population prevalence of e-cigarette use and limitations of the selected nature of the populations studied in observational studies. Evaluating the potential impact of e-cigarette use on youth cigarette uptake, for example, would require identification of youth who would start with e-cigarettes and move to combustible products <u>*over and above*</u> those youth who would smoke combustible products anyway. In short, the data required to document potential harms (or benefits) of a specific product at the population level will be difficult to acquire.

There are a number of factors to consider when interpreting the results of all of these studies. First, e-cigarette products are highly variable, so a method for systematic characterization of product characteristics is needed to be able to stratify them or rate them based on potential confounding variables. Second, there is no apparent definition of what constitutes an "experienced" user, which may complicate the interpretation of research findings. Definitions of user types should be operationalized and used consistently across studies. Third, the literature related to the health effects of e-cigarette use consists mainly of studies of small sample sizes, raising the issue of low statistical power to draw conclusions. Last, there exist gaps in the current evidence base, including longitudinal data and data on reasons for e-cigarette use that may help to explain trends. There also have been no published studies examining longer-term adverse health outcomes associated with e-cigarette use.

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APPENDIX C
REVIEW OF STUDIES ON HOOKAH

Hookah smoking is a centuries-old form of tobacco use also known as waterpipe, narghile, shisha, goza, and hubble-bubble.[1] Hookah is often smoked in group settings or at commercial establishments such as hookah bars,[2-4] and comes in a variety of fruit and candy flavors.[4-6] Hookah use has significant health effects, is highly addictive, and has disturbing ramifications for broader tobacco use initiation.[7]

Notes on Methods:
The findings below were compiled from literature searches on these topics, not a systematic review of the literature.

As described in our comments, studies are organized by five areas central to the public health standard: potential impact on 1) initiation; 2) progression to other tobacco products/dual use; 3) addictiveness; 4) cessation; and 5) health effects.

HEALTH EFFECTS

Hookah smoking poses significant health risks to users and non-users.

- On an individual level, hookah use is associated with significant nicotine and toxicant exposure including carbon monoxide, tobacco-specific nitrosamines, and polycyclic aromatic hydrocarbons.[6,8-10]
- Hookah smoke exposes users to many of the same toxicants found in cigarette smoke,[11,12] and may place users at risk for many of the same diseases as cigarette smokers.[7,13-15] Resultant work on the health effects of hookah use are limited but indicate that hookah users may have a greater risk of lung cancer and respiratory illness relative to non-hookah users[7,13-15] in addition to low birthweight,[7] periodontal disease,[7] and coronary artery disease.[16]
- Several lines of research also support serious secondhand smoke exposures resulting from hookah use[17,18] and extremely high levels of particulate matter in hookah cafes (i.e., indoor smoking venues).[19-21] Unlike other forms of tobacco smoking, indoor air quality measures often exempt or allow for hookah smoking under certain conditions despite these potential risks to employees and/or non-smoking consumers.[22]
- Hookah use is correlated with a variety of other health risk behaviors, such as polytobacco, alcohol and drug use.[2,23-27]

INITIATION (including youth and young adult prevalence)

Hookah or waterpipe tobacco smoking has experienced a surge in prevalence in the United States (U.S.), particularly among adolescent and young adult populations.[28-30]

- The National Youth Tobacco Survey began to include questions on hookah in 2011, and from 2011 to 2012 among high school students, prevalence rates increased from 4.1% to 5.4%.[31]
- In 2011, data from the Legacy Young Adult Cohort Study indicated that 17% of 18-34 year olds in the U.S. were ever hookah users, and 8% were past 30-day users.[32] Data from college and university students show that rates of initiation range from 13% to 23% over a one-year period or less.[25,33] Additionally, hookah use among young adults is not transient and approximately half of young adults who reported past-year hookah use at age 20 endorsed hookah use four years later.[34]

- Among adults aged 18 and older, data from the Tobacco Use Supplement in 2010-2011 suggest a low proportion of current hookah users (0.3%; http://appliedresearch.cancer.gov/tus-cps/results/data1011/table4.html). These data underscore hookah's tremendous popularity among youth, but likely mask increased use of hookah among young adults in this national sample.

Flavored hookah use is common among young users and may contribute to initiation.

- In its proposed tobacco deeming regulations,[35] FDA cited research by our group showing that hookah is one of the top three flavored tobacco products used by young adults and that flavored tobacco use may contribute to initiation and maintenance of tobacco use in this group.[36] This study highlighted that flavored hookah use was highly prevalent in young adults, with 59% of hookah users reporting that their typical brand was flavored, compared to 47% of little cigar/cigarillo/bidi users and 20% of cigar users.

ADDICTIVENESS

Hookah smokers are exposed to significant levels of nicotine during typical use which may be a catalyst to nicotine dependence and progression to regular tobacco use.

- A typical hookah use episode involves similar peak nicotine exposure levels as observed during cigarette smoking[6,9] and on a daily level of use, meta-analysis results indicate a nicotine absorption equivalent to approximately 10 cigarettes/day.[37]
- Hookah use has been associated with suppression of tobacco abstinence induced symptoms such as craving/urges to smoke and anxiousness,[6,8,38] characteristic of negatively reinforcing drug-taking behavior.[39] One experimental study highlighted the ability of hookah to suppress withdrawal symptoms comparably to cigarettes, noting the potential negative impact on smoking cessation.[38]
- While national estimates of hookah use are rising in several populations, particularly among young adults, less is known concerning the relative frequency and trajectories of use in the U.S.[30,31,40]
- One analysis of dependence in Egypt using two adapted dependence questionnaires for cigarette smokers (Fagerstrom Test for Nicotine Dependence[41]; Reasons for Smoking[42]) showed that male waterpipe smokers exhibited symptoms consistent with nicotine dependence observed among cigarette smokers.[43] One hookah-specific dependence questionnaire composed by researchers based in Lebanon included four sub-scales (nicotine dependence, negative reinforcement, and psychological craving) and differentiated between mild, moderate, and heavy hookah smokers.[44] This scale has yet to be validated outside of Lebanon- and Jordan-based samples.[45]
- Taken together, available data suggest hookah smokers are exposed to significant levels of nicotine during typical use, and nicotine dependence characteristics are observed in some hookah users.

PROGRESSION TO OTHER TOBACCO PRODUCTS/DUAL USE

Dual use of hookah and other combustible tobacco products is extremely high.

- Among U.S. adults in 2012, 10.6% of respondents reported being dual product tobacco users and 25.5% of dual users reported smoking cigarettes and hookah.[46]

- Young adults, aged 18-24 are more likely to use multiple tobacco products than any other age group[46,47] and dual use of cigarettes and hookah is one of the most common tobacco use profiles found in this age group.[2,40,48]
- Studies of young adults who use hookah indicate between 59%-75% are dual users of cigarettes and/or cigars.[30,48] Current dual use of cigarettes and hookah was more common than exclusive hookah use across 6 years of a cross-sectional survey (2006-2011) on one university campus (9.3% vs. 6.1%).[49] In a large sample of university students (N=105,012) surveyed in 2008-2009, 8.4% reported past 30-day hookah use and 58.7% had also used cigarettes and/or cigars.[30] In a study of over 5,000 college students, approximately 60% of alternative tobacco product (ATP) users and 60% of dual users of cigarettes and ATPs reported using hookah.[50]
- Recent work in the Legacy Young Adult Cohort Study showed that in a nationally-representative sample of 18-24 year olds, past 30-day use of cigarettes, little cigars and cigarillos and e-cigarettes was positively correlated with ever or past 30-day use of hookah at baseline.[51]

More research is needed to determine the order in which hookah and other combustible tobacco products are typically initiated.

- One longitudinal study in U.S. female college students indicated that pre-college hookah use may serve as a gateway into cigarette initiation or to resuming previous cigarette use, while pre-college cigarette use did not predict hookah use.[26] These findings were similar to a Danish study indicating that hookah use predicted progression to regular cigarette smoking among male youths over an 8-month period.[52]
- Our work in a national sample of young adults showed that among hookah never users, past 30-day use of cigarettes at baseline strongly predicted hookah trial at six-month follow-up.[51]

CESSATION

Hookah users indicate a high degree of confidence in quitting, but a low desire to quit smoking hookah.

- There have been few studies addressing hookah cessation, though one systematic review[53] and studies in U.S. samples[3,4] indicate that hookah users have a high degree of confidence that they can quit anytime, with a low desire to quit. One study conducted outside the U.S. also indicates that established users (i.e., individuals smoking hookah in hookah cafes) are less willing to quit and less likely to foresee challenges to quitting compared to beginning users (i.e., university students).[54]

Perceptions of hookah as less harmful and less addictive than cigarettes may contribute to low desire to quit hookah use.

- Of central importance to cessation, numerous studies (including one systematic review[53] and one review of the literature on waterpipe use in U.S. college students[55]) have documented the widespread perception that hookah is less harmful [3-5,56] and less addictive [3,4,56] than cigarettes. Perceptions that hookah is not as harmful and addictive as cigarettes may contribute to a low desire to quit.[57] Additionally, neither perceived nor factual knowledge of the harms of waterpipe use are associated with a desire to quit in young adults.[58]

To date, hookah-specific cessation interventions do not exist, despite the widespread use of hookah in the U.S.

- While studies have documented the need for hookah-specific cessation interventions,[57,59,60] a 2007 systematic review of cessation interventions for hookah smoking identified no completed intervention trials[61] and since then, only one pilot study has been published, demonstrating feasibility and effectiveness of this type of intervention.[62] The lack of cessation interventions for hookah use are concerning, given rapid increases in hookah use in the U.S., particularly among young people.

SUMMARY

The rapid increase in hookah use, especially among young people, as well as the significant health risks that hookah poses make it imperative that hookah tobacco is regulated by FDA. This will allow consumers to learn more about the health risks of the product and learn what is in the products, both of which may deter non-users from starting and encourage current users to quit.

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APPENDIX D
DATA ON E-CIGARETTE AND CIGAR MARKETING

The recent Surgeon General's Report (SGR) on tobacco use in youth and young adults provides conclusive evidence that tobacco industry advertising and promotional activities cause youth and young adults to start smoking,[1] based on earlier studies and reports.[2-4] Given the causal relationship between tobacco marketing and youth tobacco use, the lack of any proposal to ban tobacco product marketing to youth is a major omission in the Notice of Proposed Rulemaking.

In 2010, tobacco companies spent $8.05 billion marketing cigarettes[5] which increases tobacco use consumption[6] by attracting new users,[7,8-10] promoting continued use,[11,12] and building brand loyalty.[13] Numerous studies have documented the targeted marketing of cigarettes to youth.[14] Since our recommendations focus on the extension of youth marketing restrictions beyond cigarettes, we provide supportive evidence below on the marketing of two noncigarette products, cigars and e-cigarettes. We also highlight recent findings from Legacy studies – both published and unpublished – on these topics.

Cigars

The cigar industry markets cigars and little cigars/cigarillos using the same strategies used for marketing cigarettes.

Cigar smoking rose dramatically in the 1990s and 2000s.[15] Sales of cigars in the US increased by about 50% between 1993 and 1998 to nearly 4.5 billion due to increased cigar marketing, such as the use of cigars by celebrities and increased advertising and promotion of new cigar brands. Advertising and promotional activities increased the visibility of cigar smoking, "normalizing" cigar use. Tobacco companies promote cigar smoking as pleasurable, a symbol of status, wealth, and class. The Federal Trade Commission noted that expenditures by the cigar industry for "celebrity endorsements, and appearances, and payment for product placement in movies and television more than doubled between 1996 and 1997."[16-18]

- **Product**
  - Marketing strategies have given rise to shared attributes between small cigars and cigarettes. The packaging and marketing of small cigar products often mimic those of cigarettes. For example, small cigars are packaged in the traditional 20-cigarette soft pack. A 2004 advertisement for Smoking Joe's Small Cigars reads "the perfect everyday smoke," creating a message of smoke small cigars instead of your usual cigarettes.[19] Some research suggests that cigar users sometimes identify their products by the brand name and so respondents may not recognize their product as a cigar or tobacco.[19]
- **Price**
  - Small cigar manufacturers have capitalized (in marketing) on the visual similarities of small cigars and cigarettes. The U.S. federal tax rate for small cigars is the same as the tax rate for cigarettes at $1.01 per pack of 20, while the tax on each large cigar is 52.75% of the sales price, not to exceed $0.4026. Several little cigar brands have increased their weight slightly in order to qualify as "large cigars" under the federal tax code, making their products significantly cheaper.[20,21]
- **Place**

- Cigars and little cigars/cigarillos are largely sold in the same places as cigarettes and recent work by Legacy shows that little cigars and cigarillos were available for sale at more than 80% of tobacco retail outlets in Washington, DC.[22]
- Earlier research also confirms that cigars are marketed on websites, with limited youth access restrictions. A 2000 study examining 141 websites marketing cigars found that only 36 websites (25.5%) prohibited purchasing by minors. The websites offered low prices and 32% accepted money orders, cashier's checks, or COD orders. Almost 30% of websites included elements with potential youth appeal and only 3.5% of websites displayed health warnings.[23]

- **Promotion**
  - Lifestyle marketing: One study examining the content of two cigar "lifestyle" magazines between January 1992 and June 1998 found that 40% were cigar business-focused articles, and 12% were articles about cigar events. Celebrities were featured in 34% of articles and 96% favored cigar use. Only four (1%) articles featured health effects of cigars as a primary focus.[24] Of particular note, the appearance of cigar images in women's magazines and the portrayal of women cigar smokers increased significantly in the 1990s. Unlike cigarette images, most cigar images are not linked to a commercial product, which suggests that their promotion did not require direct advertising. The images that are displayed often feature well-known people who are admired by adolescents.[16,25] Not surprisingly, a 2002 study using data from the 1999 New Jersey Youth Tobacco Survey found that "new cigar users" are young people, including adolescent females.[16]
  - Celebrity endorsements: Recent work by Legacy showed that Snoop Dogg, a popular rapper, capitalized on his headline status at Coachella 2012 to unveil a new brand of cigars named Executive Branch. Building off his announcement at Coachella, he uploaded numerous photos to Instagram endorsing Executive Branch cigars, each garnering at least 10,000 likes, over 200 comments, and most likely additional uploads to social networks featured on Instagram, such as Pinterest, Twitter, and tumblr.[26]
  - Social media: Legacy researchers have also documented youth targeted marketing of little cigars via social media. In a study examining YouTube videos, of the 56 unique and eligible videos, 77% were pro LCC, 19% were neutral, and only 3% were anti LCC. Videos were primarily viewed by males, in the USA and Canada and most were amateur. The age range of the pro-LCC videos was 13-17. Common themes included where to purchase LCCs, their candy flavors, and that they are cheap or cheaper than cigarettes, and "smooth." The vast majority of information on YouTube about LCCs promotes their use. Given the lack of public education on LCCs, messaging promoting their use as an alternative to cigarettes could support misperceptions of their risk, and encourage initiation or continued use of the product.[27]
  - Point of sale: Research by our group also highlights the targeted marketing of little cigars/cigarillos, using both price and promotion at the point-of-sale, to vulnerable populations including young adults and African Americans in Washington, DC.[22] Of the 80% of Washington, DC stores that sold little cigars and cigarillos in September 2011 to March 2012, 95% sold these products in flavors, such as fruit, candy, and wine, and 13% sold menthol little cigars and cigarillos. Nearly 60% of these stores sold single little cigars and cigarillos, 74% sold little cigar and cigarillo packs, and 70% offered Black & Mild packs. Block groups in the higher quartiles for proportion of African American residents were significantly more likely to have little cigars and cigarillos available than were block groups in the lowest quartile. The average price per cigarillo for the lowest priced Black

& Mild pack was $0.91. Price per cigarillo in areas in the third quartile for proportion of young adults was significantly lower by $0.09 than was the first quartile. Price per cigarillo for cigarillos sold in 2-packs was significantly lower than were those sold in 5-packs; advertised prices were significantly lower than were non-advertised prices.[22]

E-CIGARETTES

E-cigarette advertising has becoming increasingly pervasive through youth-oriented channels with no safeguards to limit youth advertising exposure.

- Recent studies document rapid increases in promotional expenditures for e-cigarettes over the past three years[28,29] and advertising of e-cigarettes occurs predominantly through youth-oriented channels where marketing of other tobacco products is banned (e.g., television, sponsorships).[30,31] One study reported that on television alone, youth exposure to e-cigarette advertisements (ads) increased an estimated 256% from 2011 to 2013 and was primarily for blu e-cigarettes.[32] Specifically, blu was shown to be responsible for 81.7% of e-cigarette ads airing to youth aged 12-17 and 80.4% of those airing to young adults aged 18-24.[32] Some televised e-cigarette ads include celebrities and imagery of e-cigarette vapor that is indistinguishable from cigarette smoke.[32]
- An economics analyst group reported that e-cigarette advertising spending increased approximately 700% from 2010 to 2011 and approximately 400% from 2011 to 2012.[33] Advertising is particularly critical for promoting newly introduced products[34] and the first ad exposure has been shown to be the most influential for short-term sales or gains.[35] Although cigarette and other tobacco product manufacturers are prohibited from advertising on television or radio and from sponsoring sporting or entertainment events, e-cigarette companies are currently not subject to these regulations. Lorillard's blu eCigs and NJOY both have celebrity spokespeople in print, television, or internet ads (and in the case of NJOY, as shareholders). Lorillard has sponsored auto racing and music festivals.[31,36] These tactics provide opportunities for youth to be exposed to tobacco advertising and numerous studies have found that youth who recall more exposure to tobacco advertising are more likely to experiment with smoking or to hold favorable attitudes toward it.[3]

Legacy studies document high levels of youth and young adult exposure to e-cigarette advertising.

- Recently, Legacy undertook two studies and published a report entitled "Vaporized: E-cigarettes, advertising and youth," available for download on our website (http://legacyforhealth.org/content/download/4542/63436/version/1/file/LEG-Vaporized-E-cig_Report-May2014.pdf).[30] The first study surveyed youth and young adults using an on-line panel to measure their use and awareness of e-cigarettes and e-cigarette advertising. The second study analyzed media expenditure data to estimate whether e-cigarette advertising is potentially reaching young people.
- Results of our first study indicated that awareness of e-cigarettes among young people in this study was nearly ubiquitous, ranging from 89% for 13-17 year olds to 94% for young adults aged 18-21. For current or ever traditional cigarette smokers, awareness was even higher at over 95% among both youth and young adults. Similar levels of awareness held across racial and ethnic groups. Most respondents indicated they saw e-cigarette ads in the retail setting (convenience stores, supermarkets or gas stations) and our recent work highlights the penetrance of e-

cigarette advertising in the point-of-sale environment.[37] There was also high awareness of television advertising of e-cigarettes, with 45% of 13-17 year olds reporting they saw TV ads always, most or some of the time. Additionally 43% of 13-17 year olds responded that they saw e-cigarette ads always, most or some of the time when they were online. The numbers were even higher for young adults.

- The second study examined advertising expenditures and estimated audience exposure data for the 24 most popular brands of e-cigarettes from June to November of 2013 estimated by MediaCom, who obtained the data from paid subscriptions to proprietary data. This study highlights not only how much the e-cigarette industry spent on advertising overall, but also how much specific brands spent, on which channels they advertised, and who saw their ads. Overall, in that 6-month period, e-cigarette advertisers spent $39 million. Magazine advertising received the largest amount of money from that – 58%. National television advertising came in second at 19%. In that June to November 2013 timeframe, the three biggest-spending brand names were blu, NJOY and FIN – accounting for 86% of the overall spending. By far, blu spent the most at $22 million, with NJOY and FIN brands spending $5.6 million and $4.9 million respectively. VUSE, which was available only in Denver, CO as a test product during this time frame, spent $1.4 million.

Lorillard's widespread marketing of blu e-cigarettes is of particular concern given their targeted marketing of Newport cigarettes to youth, young adults and racial/ethnic minorities.

- Multiple studies confirm blu as the most advertised e-cigarette in the U.S. market.[28,32,38] blu's manufacturer, the Lorillard Tobacco Company, spent $12.4 million on ads in the first quarter of 2013, compared to $992,000 in the first quarter of 2012, and was expected to spend $40 million by the end of 2013 compared to $19.9 million in 2012.[33,39,40] Sales have also risen, with Lorillard reporting an increase in net sales for blu from $22 million in September 2012 to $177 million in September 2013.[41] blu is now available in over 127,000 U.S. retail outlets.[41] This is of concern because Lorillard also markets Newport cigarettes, a brand favored by youth and in particular, racial/ethnic minority youth.[42] National data from 2008-2010 indicate that Newport is the most prevalent menthol brand among White, Black and Hispanic adolescent (aged 12-17) and young adult (aged 18-25) smokers.[43] Newport represents a brand with a long history of targeted marketing to racial/ethnic minority youth and young adults.[1,44-46] The extent to which Lorillard's experience with Newport shapes the design of their marketing for blu portends the impact on youth and young adults and racial/ethnic minorities.
- Additional unpublished analyses from Legacy's randomized trial of exposure to e-cigarette advertising (described above) assessed the prevalence of prior exposure to the ads tested in the experiment and correlates of prior exposure. The half of participants (n=2,110) randomized to the exposure were presented with four different e-cigarette ads (blu, Fin, NJOY, White Cloud) and each ad was accompanied by questions assessing likeability, prior exposure to the ad, and prior use of the product advertised. The greatest percentage of participants in the experimental condition had previously seen the blu e-cigarette ad (19.0%), followed by the NJOY (8.7%), the White Cloud (4.4%), and FIN ad (2.0%). Participants in the experimental condition also reported the highest overall prior use of blu e-cigarettes (2.9%), followed by NJOY (1.8%), White Cloud (1.4%), and FIN (0.4%). Compared to all other groups, exposure to the blu ad was significantly higher among Black respondents (34.0%) and participants who had been exposed to other tobacco advertising, including visiting a tobacco company website (37.9%).

If the three biggest tobacco companies spend equally on e-cigarette advertising at 2013 levels, 97% of young and young adults aged 12-24 will be exposed to these ads in 2014.

- VUSE's advertising expenditures are likely to rise as they roll out their product nationally[47] and Philip Morris recently announced that it will launch its e-cigarette brand, MarkTen, nationwide in the second quarter of 2014.[48] According to data from Legacy's second study in the "Vaporized" report,[30] blu, Lorillard's e-cigarette brand, spent approximately $50 million on advertising in 2013. Legacy commissioned additional analyses from MediaCom to estimate youth and young adult exposure to e-cigarette advertising in 2014. Based on blu's 2013 print and television advertising schedule, if VUSE (R.J. Reynolds' e-cigarette brand), blu and Mark Ten (Altria's e-cigarette brand) each spend approximately $50 million in 2014 and assuming all other advertisers spend the same amount in 2014 as they did in 2013, an estimated 97% of youth and young adults aged 12-24 would be exposed to this advertising. That is 22.4 million, or 92%, of 12-17 year olds, and 28.9 million, or 97%, of 18-24 year olds. These findings highlight the potential of Big Tobacco to drive the messages people see about these products and the rapidity with which youth and young adult exposure to these messages will occur if unrestricted.

Unpublished data from a recent Legacy study suggests that exposure to e-cigarette advertisements is associated with curiosity and susceptibility to try an e-cigarette, as well as e-cigarette trial in young adults.

- Given the evidence surrounding tobacco advertising exposure and cigarette smoking behavior,[1-4] a central concern is that e-cigarette advertising will have a similar impact on e-cigarette initiation among youth. Legacy researchers collaborated on a randomized controlled trial to assess the impact of a brief exposure to e-cigarette ads on perceptions, curiosity, susceptibility, intention, and subsequent use of e-cigarettes in a national, longitudinal sample of 4,232 young adults aged 18-34 in January 2013 from GfK's KnowledgePanel®, of which 74% provided follow-up data at six months. Questions on e-cigarette perceptions, curiosity, susceptibility, and intention to use e-cigarettes were asked following ad exposure in the exposed group and in a similar location in the survey in the unexposed group; e-cigarette trial among never e-cigarette users was assessed at six-month follow-up. Post-stratification weights were used to offset any non-response or non-coverage bias and produce nationally representative estimates. Among the subgroup of young adults aged 18-24 who had never used cigarettes or e-cigarettes at baseline (weighted n = 891), exposure to the e-cigarette ads was associated with greater curiosity to try an e-cigarette compared to the control group (10.1% exposed vs. 3.6% unexposed; $p = 0.016$), greater susceptibility to use an e-cigarette (23.8% exposed vs. 14.5% unexposed; $p = 0.015$) and a greater likelihood of e-cigarette trial at six-month follow-up (5.9% exposed vs. 1.5% unexposed; $p = 0.03$). Cigarette trial at six months was slightly higher among those exposed (11.4%) to the e-cigarette ads versus unexposed (6.9%), but the difference was not statistically significant ($p = 0.14$). Exploratory analyses supported that curiosity to try an e-cigarette fully mediated the relationship between study group and e-cigarette trial.

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APPENDIX E
SYSTEMATIC REVIEW OF STUDIES ON FLAVORED TOBACCO PRODUCTS

Notes on Methods:
The findings below were, in part, compiled from a systematic review designed to summarize research on the use, attitudes, knowledge and perceptions of tobacco products with characterizing flavors. Eligible studies included experimental studies, quasi-experimental studies, observational studies (including case control, cohort and cross sectional studies), case reports, case series, qualitative studies and mixed methods studies in this review. Five electronic databases were searched on September 19, 2013. Other sources were obtained by emailing experts, searching grey literature and hand searching citations of included articles. This review is part of a dissertation and publication of these findings will be forthcoming.

Type of Exposure/Intervention: We included studies that examined any type of tobacco product with a characterizing flavor, excluding menthol. We excluded studies that examined the use of flavored products without tobacco (such as nicotine replacement products); however, electronic cigarettes were included for this review. Primary exposures and interventions of interest for this review assessed the use of a tobacco product with a characterizing flavor, or the attitudes/knowledge/perceptions of such products. Attitudes/knowledge/perceptions were defined broadly; these concepts included any rating of the products of interest, indication of having positive or negative perceptions of these products, and beliefs about these products.

Type of Outcomes: Because the research question for this review does not investigate a specific association but, rather, is intended to be a descriptive synthesis, we focused on outcomes at the "above skin" level; studies examining cellular, genetic and biological-level outcomes were excluded.

The results of the systematic review were supplemented with additional searches of PubMed and Google Scholar on June 6, 2014 to obtain all of the data presented below.

As described in our comments, studies are organized by five areas central to the public health standard: potential impact on 1) initiation; 2) progression to other tobacco products/dual use; 3) addictiveness; 4) cessation; and 5) health effects.

HEALTH EFFECTS

Flavored tobacco use results in detrimental health effects, including acute illness.

- A number of case studies have highlighted the detrimental health effects – including pneumonia, hemorrhagic pulmonary edema, bronchitis and hemoptysis – that may result from flavored tobacco use.[1-3] One study assessing dental health among betel quid users in Bangladesh showed that individuals who chewed betel quid with tobacco flavored with masala had significantly higher scores on four clinical parameters assessing periodontal status (bleeding on probing %, probing depth, clinical attachment level, missing teeth %) when compared with chewers of betel quid with tobacco only.[4] Another study of adult smokeless tobacco users in the U.S. found that flavored products did not appear to lead to greater exposure of carcinogens compared to nonflavored products.[5] These studies elucidate potential questions for future research around the potential health risks resulting from the use of flavored tobacco products.
- Malson et al. (2002) examined heart rate, blood pressure and exhaled carbon monoxide of participants after smoking an American Spirit cigarette, a strawberry Irie bidi, an unflavored Sher

bidi and a conventional cigarette.[6] They found that heart rate increased by 8.5 ± 6.1, 6.7 ± 7.7, 7.1 ± 7.5 and 2.5 ± 6.4 bpm, respectively, two minutes after smoking. Exhaled CO was measured 15 minutes after smoking, and increased by 3 ± 2.7, 5 ± 3.1, 3.4 ± 1.3 and 4.6 ± 1.8 ppm, respectively. At 60 minutes after smoking, CO following the strawberry Irie bidi was significantly higher than the conventional cigarette ($p < 0.05$). Increased blood pressure did not differ by cigarette type. An additional study by Malson et al. (2003) found no difference between a clove cigarette and a conventional cigarette with regard to changes in heart rate, systolic blood pressure or diastolic blood pressure.[7] CO increased more after the clove cigarette (6.0 ppm ±3.4) than the conventional cigarette (4.5 ppm ±3.1), but this difference was not significant.

Flavored tobacco use may also facilitate use of other potentially harmful non-tobacco products.

- Participants in one qualitative study noted that flavoring of cigar products serve to conceal the smell of marijuana when cigars are used for blunts.[8]

Flavored tobacco use may increase exposure to harmful chemicals beyond that of nonflavored tobacco products.

- A recent chemical analysis of flavoring additives in tobacco products reported that certain harmful chemicals were found in high concentrations in flavored tobacco products, supporting evidence pointing towards the potential unique harm that flavoring additives in tobacco products may pose.[9]

Some evidence suggests that using flavored tobacco products may cause increased or unique harm when compared to nonflavored tobacco use. Additional research is needed to further investigate this phenomenon.

INITIATION (INCLUDING YOUTH AND YOUNG ADULT PREVALENCE)

Sixteen studies have examined the use of flavored tobacco products by age or by grade. Findings from many of these studies are presented in Table 1.[5,7,10-23]

In 2011, more than six percent of all U.S. youth used flavored tobacco resulting in nearly 1.6 million flavored tobacco users in 2011.

- According to the 2011 National Youth Tobacco Survey, among youth in grades 6-12, 3.3% (95% CI: 2.9-3.9) were current users of flavored little cigars, 4.2% (95% CI: 3.5-5.1) were current users of flavored cigarettes, and 6.3% (95% CI: 5.5-7.3) of either flavored little cigars or flavored cigarettes.[14] Given that there were 25.1 million youth (aged 12-17) in 2011,[24] this means that nearly 1.6 million youth were flavored cigarette or little cigar users.
- Earlier data from the National Youth Tobacco Survey presented estimates of current (past 30-day) use of bidis (leaf-wrapped, flavored cigarettes from India) and kreteks (clove cigarettes) among middle and high school students. In 2000 and 2002, bidi use was 2.4% among middle school students and kretek use was 2.1% and 2.0%, respectively.[10] Among high school students, bidi use was 4.1% in 2000 and 2.6% in 2002 and kretek use was 4.2% and 2.7%, respectively. These estimates are consistent with between 500,000 and 1,000,000 youth using these specific flavored products in the early 2000's.
  One community-based study examining the use of flavored tobacco products in youth showed that 8.9% of selected middle school and high school students in Massachusetts had ever used kreteks in 2001 and 3.1% reported current use,[20] with higher proportions of ever use (20.1%) and current use (8.1%) among students who had heard of kreteks/clove cigarettes.[19]

- Another study reporting use of flavored products in a young sample showed that among young adult military recruits surveyed from October 1999 to September 2000, 24.8% reported ever use of kreteks and 3.0% reported current use of kreteks prior to entry into Basic Military Training.[22] Similarly, 14.7% reported ever use of bidis and 2.0% reported current use of bidis, though the authors did not specifically note these estimates as referring to flavored bidi use.

Among youth and young adult tobacco users in the U.S., the prevalence of flavored tobacco use may be as high as 95% for some products.

- Several studies have documented the use of specific flavored tobacco products among youth and young adult tobacco users.[11,15,21,23] See Table 1 for more detail.
- Multiple tobacco products: National data from the Legacy Young Adult Cohort Study indicate that in 2011, 18.5% (95% CI: 15.2-22.2) of young adults aged 18-34 who reported past 30-day use of any tobacco product used a flavored product.[23]
- Cigarettes: The 2004 National Youth Smoking Cessation Survey found that past 30 day use of any flavored cigarette (Camel Exotic Blends, Kool Smooth Fusion, or Salem Silver Label) among current smokers was 11.9% (95% CI: 10.2-13.8) among 17-26 year olds.[15] In 2011, the Legacy Young Adult Cohort Study estimated only 1% of current cigarette users smoked flavored cigarettes,[23] likely due to the 2009 FDA ban on flavored cigarettes. The 2009 ConsumerStyles survey found that ever use of flavored cigarettes among adults aged 18+ who had heard of flavored cigarettes was 27.4% (95% CI: 20.9-33.9).
- Cigars: Our 2011 data from the Legacy Young Adult Cohort Study showed that among current little cigar/cigarillo/bidi users, 35% (95% CI: 25-47) used flavored little cigars/cigarillos/bidis and among current cigar users, 13% (95% CI: 8-21) used flavored cigars in the past 30 days.[23] A study using data from the 2010-2011 National Survey on Drug Use and Health did not directly report the prevalence of flavored cigar use, but instead the proportion of respondents using a brand that also manufactures flavored cigars.[11] In this study, 75.1% (95% CI: 73.0-77.1) of cigar smokers aged 12+ reported smoking a usual brand that makes flavored cigars.[11] Among young cigar smokers aged 12-17, this reached 95.1% (95% CI: 93.0-96.6) and in young adult cigar users aged 18-25, using a brand that makes flavored cigars was 88.7% (95% CI: 87.2-90.1). Another national study using the 2009-2010 National Adult Tobacco Survey reported that 9.1% (95% CI : 7.8-10.5) of 18-24 year old ever cigar smokers and 57.1% (95% CI : 51.1-62.5) of current cigar smokers reported past 30-day use of flavored cigars. A 2009 national study of adult consumers also showed that 31.5% (95% CI: 27.3-35.7) of those aged 18+ who had ever heard of flavored cigars had used them.[17]
- E-cigarettes: Data from the Legacy Young Adult Cohort Study in 2011 reported the prevalence of flavored e-cigarette use among 18-34 year old current e-cigarette users at 13% (95% CI: 6-27).
- Hookah**:** Data from an online survey of North Carolina college students indicates that 90% of those who had ever smoked tobacco from a hookah reported ever use of flavored hookah.[21] The Legacy Young Adult Cohort Study also showed in a national sample of 18-34 year olds that 50% of current hookah users reported using flavored hookah.[23]
- Smokeless tobacco products: Our data from the Legacy Young Adult Cohort Study examined the prevalence of flavored smokeless tobacco use among 18-34 year old tobacco users which ranged from 6% (95% CI: 2-18) among current chewing tobacco users to 8% (95% CI: 3-21) among dip/snuff users and 13% (95% CI: 2-49) among current users of dissolvable tobacco products.[23]
- Pipes: Data from the Legacy Young Adult Cohort Study in 2011 reported the prevalence of flavored pipe tobacco use among 18-34 year old current pipe smokers as 38% (95% CI: 18-63).

Flavored tobacco use increases with age among middle and high school-aged youth.

- Evidence shows that older adolescents are more likely to use flavored tobacco products compared to younger adolescents.[10,14,20] This age gradient is consistent across multiple flavored products, including little cigars,[14] cigarettes,[14] bidis,[10] and kreteks.[10,20]

Frequency of smoking among youth may be higher for flavored tobacco users of certain products.

- King et al. (2014) found that middle and high school students currently smoking flavored cigarettes were more likely than nonflavored cigarette smokers to have smoked every day in the past 30 days leading up to the survey (33.9%, 95% CI: 28.3-40 versus 17.2%, 95% CI: 14.5-20.4).[14] While this relationship was not seen in flavored and nonflavored little cigar smokers, flavored little cigar smokers were more likely than nonflavored smokers to have smoked 10 to 29 of the past 30 days leading up to the survey (9.5%, 95% CI: 6.5-13.7 versus 7.4%, 95% CI: 5.5-9.8).

The prevalence of flavored tobacco use is higher in youth and young adults than adults.

- National samples show that young age is associated with flavored tobacco use. Findings from the 2010-2011 National Survey on Drug Use and Health examined brand preference by age, and found that preference for a cigar brand that makes flavored products was greater among youth aged 12-17 (95.1%, 95% CI: 93.0-96.6) and young adults aged 18-25 (88.7%, 95% CI: 87.2-90.1) when compared with 26-34 year olds (7.2%, 95% CI: 68.1-75.9) and individuals aged 35 and older (63.2%, 95% CI: 58.5-67.6).[11] The 2004 National Youth Smoking Cessation Survey found a similar trend.[15] The overall prevalence of current flavored cigarette smoking (Camel Exotic Blends, Kool Smooth Fusion, or Salem Silver Label) was 11.9% (95% CI: 10.2-13.8). Current prevalence of flavor cigarette smoking was highest among individuals aged 17 (22.8%, 95% CI: 14.8-33.4) and 18-19 (21.7%, 95% CI: 17.1-27.3), and lowest among the oldest age group, 24-26 year olds (9.0%, 95% CI: 6.2-13.1). In a study using data from the 2002 and 2003 waves of the National Survey on Drug Use and Health, flavored-only cigarette use (i.e., bidi and/or cloves) was also shown to be significantly higher in youth aged 12-17 compared to conventional-only cigarette use or use of both specialty and conventional cigarettes ($p<0.001$).[12]

The prevalence of flavored tobacco use is also higher in young adults than older adults.

- Estimates from the 2009-2010 National Adult Tobacco Survey, administered to 118,215 people, found that the overall current prevalence of flavored cigar smoking among ever cigar smokers was 2.8% (95% CI: 2.6-3.1).[13] Prevalence decreased with increasing age, from 9.1% (95% CI: 7.8-10.5) among 18-24 year olds to 0.2% (95% CI: 0.1-0.3) among individuals aged 65 and older. The 2004-2005 Assessing Hardcore Smoking Survey similarly found that current prevalence of these products was highest in its youngest respondents, 25-39 year olds (11.2%, 95% CI: 5.9-20.4) and lowest in its oldest respondents, individuals aged 55 and older (0.8%, 95% CI: 0.2-2.4).[15] A study conducted among young adult military recruits also found that individuals under 20 years had a lower prevalence (2.9%, 95% CI: 2.6-3.2) of current kretek use as compared to individuals aged 20 or older (3.2%, 95% CI: 2.8-3.6).[22] Flavored tobacco use prevalence by age or grade, and results from statistical tests that quantitatively examine the relationship between age and flavored tobacco use, can be found in Table 1.[7,10-23] Additional measures of prevalence that did not examine use by age can be found in Table 2.[5,20,22,23,25,26]
- Multivariable analyses controlling for other correlates of flavored tobacco use confirm higher flavored tobacco use among younger adults compared to older adults. Our work in the Legacy Young Adult Cohort Study showed that current tobacco users aged 18-24 reported greater use of flavored products compared to those aged 25-34 (23.8% vs. 14.8%, $p = 0.0128$) and that

younger age (18-24 vs. 25-34) remained a significant correlate of flavored tobacco use even after controlling for gender, race/ethnicity, education, and any menthol tobacco product use (OR = 1.89, 95% CI: 1.14-3.11).[23] A study of flavored cigars in the 2010-2011 National Survey on Drug Use and Health showed that youth aged 12-17 had a nine-fold increased odds and young adults had a nearly four-fold increased odds of using a brand that makes flavored cigars, compared to adults aged 35 and older, controlling for gender, age, race/ethnicity, cigarette use, blunt use and cigar frequency.[11]

Flavoring appears to drive tobacco use in youth and young adults.

- Qualitative data collected from adolescents and young adults support the idea that the flavoring drives tobacco use in these populations.[18,27,28] An additional study found that middle and high school students who endorsed statements that kreteks taste good and smell good were significantly more likely to use kreteks when compared with students who did not endorse these statements (OR=51.64, 95% CI=23.85-103.16 and OR=2.29, 95%=1.22-4.30, respectively).[19] Statements that touched on perceptions of harm, price and the "buzz" effect of kreteks did not predict use, which perhaps emphasizes the role that taste and smell play in driving tobacco use. Similarly, "taste and variety of flavors" was the most frequently cited positive aspect of e-cigarettes noted among respondents to an online internet survey of e-cigarette users.[29]

Across age groups, fruit and mint flavors appear to be the most popular in tobacco products.

- Of eight studies providing data on preferred flavor of tobacco across age groups,[25,30-36] fruit and mint flavors were found to be popular, mentioned in seven of these studies.[25,30,31,33-36] Of concern, a recent study of flavor chemicals and their levels in several brands of candy, Kool Aid, and tobacco products reveals that the chemical-specific flavor sensory cues associated with fruit flavors in candy are the same as those found in tobacco products.[37]

Altogether, the evidence shows that young age is associated with flavored tobacco use. This finding is stable across multiple national studies. Literature examining flavored tobacco use by age is consistent with the data on menthol cigarette use; prevalence of menthol cigarette use is higher in youth than in young adults and adults.[38-41] While a number of studies indicate that menthol cigarette use is higher in younger adolescents as compared to older adolescents,[42-45] existing studies of flavored tobacco use show that older adolescents are more likely to use flavored products.[10,14,20] There are no "gold standard" studies that address the mechanisms by which flavored tobacco use might encourage tobacco initiation. Additional research is needed to investigate these questions in generalizable populations.

ADDICTIVENESS

Evidence suggests that flavored tobacco use facilitates greater nicotine dependence in youth smokers.

- Huh and Timberlake (2009) compared dependence symptoms among youth and young adult smokers of conventional cigarettes versus smokers of specialty cigarettes, such as bidis and cloves, which are flavored.[12] As noted above, this study documented a higher prevalence of specialty-only cigarette use among youth and that specialty-only users smoked, on average, significantly fewer days per month compared to conventional smokers (3.8 days vs. 19.8 days). When examined overall, specialty-only smokers exhibited fewer dependence symptoms than their more established counterparts, but after accounting for smoking frequency in the past month, higher rates of nicotine dependence were observed in the specialty-only smokers (i.e., shorter time to first cigarette). This study suggests that flavored tobacco use facilitates nicotine dependence among young smokers, despite low smoking frequency.

- Evidence in adults suggests no difference in nicotine dependence between flavored and nonflavored products; this may also be due to a lower prevalence of flavored tobacco use in adults compared to youth. Oliver et al. examined differences in measures of addiction for flavored and nonflavored smokeless tobacco users.[5] Flavored tobacco did not appear to lead to greater dependence or increased exposure to nicotine in this population. When controlling for duration of use (hours of use/day), there was no significant difference in dips per day for flavored versus nonflavored users; and, after adjusting for dips per day, there was no differences in cotinine levels between flavored and nonflavored users. After adjusting for duration of use, use of smokeless tobacco within 30 minutes of awakening was higher among nonflavored users (74.7%) than flavored users (63.5%) ($p=0.73$). A study of nicotine biomarkers by Malson et al. (2002) found that plasma nicotine increased by 32.1, 26.0, 21.4 and 18.5 ng/ml when measured two minutes after participants smoked an American Spirit cigarette, strawberry Irie bidi, unflavored Sher bidi and a conventional cigarette, respectively.[6] At two minutes, plasma nicotine levels for the strawberry Irie bidi were significantly higher than levels for the conventional cigarette ($p<0.05$). In another study, Malson et al. (2003) compared the physiological effects of smoking clove versus conventional cigarettes.[7] The authors of this study found no significant difference in plasma levels of nicotine increase when comparing the two products. Greater absorption of nicotine from a flavored tobacco product may facilitate greater dependence.

E-cigarette flavors, in particular, may have appeal for adult cigarette smokers.

- Two studies related to e-cigarette flavors indicate that current[25,46] and former[25] adult smokers demonstrate interest in a variety of e-cigarette flavors. In an international online survey of e-cigarette users, 73.1% of respondents overall noted that they liked the variety of different flavors, with significantly more former cigarette smokers endorsing this item compared to current cigarette smokers (73.9% vs. 65.1%, $p < 0.001$).[25] There was no difference across former and current smokers in the importance of flavors for reducing cigarette consumption or quitting in this study. Former smokers were also more likely than current smokers to report that e-cigarette use would be less enjoyable (70.1% vs. 56.5%; $p<0.001$) and more boring (46.2% vs. 40.7%; $p = 0.036$) if flavor variability were limited, but there was no difference in response regarding the likelihood of reducing cigarette consumption or quitting if flavors were limited in former compared to current cigarette smokers. A recent unpublished study conducted in the U.S. using an internet research panel showed that adult smokers demonstrated moderate interest in e-cigarette flavors and that interest varied by individual flavors within flavor classes, with the highest interest for tobacco, menthol, and vanilla bean flavors.[46] In contrast, nonsmoking teens reported low interest in any of the e-cigarette flavors.

Analyses examining the addictiveness of flavored versus nonflavored tobacco products are heterogeneous with regard to the indicators used to measure addictiveness and products examined. Together, the results of these studies suggest that some flavored tobacco products may facilitate greater dependence than their nonflavored counterparts among youth. However, this finding was not seen consistently across youth and adults, nor over the small number of analyses that have investigated this issue thus far. Emerging research suggests that e-cigarette flavors, in particular, may have appeal for adult cigarette smokers, but further research is needed to determine whether these flavors impact appeal, addictiveness, and tobacco use patterns, including switching and cessation away from cigarettes.

PROGRESSION TO OTHER TOBACCO PRODUCTS/DUAL USE

Results from the following studies are presented in **Table 2**.

Flavored tobacco use is correlated with dual use of other tobacco products.

- Cigarette smoking[22] and smokeless tobacco use[26] have been shown to be associated with a significant increase in kretek use, and among young adult tobacco users, use of any menthol product has been shown to be associated with a significant increase in any current non-menthol flavored tobacco use.[23]
- Among e-cigarette users, results from an online survey showed that tobacco flavors were most popular at e-cigarette initiation, followed by fruits and sweets, among the total sample.[25] Current smokers were significantly more likely to use a tobacco flavored e-cigarette compared to former smokers (53.0% compared to 43.1%).[25] Former smokers are significantly more likely to use sweet and fruit-flavored e-cigarettes (63.9% and 71.7%, respectively) as compared to current smokers (52.0% and 62.8%, respectively).[25] In another online survey of e-cigarette users, flavor preference for e-cigarettes was not found to differ between current and ex-smokers.[34]
- One study examined smoking initiation precedence among smokers of kretek and other combustible tobacco products (cigars, bidis, and cigarettes).[20] In all cases, the percent of individuals who initiated with kreteks was lower than the percent who initiated with the comparator product. However, it has been noted in a qualitative study that kreteks can be difficult to locate for purchase and can therefore be inconvenient to use, despite positive perceptions that respondents had of these products.[18] Another study also found that accessibility to kreteks was an important factor impacting youth use of these products; middle and high school students in Massachusetts found that the statement "kreteks are cheaper than cigarettes" was only endorsed by 5.2% (95% CI: 4.1-6.4) of the sample.[19] Thus, these results may not apply to other flavored products that are easier to locate for purchase, or that are cheaper than cigarettes.
- Eight other studies were identified that collected prevalence data on both flavored and nonflavored products.[7,10,13,15-17,19,21] While these studies do not provide data on dual use, the authors of these papers may be able to provide additional data to FDA on dual use.

Early findings suggest that flavored tobacco use facilitates maintenance of tobacco use.

- Data from current smokeless tobacco users examining their flavored/nonflavored brand choices over time – from initiation to regular use to current use – suggests that flavoring may play a role in the maintenance of smokeless tobacco use.[5]

CESSATION

Among youth, flavored tobacco use is correlated with lower quit intentions compared to nonflavored use.

- King et al. examined quit intentions among U.S. middle and high school current smokers of flavored and nonflavored little cigars and cigarettes.[14] Among current cigar smokers, cigarette smokers, and cigar or cigarette smokers, individuals using flavored products were consistently less likely than those using nonflavored products to have quit intentions within the next 30 days. Across all three groups, individual using flavored products were also more likely than those using nonflavored products to not be thinking about quitting. These trends varied among individuals intending to quit within the next six months or within longer than the next six months. The results of this survey can be seen in **Table 3** (data extracted directly from King et al. (2014)).

There is limited research examining the effects of flavored tobacco use on tobacco cessation among adults.

- One study of adult smokeless tobacco users found no difference in the median number of quit attempts among current users of flavored and unflavored smokeless tobacco products.[5]
- An online survey of e-cigarette users showed that use of some e-cigarette flavors was correlated with cigarette smoking status, as former smokers were significantly more likely to use sweet and fruit-flavored e-cigarettes (63.9% and 71.7%, respectively) as compared to current smokers (52.0% and 62.8%, respectively).[25] Another online survey of e-cigarette users showed that flavor preference for e-cigarettes was not found to differ between current and ex-smokers.[34]

SUMMARY

Together, the evidence shows that young age is associated with flavored tobacco use. This finding is consistent over time and has been replicated across multiple national datasets. Literature examining flavored tobacco use by age is consistent with the data on menthol cigarette use, as prevalence of menthol cigarette use is higher in youth than in young adults and adults,[38-41] and similar to menthol, early research indicates that flavored tobacco use contributes to the frequency of tobacco use[14] and nicotine dependence[12] in youth and young adults. Studies also indicate that dual use of flavored tobacco products and other tobacco products is common and that the prevalence of flavored tobacco use for some products is as high as 95% in youth tobacco users.[11] There is little data on cessation behaviors among flavored tobacco product users, but among youth cigar smokers, recent evidence shows that flavored use is associated with lower intentions to quit smoking. Flavored tobacco product use may also pose unique health risks by increasing exposure to harmful chemicals used as additives[6,7,9] or by facilitating other substance use, particularly marijuana.[8] As a result, it is very likely that a ban on flavored tobacco products would reduce nicotine dependence at the population level, largely through reductions in youth and young adult initiation of tobacco use.

Table 1. Flavored Tobacco Use Prevalence by Age or Grade

Study ID	Sample (if applicable)	Measures/Analysis	Age (years) or Population	% (95% CI)	Result
Multiple Tobacco Products					
Huh, 2009[12]	2002-2003 National Survey on Drug Use and Health	Current (past 30-day) use of specialty cigarettes (bidis and/or cloves) among youth and young adult smokers	12-17 18-24	35.1 64.9	Age significantly associated with use of specialty cigarettes **(p < 0.001)**.
King, 2014[14]	2011 National Youth Tobacco Survey	Current use of flavored little cigars or flavored cigarettes among U.S. middle and high school students	Middle school (grades 6-8) High school (grades 9-12)	2.2 (1.8-2.6) 9.6 (8.3-11)	
King, 2014[14]	2011 National Youth Tobacco Survey	Current (past 30 day) use of flavored little cigars or flavored cigarettes among U.S middle and high school students	Grade 6 7 8 9 10 11 12	 0.8 (0.5-1.4) 2.2 (1.6-3.0) 3.4 (2.8-4.1) 5.8 (4.4-7.7) 8.7 (7.2-10.5) 10.4 (8.8-12.4) 14.3 (12-17)	
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Flavored tobacco product use by age among past 30 day users of any tobacco product[a]	 18-24 25-34	 23.8[1] 14.8[1]	*AOR (95% CI)*[2] **1.89 (1.14-3.11) (p<0.05)** 1.0 Referent
Bidis					
CDC, 2003[10]	2000 National Youth Tobacco Survey	Current use of bidis among all middle/high school students in the United States*	Middle school students (grades 6-8) High school students (grades 9-12)	2.4 (±0.4) 4.1 (±0.4)	
CDC, 2003[10]	2002 National Youth Tobacco Survey	Current use of bidis all middle/high school students in the United States*	Middle school students (grades 6-8) High school students (grades 9-12)	2.4 (±0.3) 2.6 (±0.5)	
Vander Weg, 2008[22]	Survey to assess alternative forms of tobacco use in a population of young adult military recruits	Current use of bidis by age among total sample of military recruits*	<20 years old ≥20 years old Total	2.1% (1.9–2.4) 1.9% (1.6–2.2) 2.0 (1.8-2.3)	No significant association by age found in multivariable logistic regression.[3]
Vander Weg, 2008[22]	Survey to assess alternative forms of tobacco use in a	Ever use of bidis among total sample of military recruits*	Young adult military recruits	14.7	

[1] Unpublished data

[2] Controls for gender, race/ethnicity, education and use of any menthol-brand tobacco product

[3] Controls for gender, race and ethnicity, educational attainment, income and marital status

	population of young adult military recruits				
Cigarettes					
Klein, 2008[15]	National Youth Smoking Cessation Survey, 2004	Past 30 day use of any flavored cigarette (Camel Exotic Blends, Kool Smooth Fusion, Salem Silver Label) among current smokers, by age	17 18-19 20-21 22-23 24-26 All	22.8 (14.8–33.4) 21.7 (17.1–27.3) 10.1 (7.4–13.6) 8.8 (6.1–12.6) 9.0 (6.2–13.1) 11.9 (10.2-13.8)	Age significantly associated with any flavored tobacco use (**p<.001**).[4]
Klein, 2008[15]	Assessing Hardcore Smoking Survey, 2004-2005	Past 30 day use of any flavored cigarette (Camel Exotic Blends, Kool Smooth Fusion, Salem Silver Label) among current smokers by age	25-39 40-54 >55	11.2 (5.9–20.4) 6.2 (3.3–11.1) 0.8 (0.2–2.4)	Age significantly associated with any flavored tobacco use (**p<.01**).[d]
Manning, 2009[16]	N/A	Use of flavored cigarettes "at least once in a while" among 253 high school students at a school in either the central or south-east United States	High school students at a school in either the central or southeast United States; mean age 15.7	19	
Regan, 2012[17]	2009 ConsumerStyles	Ever use of flavored cigarettes among those who had heard of flavored cigarettes	Adults aged ≥18 years, nationally representative, who had heard of flavored cigarettes	27.4 (20.9-33.9)	
King, 2014[14]	2011 National Youth Tobacco Survey	Current (past 30 day) use of flavored cigarettes among U.S middle and high school students	Youth in grades 6-12	4.2 (3.5-5.1)	
King, 2014[14]	2011 National Youth Tobacco Survey	Current (past 30 day) use of flavored cigarettes among U.S middle and high school students	Middle school (grades 6-8) High school (grades 9-12)	1.3 (1-1.7) 6.4 (5.3-7.7)	
King, 2014[14]	2011 National Youth Tobacco Survey	Current (past 30 day) use of flavored cigarettes among U.S middle and high school students	Grade 6 7 8 9 10 11 12	 0.5 (0.3-1.0) 1.3 (0.9-2.0) 2 (1.5-2.7) 3.9 (2.9-5.2) 6.3 (5.0-7.9) 6.9 (5.4-8.9) 9.3 (7.4-11.6)	
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored cigarettes among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	1% (95% CI: 0-2)	
Cigars					
Delnevo, 2014[11]	2010-2011 National Survey on Drug Use and Health	Preferred cigar brand makes flavored cigars among current (past 30-day) cigar smokers	 12-17 18-25	 95.1 (93.0-96.6) 88.7 (87.2-90.1)	*AOR (95% CI)*[5] **9.0 (5.7-4.2) (p<0.05)** **3.9 (2.9-5.0) (p<0.05)**

[4] Chi-squared test for independence.

[5] Controls for gender, age, race/ethnicity, cigarette use, blunt use and cigar frequency

			26-34 35 or older Overall	72.2 (68.1-75.9) 63.2 (58.5-67.6) 75.1 (73.0-77.1)	1.2 (0.8 to 1.6) 1.0 Referent
King, 2013[13]	2009-2010 National Adult Tobacco Survey	Past 30 day flavored cigar smoking among ever cigar smokers	18-24 25-44 45-64 ≥65 All	9.1 (7.8–10.5) 3.1 (2.7–3.6) 1.4 (1.2–1.7) 0.2 (0.1–0.3) 2.8 (2.6-3.1)	No statistical test performed
King, 2013[13]	2009-2010 National Adult Tobacco Survey	Past 30 day flavored cigar smoking among current cigar smokers	18-24 25-44 45-64 ≥65 All	57.1 (51.4–62.5) 43.2 (38.7–47.8) 28.9 (25.1–33.2) 13.4 (9.3–18.9) 42.9 (40.1-45.7)	No statistical test performed
King, 2014[14]	2011 National Youth Tobacco Survey	Current use of flavored little cigars among U.S. middle and high school students	Youth in grades 6-12	3.3% (95% CI: 2.9-3.9)	
King, 2014[14]	2011 National Youth Tobacco Survey	Current use of flavored little cigars among U.S. middle and high school students	Middle school (grades 6-8) High school (grades 9-12)	1.2 (1-1.5) 5 (4.2-5.8)	
King, 2014[14]	2011 National Youth Tobacco Survey	Current (past 30 day) use of flavored little cigars among U.S middle and high school students	Grade 6 7 8 9 10 11 12	 0.4 (0.2-0.8) 1.3 (0.9-1.9) 1.9 (1.5-2.5) 3 (2.2-4.2) 4.1 (3.1-5.4) 5.3 (4.3-6.6) 8 (6.4-10)	
Regan, 2012[17]	2009 ConsumerStyles	Ever use of flavored little cigars among those who had heard of flavored cigarettes	Adults aged ≥18 years, nationally representative, who had heard of flavored cigars	31.5 (27.3-35.7)	
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored cigars/cigarillos/bidis among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	35% (95% CI: 25-47)	
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored cigars among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	13% (95% CI: 8-21)	
E-cigarettes					
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored e-cigarettes among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	13% (95% CI: 6-27)	
Kreteks					
CDC, 2003[10]	2000 National Youth Tobacco Survey	Current use of kreteks among all middle/high school students in the United States	Middle school students (grades 6-8) High school students (grades 9-12)	2.1 (±0.4) 4.2 (±0.5)	
CDC,	2002 National	Current use of kreteks among all middle/high	Middle school students	2.0 (±0.3)	

2003[10]	Youth Tobacco Survey	school students in the United States	(grades 6-8) High school students (grades 9-12)	2.7 (±0.5)	
Malson, 2003[7]	N/A	Ever use of kreteks among community volunteers aged 19-46 who had previous smoked either clove or bidi cigarettes without adverse reactions	10 local community volunteers	40	
Richter, 2008[18]	N/A	Ever use of kreteks among young adult smokers who had tried or used nontraditional tobacco products	Young adult smokers aged 18-22 in Dallas, Texas and Chattanooga, Tennessee who had tried or used nontraditional tobacco products	4	
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Ever use of kreteks among middle and high school students in Massachusetts	Middle and high school students from 12 school districts across Massachusetts	8.9 (7.8-10.1)	
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Current use of kreteks among middle and high school students in Massachusetts	Middle and high school students from 12 school districts across Massachusetts	3.1 (2.4-3.9)	
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Ever use of kreteks among middle and high school students in Massachusetts	Middle school High school	5.0 (3.9–6.4) 11.4 (9.9–13.1)	
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Current use of kreteks among middle and high school students in Massachusetts	Middle school High school	1.7 (1.2–2.4) 3.1 (2.5–4.0)	
Soldz, 2005[19]	Cigar Use Reasons Evaluation	Ever use of kreteks among middle and high school students in Massachusetts who had heard of kreteks/cloves	Middle and high school students from 12 school districts across Massachusetts who had heard of kreteks/cloves	20.1	
Soldz, 2005[19]	Cigar Use Reasons Evaluation	Current use of kreteks among middle and high school students in Massachusetts who had heard of kreteks/cloves	Middle and high school students from 12 school districts across Massachusetts who had heard of kreteks/cloves	8.1	
Vander Weg, 2008[22]	Survey to assess alternative forms of tobacco use in a population of young adult military recruits	Current use of kreteks by age among total sample of military recruits	<20 years old ≥20 years old Total	2.9% (2.6–3.2) 3.2% (2.8–3.6) 3.0 (2.7-3.2)	No significant association by age found in multivariable logistic regression.[6]
Vander Weg, 2008[22]	Survey to assess alternative forms of tobacco use in a	Ever use of kreteks among total sample of military recruits	Young adult military recruits	24.8	

[6] Controls for gender, race and ethnicity, educational attainment, income and marital status

	population of young adult military recruits			
Hookah				
Sutfin, 2014[21]	Online survey, part of the Study to Prevent Alcohol-Related Consequences	Ever use of flavored hookah among students who reported ever smoking tobacco from a hookah	Students from eight colleges in North Carolina reporting ever smoking tobacco from a hookah	90
Richter, 2008[18]	N/A	Ever use of flavored hookah among young adult smokers who had tried or used nontraditional tobacco products*	Young adult smokers aged 18-22 in Dallas, Texas and Chattanooga, Tennessee who had tried or used nontraditional tobacco products	4
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored hookah among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	50% (95% CI: 36-64)
Smokeless Tobacco				
Oliver, 2013[5]	Data drawn from five studies	Current mint flavor smokeless tobacco use among smokeless tobacco users	Smokeless tobacco users aged 18-70	55.8
Oliver, 2013[5]	Data drawn from five studies	Ever mint flavor smokeless tobacco use among smokeless tobacco users	Smokeless tobacco users aged 18-70	79.4
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored chewing tobacco among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	6% (95% CI: 2-18)
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored dip/snuff among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	8% (95% CI: 3-21)
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored dissolvable tobacco among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	13% (95% CI: 2-49)
Pipes				
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Current use of flavored pipes among past 30 day users of any tobacco product	18-34 year olds, nationally representative sample	38% (95% CI: 18-63)

*Product was described by authors as being flavored, but question was not given confirming that participants were asked about the flavored version of these products

Table 2. Flavored Tobacco Use, Assessed by Tobacco Use Status

Study ID	Sample	Measures/Analysis	Measures	% (95% CI)	Result
Dawkins, 2013[34]		Preferred flavor[7]:		53	
		Tobacco	Whole sample	51	Chi-squared test for independence produced non-significant results for all comparisons
			Ex-smokers	61	
			Current smokers	33	
		Fruit	Whole sample	34	
			Ex-smokers	29	
			Current smokers	28	
		Mint/menthol	Whole sample	28	
			Ex-smokers	28	
			Current smokers	18	
		Chocolate/sweet flavor	Whole sample	18	
			Ex-smokers	18	
			Current smokers	13	
		Coffee	Whole sample	13	
			Ex-smokers	13	
			Current smokers	16	
		Other	Whole sample	17	
			Ex-smokers	9	
			Current smokers	12	
		Vanilla	Whole sample	12	
			Ex-smokers	13	
			Current smokers	4	
		Alcohol related	Whole sample	4	
			Ex-smokers	4	
			Current smokers	1	
		Flavorless	Whole sample	1	
			Ex-smokers	0	
			Current smokers		
Farsalinos, 2013	Data from survey given website of non-profit e-cigarette advocates group	Use of e-cigarettes with the following characteristics:			
		Tobacco	Former smokers	41.3	x^2=14.6, p<0.001
			Current smokers	53.0	
		Mint/menthol	Former smokers	32.5	x^2=0.0, p=0.964
			Current smokers	32.4	
					x^2=21.8, p<0.001

[7] Respondents could choose more than one option

		Sweet	Former smokers Current smokers	63.9 52.0	x^2=3.5, p=0.060
		Nuts	Former smokers Current smokers	15.6 12.1	x^2=14.0, p<0.001
		Fruits	Former smokers Current smokers	71.7 62.8	x^2=1.9, p=0.167
		Drinks/beverages	Former smokers Current smokers	37.9 34.4	x^2=1.2, p=0.281
		Other	Former smokers Current smokers	23.0 20.6	
Oliver, 2013[5]	Data drawn from five studies	Percent of users who started with a nonflavored product and now use a flavored product and percent of users who started with a flavored product and now use a nonflavored product	Users who started with a nonflavored product and now use a flavored product Users who started with a flavored product and now use a nonflavored product	51.3 35.6	ST users who started by using nonflavored products were more likely to switch to mint-flavored products compared with the other way around (**p<.0001**).[8] No coefficient given.
Oliver, 2013[5]	Data drawn from five studies	Percent of users who started with a nonflavored product and now use a nonflavored product and percent of users who started with a flavored product and now use a flavored product	Users who started with a nonflavored product and now use a nonflavored product Users who started with a flavored product and now use a flavored product	48.7 64.4	ST users who started with a mint-flavored product were more likely to currently use a mint-flavored product compared with those who continue with nonflavored products (**p=.001**). No coefficient given.
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Smoking initiation precedence among users of kreteks and cigars	Initiated with kreteks Initiated with cigars Initiated both at same age	17.8 (13.5-23.0) 49.7 (43.9-55.4) 32.5	N/A
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Smoking initiation precedence among users of kreteks and bidis	Initiated with kreteks Initiated with bidis Initiated both at same age	23.9 (17.8-31.2) 30.1 (24.0-37.1) 46	N/A
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Smoking initiation precedence among users of kreteks and cigarettes	Initiated with kreteks Initiated with cigarettes Initiated both at same age	7.5 (5.3-10.6) 71.7 (67.0-75.9) 20.8	N/A
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Current kretek use, by cigarette use	Current cigarette smokers Ever cigarette smokers	75.8 (67.0-82.8) 94.5 (88.9-97.3)	N/A
Soldz, 2003[20]	Cigar Use Reasons Evaluation	Ever kretek use, by cigarette use	Current cigarette smokers Ever cigarette smokers	61.6 (56.6-66.5)	N/A

[8] Z-test

				90.8 (87.8-93.2)	
Vander Weg, 2005[26]	Female military recruits	Ever use of kreteks by smokeless tobacco use status (unadjusted)	Lifetime smokeless tobacco use Never smokeless tobacco use		*OR (95% CI)* OR=4.49 (3.79-5.31), **p<.001** 1.0 Referent
Vander Weg, 2005[26]	Female military recruits	Ever use of kreteks by smokeless tobacco use status (adjusted)	Lifetime smokeless tobacco use Never smokeless tobacco use		*AOR (95% CI)*[9] OR=1.23 (1.01-1.49), **p=.04** 1.0 Referent
Vander Weg, 2008[22]	Survey to assess alternative forms of tobacco use in a population of young adult military recruits	Use of kreteks by cigarette smoking status	Cigarette smokers Non-cigarette smokers		*OR (99% CI)* OR=10.53 (98.41-13.20), **p<.001** 1.0 Referent
Villanti, 2013[23]	Legacy Young Adult Cohort Study, Wave 2	Any current flavored tobacco use among current tobacco users	Any menthol use No menthol use	N/R	*AOR (95% CI)*[10] **2.28 (95% CI: 1.42-3.67) (p<0.001)** 1.0 Referent

[9] Controls for factors found to have a significant relationship with smokeless tobacco use at p <0.10

[10] Controls for gender, race/ethnicity, and education

Table 3. Quit intentions and smoking frequency among U.S. middle and high school student smokers, by flavored-cigarette and flavored little cigar use, 2011 (NYTS data)						
	Current cigar smokers		**Current cigarette smokers**		**Current cigar or cigarette smokers**	
	Not flavored little cigar smokers % (95% CI)	Flavored little cigar smokers % (95% CI)	Not flavored cigarette smokers % (95% CI)	Flavored cigarette smokers % (95% CI)	Not flavored little cigar or cigarette smokers % (95% CI)	Flavored little cigar or cigarette smokers % (95% CI)
Intention to quit using tobacco						
Within next 30 days	20 (16.3-24.3)	12.4 (9-17)	18.4 (15.3-21.9)	**9.8 (7-13.5)**	22.3 (18.7-26.4)	**12.1 (9.3-15.5)**
Within next 6 months	11.3 (8.4-15.1)	9.8 (7.1-13.4)	10.9 (8.7-13.7)	13.6 (10.7-17.2)	10 (7.8-12.6)	12.8 (10.3-15.9)
Within longer than next 6 months	19.3 (15.7-23.6)	18.1 (14-23)	21.7 (18.6-25.1)	24.9 (20.9-29.4)	19.6 (16.5-23.2)	21 (17.8-24.5)
Not thinking about quitting	49.3 (44.5-54.2)	**59.7 (54.5-64.7)**	49 (44.3-53.7)	51.7 (46.7-56.6)	48.1 (44-52.2)	54.2 (50.1-58.2)

Bold indicates comparisons where the confidence intervals do not overlap.

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APPENDIX F
CONTINUUM OF HARM

Legacy endorses tobacco harm reduction, a tobacco control strategy that prioritizes achieving a society free of all nicotine and tobacco use (total abstinence), but recognizes that some users will not be able or willing to stop using tobacco products altogether. Thus, harm reduction incorporates a secondary priority of moving those users to less-harmful, non-combustible tobacco products and eliminating combustible product use entirely. This is feasible only if alternative, demonstrably lower harm, non-combustible products that can deliver nicotine are available. Regulations can play an important role in achieving this goal.

Based on the recent Surgeon General's Report,[1] Legacy urges FDA to consider combustible tobacco products – the most toxic tobacco products – as the primary comparator under both current and proposed regulatory policy when considering population-level harms. This can be implemented by monitoring total population prevalence of combustible tobacco use, including youth prevalence, and the population combustible product quit rate in premarket and post-market surveillance. Regulatory actions that maintain or speed current trends of reduction in combustible tobacco use should be viewed as beneficial, and those that reverse trends in combustible use should be identified as harmful.

A key question regarding e-cigarettes is their potential role in effectively facilitating cessation of combustible cigarettes in current smokers or significant harm reduction, both in individual users and in terms of overall population impact.[a] Previous reviews on this subject have concluded that e-cigarettes may be helpful to some smokers in quitting[2] and that there is suggestive evidence that e-cigarettes are as effective as nicotine replacement therapy for smoking cessation.[3] In order to assist the FDA in considering these complex issues, we have prepared a systematic literature review of studies on e-cigarettes and smoking cessation and a synthesis of how the findings of these studies fit with the established literature on the use of nicotine replacement therapies (NRT) for cessation of combustible cigarettes.

METHODS

The findings below were compiled from a systematic review of all published scientific literature on e-cigarettes conducted via a PubMed search through July 3, 2014. The search strategy consisted of the following keywords: "e-cigarette*" OR "electronic cigarette" OR "electronic cigarettes" OR "electronic nicotine delivery." Eligible studies were experimental studies, quasi-experimental studies, observational studies (including case control, cohort and cross sectional studies), case reports, case series, qualitative studies and mixed methods studies providing empirical data on e-cigarettes. Other sources were obtained by emailing experts and internal discussion of studies underway at Legacy.

Upon retrieval from PubMed, studies were catalogued based on title and abstract review to one or more of the following topic areas: 1) Product Features; 2) Health and safety; 3) Consumer perceptions; 4) Patterns of Use; 5) Marketing; 6) Sales; 7) Policies; and 8) Statements from public health organizations. Reviews were catalogued separately and are not included in the detailed summary of study findings; similarly, commentaries and editorials on e-cigarettes were not included in this review. For the purposes of this Appendix, the review below focuses on studies that addressed the use of e-cigarettes for cessation of combustible cigarettes.

[a] Note: We use the phrase "smoking cessation" throughout the text to refer to cessation of combustible tobacco products.

RESULTS

Although independent, objective, high-quality data remain relatively sparse, the current review presents evidence from 20 studies that have reported on the impact of e-cigarette use on abstinence from combustible cigarettes or on the reduction in number of cigarettes consumed.[4-22] Of these, two were randomized controlled trials,[4,5] three were longitudinal observational studies with a comparison group,[6-8] one was a clinical laboratory study,[9] four were longitudinal observational studies without a comparison group,[10-13] nine were cross-sectional surveys,[14-21] and one was a case series.[22] An overview of study methods is presented in Table F-1.

Cessation outcomes and follow-up periods were heterogeneous across studies. Outcomes included self-reported or biochemically-verified continuous abstinence,[4,5,22] 30-day point prevalence abstinence,[5,7,11] quit attempt,[18,20] or quit status.[6,8,16,17] Several studies by the same group used greater than 50% reduction in cigarettes per day as a cigarette reduction outcome[5,11,12] and others captured cigarette consumption over time [6,8,13] or before and after e-cigarette use.[9,23] Of note, the 7-day point prevalence abstinence outcome at least at five months follow up or longer, is the gold standard criterion used in the meta-analysis used to inform the U.S. Public Health Service(PHS) clinical guidelines for treating tobacco dependence.[24] Thus, it provides a useful metric to compare e-cigarette outcomes to NRT treatment outcomes,[25] particularly in studies with follow-up at or beyond five months. It should be noted that outcomes more stringent than the PHS criterion of 7-day point prevalence abstinence (e.g., 30-day point prevalence abstinence, continuous abstinence) will yield more conservative results (i.e., lower cessation rates). Table F-2 presents abstinence outcomes and Table F-3 presents cigarette reduction outcomes for the longitudinal studies with comparison groups, sorted by study design.

One reviewer assessed the quality of the two included randomized controlled trials [4,5] using the Cochrane Collaboration tool for assessing risk of bias[26] and this is presented in Table F-4. In the Bullen et al. study,[4] participants were not blinded to intervention condition (i.e., e-cigarette versus voucher for nicotine patch), but outcome assessors were blinded; additionally, there was differential loss to follow-up between the study groups with the greatest attrition in the nicotine patch group. The authors do not describe whether loss to follow-up was independent of intervention and outcome. Since an intention-to-treat analysis was used, incomplete outcome data were adequately addressed for the primary outcome and the study was deemed at low risk of bias across other areas. The Caponnetto et al. study[5] was deemed at low risk of bias across most domains, though the authors did not provide information on allocation concealment.

In treatment outcome studies, ideally it is important to know what specific treatment components were used and whether they were used “as intended” and if not to what degree of adherence was utilized (i.e., measures of process to outcome or of some indicators of internal validity to establish that a reasonable dose of treatment was delivered). Many observational studies do not describe which specific products were used or for how long or in what manner. As examples: there are no studies we know of to date that have measured whether or if participants were instructed on how best to use an e-cigarette to quit; how to use them to reduce craving; initial dual use as a “reduce to quit strategy” or as a relapse prevention strategy, without setting a fixed date to quit all combustible use; and for how long to use them (e.g., instructions and brief behavioral advice that is routinely provided for NRT users such as how to use nicotine gum). Studies to date have rarely reported use of any cognitive-behavioral skills training or adjunctive components (e.g., use of internet or telephone quit lines in conjunction with use of e-cigarettes to quit combustible cigarette use) or evaluated the so-called second generation personal vaporizer products that appear to have better consumer appeal and better nicotine delivery.[27]

Prospective data collection on the use of e-cigarettes to aid cessation of combustible cigarettes has been limited to a small number of studies in which the underlying samples vary widely from smokers interested in quitting[4] to quitline callers[7] and a general sample of adult smokers.[6] Some existing observational studies have claimed to be evaluating cessation of combustible cigarettes but have included and assessed e-cigarette use per se, for any reason not necessarily with an intention to quit combustible cigarettes (e.g., some studies assessed ever use even once, or current use for any reason as the central measure of exposure (independent variable)). Additionally, the quality of cessation outcome measures in a number of the observational and cross-sectional studies is poor.

More generally, the constantly evolving nature of e-cigarette products and especially the heterogeneity and poor consumer acceptability of early "first generation" products used – even during the relatively brief period in which this review was prepared – make an accurate, data-based description of the effectiveness of e-cigarettes in general as a quitting tool quite challenging.

Abstinence outcomes

Abstinence outcomes for the randomized controlled trials are presented in Table F-2.
A common concern with the three observational studies with comparison groups is that they assessed abstinence among e-cigarette users generally, rather than among these respondents who were using e-cigarettes as a cessation aid, and did not account for the actual number of times e-cigarettes were used or duration of use. Thus, findings from these observational studies do not provide evidence of the effectiveness of e-cigarettes as a cessation aid in adult smokers trying to quit and we have excluded them from Tables F-2 and F-3.

Randomized controlled trials (n = 2)

Bullen et al. conducted a randomized controlled trial from 2011-2013 among current adult smokers interested in quitting in New Zealand (N=657) and found that biochemically-verified continuous abstinence at 6 months follow up between the treatment arm (nicotine e-cigarette, 7.3%) was higher compared to two control arms (placebo e-cigarette, 4.1% and nicotine patch, 5.8%), but these differences were not significantly different.[4] Participants received vouchers for nicotine patches or e-cigarette study products for a 13-week use period (1 week prior and 12 weeks post quit day) and some have suggested that differential adherence may be a confounder that could have weakened the potential efficacy of the NRT patch arm if it was delivered under ideal conditions of adherence). Bullen et al. did, however, also report the 7-day point prevalence abstinence (ppa) outcomes at six months were similar in the nicotine e-cigarette group (21.1%) and the placebo e-cigarette group (21.9%) and both e-cigarette arms were arithmetically but not statistically significantly higher compared to nicotine patch group (15.6%).

Bullen et al. pointed to insufficient statistical power as a probable cause to this lack of effect, but this may also be due to the use of three groups that were not very different in terms of treatment delivery (i.e., no true placebo control group). Table F-5 presents findings from meta-analyses of the impact of smoking cessation medications, including nicotine replacement therapy presented in the 2008 update to the PHS guidelines for Treating Tobacco Use and Dependence.[25] Bullen et al.'s result of 7-day point prevalence abstinence of 21.1% (nicotine e-cigarette) and 21.9% (placebo e-cigarette) at six months are in line with the combined results of 32 randomized controlled trials of short-term (6-14 weeks) use of the nicotine patch among smokers interested in quitting which found six-month abstinence of 23.4% (95% CI 21.3-25.8) and six trials of use of the nicotine inhaler (24.8%).

Caponnetto et al. conducted a randomized controlled trial from 2010-2011 of placebo and nicotine-containing e-cigarettes (products provided for 12 weeks) among current smokers in Italy who were not interested in quitting (N=300).[5] Findings indicated that at six-month follow-up, 11% of participants in the nicotine-containing e-cigarette groups had quit smoking compared to 5% in the placebo e-cigarette group. Across groups 8.7% quit smoking and 10.3% reduced their smoking by ≥50% at 52 weeks, with 11% of those in the nicotine-containing e-cigarette groups reporting quitting compared to 4% in the placebo group. Quit rates were not statistically different whether given e-cigarettes with or without nicotine. These results are also similar to findings from meta-analyses of the impact of smoking cessation medications among smokers not willing to quit [25]; specifically, the 8.7% of smokers using placebo and nicotine-containing e-cigarettes and the 11% using nicotine-containing e-cigarettes who quit at one-year in this study compares favorably to the 8.4% abstinence rate among nicotine replacement users in five randomized controlled trials among smokers unmotivated to quit (Table F-5).

Observational studies with comparison groups (n = 3)
Two waves (Wave 7, October 2008 to July 2009; Wave 8, July 2010 to June 2011) of the International Tobacco Control Four-Country Survey were used to examine e-cigarette (ENDS) use and related outcomes among current and former smokers.[8] The sample size was 5939 participants from Canada (n= 1581), the US (n=1520), the United Kingdom (n=1325), and Australia (n=1513) who completed both waves. Eleven percent of current ENDS users reported having quit since Wave 7 and quitting did not differ between users and non-users (p =0.516).

An online panel study conducted in the U.S. from November 2011 to November 2012 among 1,549 adult current smokers showed that 10.2% of those who had used e-cigarettes in the past month at baseline reported quitting smoking at one-year follow-up compared to 13.8% of those who had not used e-cigarettes in the past month at baseline.[6] This difference was not statistically significant (p = 0.35).

An observational study of 2,758 cigarette smoking quitline callers from six U.S. states in 2011-2012 compared cessation outcomes among adult tobacco users who used e-cigarettes (for 1 month or more vs. less than 1 month) to those who had never used e-cigarettes. At the 7-month follow-up survey, e-cigarette user groups (used for 1 month or more, 21.7%; less than 1 month, 16.6%) were significantly less likely to report 30-day point prevalence abstinence compared with participants who had never tried e-cigarettes (31.3%, $p<0.001$).[7]

Adkison et al.[8] note that 85% of ENDS users stated that they used ENDS as a tool to quit smoking and Vickerman et al.[7] report that 51% of quitline callers reported using e-cigarettes to help quit other tobacco products, but reason for e-cigarette use was not reported in the Grana, Popova & Ling study.[6] ***For the reasons noted above, findings from these observational studies do not provide evidence of the effectiveness of e-cigarettes as a cessation aid in adult smokers trying to quit and we have excluded them from Tables F-2 and F-3.***

Observational studies with no comparison group (n = 3)
A prospective observational study of 14 smokers in Italy with schizophrenia and no intention to quit found that following an e-cigarette trial (products provided for 12 weeks) about 14% quit cigarette smoking at the 1-year follow-up.[10]

A prospective observational study of current cigarette smokers in Italy (N=40) found that, following an e-cigarette trial (products provided for 24 weeks), 22.5% of smokers had quit cigarette smoking using e-cigarettes at 6 month follow-up (24 week study visit).[11] Participants were followed for an additional 18

months and at the 2 year post-intervention follow-up, smoking abstinence was reported by 12.5% of participants.[12]

A longitudinal observational study of adults aged 18 and older (n=367) from the US (34%), France (24%), UK (8%), Switzerland (6%), and other countries (28%) found that among daily or occasional cigarette smokers who were using e-cigarettes at baseline (i.e., dual users), 22% reported 7-day point prevalence abstinence from traditional cigarettes at one month and 46% at one year.[13]

Cross-sectional studies (n = 6)

A household survey was conducted in England between July 2009 and February 2014 with 5,863 adults who smoked daily or occasionally, had made at least one quit attempt, and had used either e-cigarettes or nicotine replacement therapy (NRT) bought over the counter during their most recent quit attempt.[21] In this sample, e-cigarette users were more likely to report abstinence than either those who used NRT bought over-the-counter (odds ratio 2.23, 95% confidence interval 1.70 to 2.93, 20.0% vs. 10.1%) or no aid (odds ratio 1.38, 95% confidence interval 1.08 to 1.76, 20.0% vs. 15.4%).

An online, international survey of adult e-cigarette users (N=1347) run between September 2011 and May 2012 found that 74% reported not smoking for at least a few weeks and 70% reported a reduced urge to smoke.[15]

A web-based survey of 179 e-cigarette users in Poland (unclear dates of collection) found that 64% who smoked at the time they started using e-cigs had stopped smoking cigarettes at the time of the survey.[16]

A nationally representative study of 1,836 current or recently former smoking adults in the U.S. in 2011 found that smokers who intended to quit within the next month, within 6 months, or in the future had higher openness to try e-cigarettes (mean=4.6, 4.1 and 3.9, respectively, on a 9-point Likert scale) than those who did not ever plan on quitting (mean=2.7, $p<0.001$). This study also found that e-cigarette ever users were 78% more likely to be an unsuccessful quitter compared with non-users of e-cigarettes (OR: 1.78, $p<0.05$) and unsuccessful quitters were the most open to using e-cigarettes in the future.[17]

A South Korean nationally representative web-based survey of middle and high school students (n=75,643) in 2011 found that among ever cigarette smokers (n = 19,698), current e-cigarette users and former e-cigarette users were significantly less likely to have quit smoking (OR = 0.10 for current e-cigarette users and OR = 0.32 for former e-cigarette users).[20]

A 2010 study of first time blu e-cigarette purchasers (who reported previous cigarette smoking; N=216) found that the 6-month point prevalence of smoking abstinence among the e-cigarette users in the sample was 31.0% and almost half reported abstinence from smoking for a period of time (48.8%).[14]

As noted above, the heterogeneity of outcomes assessed, in addition to highly selected study samples in these cross-sectional studies, limit the ability to draw conclusions on temporal relationships between e-cigarette use and smoking cessation and the effectiveness of e-cigarettes as a cessation tool.

Case series (n = 1)

A small study of three heavy cigarette smoking adults who had history of smoking relapses found that e-cigarettes assisted all three smokers to successfully quit.[22]

<u>Cigarette reduction outcomes</u>

E-cigarette use has also been associated with *reductions* in traditional cigarette use, as compared to complete abstinence. Therefore, cigarette reduction outcomes for the randomized controlled trials and observational studies with comparison groups are presented in Table F-3.

Randomized controlled trials (n = 2)
The Bullen et al. study in current adult smokers interested in quitting in New Zealand (N=657) found significant differences in smoking reduction by ≥50% at 6 months between the treatment arm (nicotine e-cigarette, 57%) and NRT patch (41%; p = 0.0002) but not compared to placebo e-cigarette (45%; p = 0.08).[4]

The 2010-2011 Caponnetto et al. study conducted among current smokers in Italy who were not interested in quitting (N=300) showed that 18% of participants in the nicotine-containing e-cigarette groups (19% in the 7.2 mg group and 17% in the 5.4 mg group) reduced their smoking by ≥50% at six months compared to 15% of those in the placebo e-cigarette group.[5] At one-year follow-up, 9.5% of those in the nicotine-containing e-cigarette groups (10% in the 7.2 mg group and 9% in the 5.4 mg group) reduced their smoking by ≥50% compared to 12% in the placebo e-cigarette group. Differences in cigarette reduction were not statistically significant at either timepoint. Overall, 10.3% of participants reduced their cigarette smoking by at least 50% at the one-year follow-up.

Clinical laboratory study (n = 1)
A study examining changes in smoking behavior in daily smokers naïve to e-cigarettes (n=16) after one week of ad libitum e-cigarette use found a significant reduction (44%) in regular cigarettes smoked per day from baseline to the end of the ad libitum phase (p<0.001).[9] No changes in total tobacco units per day (cigarettes + e-cigarettes) were observed during this time period.

Observational studies with comparison groups (n = 1)
Adkison et al. used two waves (Wave 7, October 2008 to July 2009; Wave 8, July 2010 to June 2011) of the International Tobacco Control Four-Country Survey, a longitudinal study, to examine e-cigarette use and related outcomes among 5,939 current and former smokers (Canada (n= 1581), the United States (n=1520), the United Kingdom (n=1325), and Australia (n=1513)).[8] Across samples, current e-cigarette use was associated with a greater reduction in cigarettes per day compared to non e-cigarette users at Wave 8 relative to Wave 7 (p<0.05). E-cigarette users reported mean use of 20.10 cigarettes per day at Wave 7 (SD=12.36) and 16.32 cigarettes per day at Wave 8 (SD=12.35). Non-e-cigarette users reported mean use of 16.86 cigarettes per day at Wave 7 (SD=9.95) and 15.01 cigarettes per day at Wave 8 (SD=10.83).

An online panel study conducted in the U.S. from November 2011 to November 2012 among 1,549 adult current smokers showed that those who had used e-cigarettes in the past month at baseline reported smoking an average of 16.1 (SD 10.4) cigarettes per day at 1-year follow-up compared to 14.4 (SD 9.6) among those who had not used e-cigarettes in the past month at baseline.[6] This difference was not statistically significant (p = 0.41).

Since these two studies did not account for reason of e-cigarette use as a cessation aid, findings from these studies are excluded from Table F-3.

Observational studies with no comparison group (n = 3)
In Caponnetto et al.'s study of 14 current cigarette smokers with schizophrenia and no intention to quit in Italy, following e-cigarette trial (products provided for 12 weeks) 50% of respondents had sustained a

50% reduction in cigarettes at the 1-year follow-up.[10] Sixty-four percent of participants reported either 30-day point prevalence abstinence or 50% reduction in cigarette use at one-year.

Polosa et al.'s study of 40 current cigarette smokers in Italy following an e-cigarette trial for 24 weeks found that 33% of participants reported smoking reduction by ≥50% at the 6-month follow-up and there was a combined cigarette reduction and smoking abstinence found in 55% of participants.[11] At a 2 year post-intervention follow-up, a 50% cigarette reduction was shown in 27.5% of participants, with combined cigarette reduction and abstinence found in 40% of participants.[12]

A longitudinal observational study of adults aged 18 and older (n=367) from the US (34%), France (24%), UK (8%), Switzerland (6%), and other countries (28%) found that dual users who smoked and used e-cigarettes daily or occasionally at baseline, one month, and one year experienced a significant decrease in cigarette consumption of 5.3 cigarettes per day at one month (p=0.006), but no change at one year.[13]

Cross-sectional studies (n = 2)

A 2010 study of first-time blu e-cigarette purchasers (N=216) found that 66.8% of respondents reported 6-month point prevalence of cigarette reduction.[14] This study did not provide additional detail on the number of cigarettes per day before and after respondents initiated e-cigarette use.

A multi-national study of e-cigarette use among current (n=398) and former (n=4,117) smokers found that former and current smokers reported similar intensity of cigarette use prior to e-cigarette initiation (25 cigarettes per day vs. 20 cigarettes per day, p = 0.189) and current smokers reported a substantial reduction in cigarette consumption since initiation of e-cigarette use (20 to 4 cigs/day).[23]

Other outcomes

Quit attempts (n = 2)

A cross-sectional study from 2012 conducted in a nationally representative survey of U.S. adults aged 18 and older (N=10,041) found that current e-cigarette users were significantly more likely to have tried to quit smoking in the last 12 months than non-users (p<0.05) and more likely to have made an attempt that lasted for at least 24 hours (p<0.05).[18]

A South Korean nationally representative web-based cross-sectional survey of middle and high school students (n=75,643) in 2011 found that current smokers who tried to quit in the past 12 months were significantly more likely to use e-cigarettes than those who had not (40.0% vs. 29.1%, p<0.001). Although quit attempts were associated with current e-cigarette use, current users were less likely to successfully quit (OR=0.1, 95% CI=0.09-0.12).[20]

Relapse (n = 2)

Caponnetto et al.'s randomized controlled trial in Italy from 2010-2011 (N=300) of placebo and nicotine-containing e-cigarettes showed that dual users of both the e-cigarette and regular cigarettes who tried to quit were more likely to relapse and return to smoking.[5]

Etter et al.'s longitudinal observational study of adults aged 18 and older (n=367) from the US (34%), France (24%), UK (8%), Switzerland (6%), and other countries (28%) found that 6% of former smokers who were using e-cigarettes daily at baseline relapsed to cigarette smoking at one month and 6% at one year. Eight percent of recent quitters (quit smoking for <1 month and were using daily at baseline) relapsed to occasional smoking at one month and 5% at one year, although none relapsed to daily smoking.[13]

Impact of flavored e-cigarette use on cessation (n = 1)
A multinational online cross-sectional survey of current (n=398) and former smokers (n=4,117) found that the most commonly used e-cigarette flavors were fruits, followed by sweets and tobacco; tobacco flavors were most popular at initiation, followed by fruits and sweets. Respondents used three different flavors regularly. [23] This study found that male gender (p=0.001), consumption of e-cigarettes (p=0.044), and number of flavors consumed (p=0.038) were significantly associated with smoking abstinence.

Nicotine concentration among quitters (n = 1)
One study conducted personal interviews to examine e-cigarette use patterns among 111 subjects (aged 20-55 years) based in Italy/Greece who had completely substituted smoking with e-cigarettes during the first month of e-cigarette use. This study found that 42% of participants reported quitting smoking during the first month of e-cigarette use. Almost three-quarters (74%) of users used a nicotine concentration of 15 mg/mL at initiation of e-cigarette use, and 16.2% had to increase their initial nicotine levels in order to achieve complete smoking abstinence. Over the 8-month period, 64.9% of the study's participants reported that they had reduced the nicotine concentration they were consuming. Only 12% of the total sample was using a nicotine concentration of 5 mg/mL or less at the time of the interview after the 8 month period.[19]

SUMMARY
Two randomized controlled trials to date show that e-cigarettes are effective in helping some adult smokers to quit or to reduce their cigarette consumption.[4,5] In both of these studies, rates of smoking cessation in the e-cigarette study groups were similar to rates of cessation seen in previous clinical trials of nicotine replacement therapy.[25] Other prospective studies with comparison groups report use of e-cigarettes may be associated with no change or reduced cessation,[6-8] but these associations may be due to other factors (e.g., smokers who are more nicotine dependent are more likely to try e-cigarettes).[28] Most longitudinal studies without comparison groups, cross-sectional studies, and case series suggest that e-cigarettes can help some adult smokers quit smoking combustible cigarettes [10-16,21,22] with a few exceptions,[17,20] though cessation outcomes assessed vary widely in terms of quality. Both observational studies and randomized clinical trials indicate that some cigarette smokers who initiate e-cigarette use cut down on the number of cigarettes that they smoke.[4,8-14,23] More research – especially independent, high quality randomized controlled trials with appropriate control groups – is needed to further determine whether and how e-cigarettes can be an effective cigarette cessation or harm reduction aid, but results to date are promising for some adult smokers.

The results from these studies suggest several areas for consideration in FDA's evaluation of treatment outcomes research on e-cigarettes. First, they raise questions about the appropriate control group for e-cigarette trials and the active ingredients in a non-nicotine (placebo) e-cigarette that could facilitate a treatment impact. If an e-cigarette can have a significant effect even without nicotine delivery, this means that a non-nicotine e-cigarette is only an appropriate control of whether additional nicotine delivery adds in an incremental manner to the outcome, over and above the effect of a non-nicotine e-cigarette. The non-nicotine e-cigarette may also therefore be comparable to other non-pharmacological treatments - such as brief behavioral advice, a telephone quit line or an Internet-cessation program. These comparisons will need to be further tested in future research. A non-nicotine e-cigarette may also have a significant effect if compared to a control such as no treatment or a minimal self-help treatment. Since the behavioral ritual of hand-to-mouth and sensorimotor activity of using an e-cigarette (i.e., vaping) mimics the ritual of using a combustible cigarette, it is not surprising on theoretical grounds (i.e., conditioning and extinction of cues) that a non-nicotine e-cigarette could be a useful tool to facilitate

cessation of use of combustible cigarettes. These ideas will need to be tested in future research to determine their potential to increase smoking cessation.

Second, there are internal validity considerations regarding whether nicotine-containing e-cigarettes can deliver sufficient nicotine to test their efficacy as equal to or better than comparable blood nicotine levels that are known to be delivered with NRTs. The nicotine in the first generation e-cigarette used in Bullen et al.,[4] may not have outperformed the non-nicotine e-cigarette arm of the study or the NRT arm of the study because the e-cigarette was a first generation product that may not have delivered much nicotine at all to naïve users. This means that internal validity of delivering an adequate "dose of nicotine" to test the hypothesis may not have been achieved as intended. Thus, another consideration is that a more effective and efficient second generation e-cigarette, or better instruction to users on how to maximize the delivery of nicotine (e.g., slower longer puff rates) may well result in a study where the nicotine e-cigarette arm would, in fact, be able to outperform both the non-nicotine e-cigarette and NRT. This hypothesis was likely not tested in the Bullen et al. study because of poor or no nicotine delivery (i.e., the nicotine e-cigarette may have delivered so little nicotine that, in effect, it was not different from the non-nicotine, so-called "placebo e-cigarette" arm). These factors need be considered and measured to assure internal validity of dose of nicotine delivered in future studies.

Third, it should be noted that it is important to compare apples to apples in terms of outcome criteria. When comparing the outcomes of the two randomized controlled trials, e-cigarettes produce similar abstinence rates to NRTs in smokers who are either motivated or unmotivated to quit. Future studies should use the same outcome metrics as previous studies of smoking cessation treatments, particularly the 7 day ppa measure at 6-month follow up used in the PHS guidelines,[24] to facilitate direct comparison to established cessation treatments.

Finally, the proposed rule represents the first, highly critical, phase in determining how nicotine products, other than products currently regulated as pharmaceuticals, will be designed, marketed and sold to consumers. Currently, NRTs are expensive, with limited access through pharmacies, and are not widely appealing to consumers. E-cigarettes and other new nicotine-delivery products, on the other hand, may have a greater public health impact because of their widespread marketing, appeal, availability and attractiveness of use. If e-cigarettes (and other novel non-combustible tobacco products) are carefully regulated, they have the potential to shift smokers permanently away from combustible products including cigarettes, cigars and hookah, to cleaner, less harmful forms of nicotine. If we consider combustible tobacco use as the most toxic comparator, we can distinguish between different types of nicotine-containing products, per Fiore et al.: "we need to communicate intelligently…[that] not all nicotine-containing products are equal, and the public health focus should be on eliminating combustible tobacco products, even if some people who give up combustibles will continue using FDA-approved medications, e-cigarettes, or smokeless tobacco products indefinitely."[29] In the context of harm reduction, tobacco cessation fits with the primary goal of total abstinence and the secondary goal of moving combustible tobacco users to reduced harm products. The potential exists for products approved by CTP as modified risk to assist current smokers with craving reduction, in combination with other nicotine replacement therapies, and as part of a reduce-to-quit strategy in line with FDA's recent NRT labeling changes.[30,31] As such, Legacy strongly supports the comprehensive regulation of nicotine by the FDA across all of its divisions, particularly CTP and CDER, to ensure that FDA uses all of the tools at its disposal to communicate with the public regarding minimizing tobacco-related harm.

Table F-1. Overview of cessation study methods

Study	Study design	Setting	Study dates	Study population	Intervention (Exposed)	Control (Unexposed)	Initial sample size	Measures	Study retention
Bullen (2013)[4]	Randomized controlled trial	Community-based trial in Auckland, New Zealand	September 2011 - July 2013	Adult (18 years or older) who smoked 10+ cigarettes per day for the past year and wanted to quit	Nicotine e-cigarettes (16mg cartridges)	Two control groups: 1) placebo e-cigarette (non-nicotine cartridges); 2) vouchers for nicotine patches (21 mg/24 hours)	n = 657	Continuous abstinence at 1, 3, and 6 months; 7-day point prevalence abstinence at 1, 3, and 6 months; biochemically-verified (CO) continuous abstinence at 6 months	78% at 6 months
Caponnetto (2013)[5]	Randomized controlled trial	Community-based trial in Catania, Italy	June 2010 - February 2012	Adults (18-70 years of age) who smoked at least 10 cigarettes per day for the past five years, were in good general health, and were not interested in quitting smoking.	Two intervention groups: 1) E-cigarettes with 7.2 mg nicotine cartridges; 2) E-cigarettes with 5.4 mg cartridges	E-cigarettes with no nicotine cartridges	n = 300	≥ 50% reduction in number of cigarettes per day; biochemically-verified (eCO) continuous abstinence since last study visit; biochemically-verified abstinence using saliva cotinine at week 6 and week 12	75.0% at 12 weeks; 70.3% at 6 months; 61.0% at 1 year

Study	Study design	Setting	Study dates	Study population	Intervention (Exposed)	Control (Unexposed)	Initial sample size	Measures	Study retention
Grana (2014)[6]	Observational study with comparison group	Online panel study in the U.S.	November 2011 - November 2012	Adult current smokers	Past 30-day e-cigarette use at baseline	No past 30-day e-cigarette use at baseline	n = 1549	Quit at 1 year follow-up; consumption at 1 year follow-up	81.3% at 1 year
Vickerman (2013)[7]	Observational study with comparison group	Telephone survey in six states in the U.S.	June 2011 - October 2012	Adult tobacco users who registered for tobacco cessation services and consented to evaluation follow-up	Two exposed groups: 1) used e-cigarettes 1 month or more; 2) used e-cigarettes less than one month	Never used e-cigarettes	n = 7,966	30-day point prevalence abstinence at 7 months	34.6 at 7 months
Adkison (2013)[8]	Observational study with comparison group	Phone interviews or web-based surveys in Canada, the U.S., the U.K., and Australia	July 2010 - June 2011	Adult current and former smokers aged 18 and over	ENDS use	No ENDS use	n = 5939	Cigarettes per day (Wave 7 to Wave 8); quitting (Wave 7 to Wave 8)	70% (completing Waves 7 and 8)

Study	Study design	Setting	Study dates	Study population	Intervention (Exposed)	Control (Unexposed)	Initial sample size	Measures	Study retention
Wagener (2014)[9]	Clinical laboratory study	Lab-based study in the U.S.	May 2012-June 2012	Adult (aged 18-55) current smokers who smoked at least 15 cigarettes per day for the past year, were not currently trying to quit and had no intention to quit in the next 30 days, and were not using noncigarette tobacco	ProSmoke, BluCig, or SmokeTip e-cigarettes matched by flavor and nicotine level to own brand cigarettes		n = 20	Cigarettes smoked per day at baseline and after 1 week of ad libitum use	80%
Caponnetto (2013)[10]	Observational study with no comparison group	Clinic-based study in Catania, Italy	NR	Current adult smokers with schizophrenia who smoked at least 20 cigarettes/day for the past 10 years and had no intention to quit	Nicotine e-cigarettes (7.4 mg cartridges)		n = 14	50% reduction in cigarettes/day for 30 days at 1 year; 30-day point prevalence abstinence at 1 year	100%

Study	Study design	Setting	Study dates	Study population	Intervention (Exposed)	Control (Unexposed)	Initial sample size	Measures	Study retention
Polosa (2011)[11]	Observational study with no comparison group	Clinic-based study in Catania, Italy	NR	Adults (18-60 years of age) who smoked >= 15 cigarettes per day for at least last 10 years and are not attempting to or interested in quitting in the next 30 days	Nicotine e-cigarettes (7.4 mg cartridges)		n = 40	50% reduction in cigarettes/day from baseline for 30 days at 24-weeks; 80% reduction in cigarettes/day from baseline for 30 days at week 24; 30-day point prevalence abstinence at week 24 (CO verified)	67.5% at Week 24
Polosa (2013)[12]	Observational study with no comparison group	Clinic-based study in Catania, Italy	NR	Adults (18-60 years of age) who smoked >= 15 cigarettes per day for at least last 10 years and are not attempting to or interested in quitting in the next 30 days	Nicotine e-cigarettes (7.4 mg cartridges)		n = 40	50% reduction in cigarettes/day from baseline (CO verified); 80% reduction in cigarettes/day from baseline (CO verified); smoking abstinence (CO verified)	57.5% at 24 months

Study	Study design	Setting	Study dates	Study population	Intervention (Exposed)	Control (Unexposed)	Initial sample size	Measures	Study retention
Etter (2014)[13]	Observational study with no comparison group	Online survey in the U.S., France, U.K., Switzerland, and other countries	August 2011 - January 2014[b]	Adult e-cigarette users			n = 1329	Cigarettes per day (among smokers) at 1 month and at 1 year	28% at 1 year
Siegel (2011)[14]	Cross-sectional survey	Online survey in the U.S.	March 2010	First-time purchasers of blu e-cigarettes			n = 222	Point prevalence abstinence from cigarettes at 6 months post-purchase	N/A
Dawkins (2013)[15]	Cross-sectional survey	Online survey hosted at the University of East London with links from TECC/TWEL websites	September 2011 - May 2012	Adult e-cigarette users			n = 1347	Dramatic decrease in tobacco consumption; not smoked for several weeks; not smoked for several months	N/A
Goniewicz (2013)[16]	Cross-sectional survey	Online survey in Poland	NR	E-cigarette users			n = 179	Stopped smoking conventional cigarettes	N/A
Popova (2013)[17]	Cross-sectional survey	Online survey in the U.S.	November 2011	Adult (aged 18+) current or recent former smokers			n = 1836	Quit status (successful, unsuccessful, never tried)	N/A

[b] Study dates estimated from description in manuscript.

Study	Study design	Setting	Study dates	Study population	Intervention (Exposed)	Control (Unexposed)	Initial sample size	Measures	Study retention
Zhu (2013)[18]	Cross-sectional survey	Online survey in the U.S.	February 2012 - March 2012	Adults aged 18+			n = 10,041	Past year quit attempt; quit attempt lasting more than 24 hours	N/A
Farsalinos (2013)[19]	Cross-sectional survey	Clinic-based study in Greece	2012-2013	Former smokers who had completely substituted smoking with e-cigarette use for at least 1 month.			n = 111	Nicotine concentration at initiation (smoking cessation) and at the time of the interview	N/A
Lee (2014)[20]	Cross-sectional survey	School-based youth risk behavior online survey in Korea	2011	Nationally representative cross-section of Korean middle and high school students aged 13-18			n = 75,643	Past year quit attempt; not smoked in the past 30 days	N/A
Brown (2014)[21]	Cross-sectional survey	Household survey in England	July 2009 - February 2014	Adults (aged 16+) who smoked daily or occasionally, had made at least one quit attempt, and had used either e-cigarettes or NRT bought over the counter during	Used e-cigarettes in last quit attempt	Used NRT in last quit attempt	n = 5,863	Self-reported abstinence since last quit attempt	N/A

Study	Study design	Setting	Study dates	Study population	Intervention (Exposed)	Control (Unexposed)	Initial sample size	Measures	Study retention
				their most recent quit attempt					
Caponnetto (2011)[22]	Case series	Clinic-based study in Catania, Italy	NR	Adult heavy smokers with an established history of relapse			n = 3	CO-verified smoking abstinence	N/A
Farsalinos (2013)[23]	Cross-sectional survey	Online survey in the U.S., Europe, Asia, and Australia	NR	E-cigarette users of any age			n = 4,515	Cigarette consumption before and after e-cigarette use	N/A

NR, not reported

Table F-2. Abstinence outcomes for randomized controlled trials, sorted by outcome and follow-up period

Outcome	Study	Intervention (events/ total n)	Control (events/ total n)	OR	95% CI	Other Notes
7-day point prevalence abstinence						
1 month	Bullen (2013)[4]	69/289	51/295	1.50	(1.00-2.25)	Control: voucher for nicotine patch
	Bullen (2013)[4]	69/289	12/73	1.59	(0.81-3.13)	Control: placebo e-cigarettes
3 months	Bullen (2013)[4]	62/289	50/295	1.34	(0.89-2.03)	Control: voucher for nicotine patch
	Bullen (2013)[4]	62/289	12/73	1.39	(0.70-2.74)	Control: placebo e-cigarettes
6 months	Bullen (2013)[4]	61/289	46/295	1.45	(0.95-2.21)	Control: voucher for nicotine patch
	Bullen (2013)[4]	61/289	16/73	0.95	(0.51-1.78)	Control: placebo e-cigarettes
Biochemically-verified continuous abstinence since prior study visit						
2 weeks	Caponnetto (2013)[5]	20/100	5/100	4.75	(1.71-13.23)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	12/100	5/100	2.59	(0.88-7.65)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	32/200	5/100	3.62	(1.36-9.60)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
1 month	Caponnetto (2013)[5]	14/100	6/100	2.55	(0.94-6.93)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	14/100	6/100	2.55	(0.94-6.93)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	28/200	6/100	**2.55**	**(1.02-6.38)**	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
6 weeks	Caponnetto (2013)[5]	11/100	2/100	**6.06**	**(1.31-28.07)**	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	15/100	2/100	**8.65**	**(1.92-38.90)**	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	26/200	2/100	**7.32**	**(1.70-31.51)**	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
2 months	Caponnetto (2013)[5]	9/100	4/100	2.37	(0.71-7.98)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	12/100	4/100	**3.27**	**(1.02-10.52)**	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	21/200	4/100	2.82	(0.94-8.44)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
10 weeks	Caponnetto (2013)[5]	7/100	3/100	2.43	(0.61-9.69)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	15/100	3/100	**5.71**	**(1.60-20.39)**	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	22/200	3/100	**4.00**	**(1.17-13.69)**	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
3 months	Caponnetto (2013)[5]	11/100	4/100	2.97	(0.91-9.66)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	17/100	4/100	**4.92**	**(1.59-15.19)**	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	28/200	4/100	**3.91**	**(1.33-11.47)**	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)

Outcome	Study	Intervention (events/ total n)	Control (events/ total n)	OR	95% CI	Other Notes
Biochemically-verified continuous abstinence						
6 months	Bullen (2013)[4]	21/289	17/295	1.28	(0.66-2.48)	Control: voucher for nicotine patch
	Bullen (2013)[4]	21/289	3/73	1.83	(0.53-6.31)	Control: placebo e-cigarettes
	Caponnetto (2013)[5]	12/100	5/100	2.59	(0.88-7.65)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	10/100	5/100	2.11	(0.70-6.42)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	22/200	5/100	2.35	(0.86-6.40)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
1 year	Caponnetto (2013)[5]	13/100	4/100	**3.59**	**(1.13-11.41)**	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	9/100	4/100	2.37	(0.71-7.98)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	22/200	4/100	2.97	(0.99-8.86)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
Continuous abstinence						
1 month	Bullen (2013)[4]	67/289	12/73	1.53	(0.78-3.02)	Control: placebo e-cigarettes
	Bullen (2013)[4]	67/289	47/295	**1.59**	**(1.05-2.41)**	Control: voucher for nicotine patch
3 months	Bullen (2013)[4]	38/289	27/295	1.50	(0.89-2.53)	Control: voucher for nicotine patch
	Bullen (2013)[4]	38/289	5/73	2.06	(0.78-5.43)	Control: placebo e-cigarettes
6 months	Bullen (2013)[4]	30/289	21/295	1.51	(0.84-2.71)	Control: voucher for nicotine patch
	Bullen (2013)[4]	30/289	4/73	2.00	(0.68-5.86)	Control: placebo e-cigarettes

Confidence intervals that do not include the null (OR = 1.00) are noted in bold.

Table F-3. Cigarette reduction outcomes for randomized controlled trials, sorted by outcome and follow-up period

Outcome	Study	Intervention (events/total n)	Control (events/total n)	OR	95% CI	Other Notes
≥ 50% reduction in number of cigarettes per day						
2 weeks	Caponnetto (2013)[5]	38/100	36/100	1.09	(0.61-1.94)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	67/200	36/100	0.90	(0.54-1.48)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
	Caponnetto (2013)[5]	29/100	36/100	0.73	(0.40-1.32)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
1 month	Caponnetto (2013)[5]	29/100	29/100	1.00	(0.54-1.84)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	33/100	29/100	1.21	(0.66-2.20)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	58/200	29/100	1.00	(0.59-1.70)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
2 months	Caponnetto (2013)[5]	23/100	20/100	1.20	(0.61-2.35)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	21/100	20/100	1.06	(0.54-2.11)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	44/200	20/100	1.13	(0.62-2.04)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
6 weeks	Caponnetto (2013)[5]	24/100	25/100	0.95	(0.50-1.81)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	26/100	25/100	1.05	(0.56-1.99)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	50/200	25/100	1.00	(0.57-1.74)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
10 weeks	Caponnetto (2013)[5]	26/100	19/100	1.50	(0.77-2.93)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	15/100	19/100	0.75	(0.36-1.58)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	41/200	19/100	1.10	(0.60-2.02)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
3 months	Caponnetto (2013)[5]	26/100	21/100	1.32	(0.69-2.55)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	20/100	21/100	0.94	(0.47-1.87)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	46/200	21/100	1.12	(0.63-2.01)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
6 months	Caponnetto (2013)[5]	17/100	15/100	1.16	(0.54-2.48)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	19/100	15/100	1.33	(0.63-2.79)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	36/200	15/100	1.24	(0.65-2.40)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)
1 year	Caponnetto (2013)[5]	10/100	12/100	0.82	(0.34-1.98)	Intervention: Nicotine e-cigarettes (7.2 mg; Group A)
	Caponnetto (2013)[5]	9/100	12/100	0.73	(0.29-1.81)	Intervention: Nicotine e-cigarettes (5.4 mg; Group B)
	Caponnetto (2013)[5]	19/200	12/100	0.77	(0.36-1.66)	Intervention: All nicotine e-cigarettes (Groups A & B collapsed)

Confidence intervals that do not include the null (OR = 1.00) are noted in bold.

Table F-4. Assessment of risk of bias in included randomized controlled trials

Criteria	Bullen (2013)[4]	Caponnetto (2013)[5]
Was the allocation sequence adequately generated?	Y	Y
Was allocation adequately concealed?	Y	U
Were intervention and control groups comparable on background characteristics at baseline?	Y	Y
Was knowledge of the allocated intervention adequately prevented during the study (for participants, personnel and analysts)?	N	Y
Were outcomes ascertained without bias?	Y	Y
Were all randomized individuals included in the final analysis of primary outcome(s)?	Y	Y
Were rates of follow-up similar in the intervention and comparison groups?	N	Y
Were reasons for loss to follow up independent of intervention (exposure) and outcome?	U	Y
Were incomplete outcome data adequately addressed for primary outcome(s)?	Y	Y
Are reports of the study free of suggestion of selective outcome reporting?	Y	Y
Are reports of the study free of suggestion of publication bias?	Y	Y
Was the study apparently free of other problems that could put it at a high risk of bias?	Y	Y

Table F-5. Findings from meta-analysis of smoking cessation studies with six-month outcomes in "Treating Tobacco Use and Dependence: 2008 Update"[25]

Intervention	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Among smokers not willing to quit (but willing to change their smoking patterns or reduce their smoking)			
Placebo	5	1.0 (ref.)	3.6
Nicotine replacement (gum, inhaler, or patch)	5	2.5 (1.7–3.7)	8.4 (5.9–12.0)
Among smokers interested in quitting			
Placebo	80	1.0 (ref.)	13.8
Nicotine Patch (6–14 weeks)	32	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Long-Term Nicotine Patch (> 14 weeks)	10	1.9 (1.7–2.3)	23.7 (21.0–26.6)
Nicotine Inhaler	6	2.1 (1.5–2.9)	24.8 (19.1–31.6)

NOTE: Data extracted from Tables 6.26 (http://www.ncbi.nlm.nih.gov/books/NBK63958/table/A29582/?report=objectonly) and 6.29 (http://www.ncbi.nlm.nih.gov/books/NBK63943/table/A29585/?report=objectonly)

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