August 8, 2014

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

Re: Docket No. FDA-2014-N-0189, RIN 0910-AG38, 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; Regulations on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products

To Whom It May Concern:

The American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) appreciate the opportunity to provide input on the United States Food and Drug Administration's (FDA's) proposed rule deeming additional tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act (Docket No. FDA-2014-N-0189, RIN 0910-AG38). The AACR and ASCO are the preeminent scientific organizations for cancer physicians and researchers. The AACR, which has 34,000 members, is the world's oldest and largest professional organization dedicated to preventing and curing cancer through research, education, communication, and collaboration. The ASCO is a professional society committed to conquering cancer through research, education, prevention, and delivery of high quality patient care. ASCO's 35,000 members comprise the only organization that encompasses all oncology subspecialties.

The AACR and ASCO strongly support the development of evidence-based tobacco control policies aimed at reducing the burden of death and disease caused by tobacco use, and we applaud the FDA's proposal to extend its regulatory authority to additional tobacco products. We *urge the agency to regulate all products that meet the statutory definition of tobacco products and their component parts*, including electronic cigarettes, all cigars, hookah tobacco, nicotine gels, and dissolvable nicotine products, and to strengthen the proposed rule as described below.

Tobacco use is the leading, preventable cause of death in the U.S., causing 18 types of cancer, 30% of all cancer related deaths, and numerous other diseases and conditions, including cardiovascular disease, diabetes, macular degeneration, and rheumatoid arthritis. Additionally, all of the tobacco products that the FDA is proposing to regulate contain nicotine, a known addictive drug. Nicotine activates multiple biological pathways through

which smoking increases risk for disease, adversely affects maternal and fetal health during pregnancy and has lasting adverse consequences for brain development when exposed to the developing fetus. Nicotine exposure during adolescence may also adversely affect the developing brain.[1]

Although there is no safe form of tobacco use, there is a continuum of risk associated with the use of various tobacco products. Combustible tobacco products, which contain over 7,000 chemicals and hundreds of toxic compounds, in addition to nicotine, are particularly dangerous. Rapid elimination of all combusted tobacco, including premium cigars, would dramatically reduce the burden of tobacco-related death and disease, and AACR and ASCO support every effort toward this goal.

While data specific to the health impacts of dissolvable products and gels are limited, certain forms of smokeless tobacco can lead to oral cancer, gum disease, and nicotine addiction, and increase the risk of cardiovascular disease.[2] Moreover, as the FDA has noted, dissolvable tobacco products may be particularly appealing to children "given the brightly colored packaging, candy-like appearance, and easily concealable size." In light of these concerns, we strongly agree with the FDA's proposal to regulate these products under its tobacco authority.

The AACR and ASCO also support FDA regulation of e-cigarettes and other electronic nicotine delivery systems (ENDS), which have both potential harms and potential benefits. ENDS may be beneficial if they reduce smoking rates or prevent or reduce the known adverse health effects of smoking. However, they may be harmful, particularly to youth, if they increase the likelihood that nonsmokers or formers smokers will use combustible tobacco products or if they discourage smokers from quitting. At the present time, there are insufficient data on the long term health consequences of ENDS, their value as tobacco cessation aids, or their effects on the use of combustible tobacco products by nonsmokers and current smokers. The potential benefits of ENDS are most likely to be realized in a regulated environment in which appropriate safeguards can be implemented to reduce the potential harms posed by these products.

In the body of this letter, we provide our recommendations with regard to how the FDA should regulate newly deemed tobacco products, and we also address specific questions posed in the proposed rule. These recommendations were developed in coordination with tobacco control experts serving on the AACR Tobacco and Cancer Subcommittee, the ASCO Tobacco Cessation and Control Subcommittee, and the AACR and ASCO Electronic Cigarette Policy Statement Writing Group. Committee members are listed in Appendix 1.

A. Manufacturer Registration and Product Reporting

The AACR and ASCO support the FDA's proposals to require all tobacco product manufacturers to register with the agency and report all product and ingredient listings, including harmful and potential harmful components. We urge the agency also to require manufacturers to include the nicotine concentration on all tobacco product packaging and advertising. The FDA should also require full disclosure of all data related to composition,

use, and health effects of all tobacco products for dissemination and independent review as well as to enhance product regulation.

B. Sales, Marketing, and Advertising Restrictions

The AACR and ASCO support the FDA proposals to require manufacturers to market new tobacco products only after FDA review and only to make direct and implied claims of reduced risk if the agency confirms that scientific evidence supports the claim and that reduced risk product marketing will benefit public health as a whole.

Every effort should be made to prevent youth from using tobacco products. Therefore, the AACR and ASCO strongly support the FDA's proposals to prohibit the sale of all deemed tobacco products to individuals under 18 years of age; to require retailers to verify the birth date of any purchaser under the age of 26 years by reviewing the individual's photographic identification; to prohibit the sale of these products through vending machines except in adults-only facilities; and to prohibit the distribution of free samples of tobacco products.

To further prevent youth from accessing tobacco products, we strongly encourage FDA to strengthen the proposed rule by prohibiting:

- self-service displays of tobacco products in retail establishments;
- the provision of gifts and other giveaways with purchase of all tobacco products;
- the sale and distribution of items such as hats or t-shirts with tobacco product brand logos;
- brand name sponsorship of athletic, musical, or other social or cultural events, or any team entry into those events; and
- youth-oriented advertising of tobacco products, including the use of cartoon characters in tobacco product advertising, promotion, packaging, or labeling.

Even with these sensible regulations in place, however, it may be possible for minors to purchase tobacco products over the Internet unless steps are taken to verify the age of individuals making online purchases. To prevent youth from buying tobacco products online, the FDA should adopt age verification procedures for Internet sellers of all tobacco products analogous to the procedures required under the Prevent All Cigarette Trafficking (PACT) Act, which requires Internet and other mail-order sellers of tobacco products to check the age and identification of customers at the point of purchase and delivery.

C. Cigar Regulation

The AACR and ASCO support FDA regulation of all cigars, and we encourage the agency to apply all of the proposed regulations described in sections A and B of this letter to all cigars. We strongly oppose exempting premium or large cigars from regulation. All cigars—large and small—are dangerous. In fact, the proposed rule cites the following hazards associated with cigar use:

- all cigars, regardless of size, produce higher levels of carcinogenic tobacco-specific nitrosamines per gram in mainstream cigar smoke than cigarettes produce in mainstream cigarette smoke;

- cigar smokers who do not inhale have a 7 to 10 times higher overall risk of mouth and throat cancer than persons who have never smoked;
- cigar tobacco contains nicotine in concentrations similar to those observed in cigarettes, and since most cigars contain more tobacco, many typically contain greater quantities of nicotine than cigarettes;
- a large cigar may contain as much tobacco as a whole pack of cigarettes; and
- nicotine levels in cigar smoke can be up to 8 times higher than levels in cigarette smoke.

Moreover, both large and small cigars are of increasing interest to adults and youth. The 2012 Surgeon General's Report, entitled, "Preventing Tobacco Use Among Youth and Young Adults," reported that youth are known to have higher rates of cigar use than adults.[3] Data from the Centers for Disease Control and Prevention's August 2012 Morbidity and Mortality Weekly Report (MMWR) showed that while cigarette consumption by youth and young adults decreased by 32.8% from 2000-2011, youth consumption of non-cigarette combustibles, including premium cigars and cigarillos, increased by 123% during that same time period.[4] MMWR also reported that from 2000-2011, consumption of small cigars among all users decreased by 65%, while large cigar consumption increased by 233%.[5]

Due to the rapidly increasing use of large cigars in the U.S., and the serious health hazards posed by cigar use, which FDA has recognized, it is not in the interest of the public health to exempt premium or large cigars from FDA regulation. Exempting any cigars would set a dangerous precedent, opening the door to further FDA tobacco product exemptions. Moreover, the continued availability of these products in an unregulated market, compounded with the ability of the tobacco industry to strategically market its products to youth and young adults, could reverse progress made in reducing youth tobacco use. Should the FDA decide not to hold premium or large cigars to the same regulatory standard as other tobacco products, an appropriate set of applicable requirements for these products should be developed without completely exempting them from regulation.

D. Electronic Cigarette Regulation

As discussed above, e-cigarettes and other ENDS products have potential benefits as well as potential harms, and the AACR and ASCO fully support FDA's proposal to regulate all ENDS that meet the statutory definition of tobacco products, as well as their component parts, using its authority under the Tobacco Control Act. The FDA should regulate both ENDS delivery systems and e-liquids containing tobacco-derived nicotine whether they are sold together or separately. The agency should apply all of the proposed regulations described in sections A and B of this letter to these products.

In addition, the FDA should develop a product standard that would require all e-liquid refill bottles to be childproof, including childproof caps for eye-dropper refill bottles. Future research may point to the need for additional product changes for ENDS, including standards regulating design, constituents, nicotine levels, or other chemicals included in ENDS vapor, and we encourage FDA to require such changes as appropriate to protect the public health.

In support of our recommendation that the FDA regulate ENDS, we have summarized the current research on the use and public health effects of these products in the attached appendix. We have also outlined areas in which ENDS research is need to inform FDA regulation of these products and guide the decisions of consumers and healthcare providers related to ENDS use. We encourage the FDA to support research on these topics as appropriate.

E. Flavorants

Flavored combustible and smokeless tobacco

The AACR and ASCO support a ban on the addition of non-tobacco characterizing flavors, including menthol, to all combustible and smokeless tobacco products, including cigarettes, all cigars, hookah tobacco, and pipe tobacco. We are particularly concerned about the proliferation of flavored cigars. A recent study found that 75% of the growth in cigar sales from 2008-2011 was due to growth in sales of flavored cigars,[6] and according to the Florida Youth Tobacco Survey, nearly 60% of high school cigar smokers smoke flavored cigars.[7]

Not only are flavored tobacco products particularly appealing to youth, but research shows that some flavored combustible products potentiate continued use of, and addiction to, tobacco products.[8,9] For example, as we noted in our comments on the FDA's request for information on menthol in cigarettes,[10] multiple lines of evidence support a role for menthol in cigarettes in increasing experimentation and progression to regular smoking. Youth who initiated smoking with menthol cigarettes are more likely to become daily, regular, or established smokers than those who initiated with non-menthol cigarettes, and adolescent menthol cigarette smokers have a higher prevalence of nicotine dependence and more severe nicotine addiction than those who smoke non-menthol cigarettes.

Moreover, the danger of menthol-flavored cigarettes falls disproportionately on African Americans. For example, African Americans are more likely to smoke menthol cigarettes, and African-American menthol smokers are also less likely to quit smoking successfully than are non-menthol smokers. Banning menthol flavoring in all combustible and smokeless tobacco products would be an important step toward reducing tobacco-associated harm to this population and protecting all youth from the dangers of tobacco addiction.

Flavored ENDS

Flavored ENDS have proliferated, and a recent study reported that there are now 7,764 unique e-cigarette flavors on the market.[11] We are concerned that, like flavored combustible tobacco products, flavored ENDS may appeal to youth and potentiate continued use of and addiction to these products. However, some experts believe that the availability of flavored ENDS may encourage adult smokers to switch from combustible products to ENDS, prevent youth who use flavored ENDS from transitioning to combustible products, and enhance the efficacy of ENDS as cessation aids. Today, there is no evidence for or against this, and the public health benefits of flavored ENDS are currently unknown. Therefore, priority should be placed on preventing youth from using these products.

The AACR and ASCO recommend a prohibition on ENDS and ENDS liquid containing candy and other youth-friendly flavors unless there is evidence demonstrating that these products do not encourage youth uptake of ENDS. Flavors or flavor names that are brand and/or trademarked names for candy, cookies, soda, ice cream, and other nontobacco products that are especially attractive or recognizable to youth should also be prohibited.

F. Warning Labels

In light of the addictiveness and adverse health consequences of nicotine, the AACR and ASCO support FDA's proposal to require all nicotine-containing tobacco product packaging and advertising to carry a warning stating, "WARNING: This product contains nicotine. Nicotine is an addictive chemical." We also support FDA's proposal to require four additional rotating health warning for cigars addressing 1) the risks of cancer of the mouth and throat, 2) the risk of lung cancer and heart disease, 3) the risk of lung cancer and heart disease from secondhand smoke, and 4) that cigars are not a safe alternative to cigarettes. All cigars, including premium cigars and those currently sold without product packaging, should be required to carry these warnings. The FDA should also require additional warnings as appropriate to protect the public health.

As early as 1992, studies have shown that warning labels are most effective when designed to grab the consumer's attention.[12] Additionally, warning labels need to be large enough to confer readability.[13] Studies examining the font size and overall size of warning labels found that larger labels and those with larger font sizes are more effective, and that recall of the message and noticeability of the warning label is tied to size.[14,15] These data demonstrate that the size of an addictiveness warning does matter, and FDA should require all warning labels to be large enough to be noticeable by the consumer, and the font size should be large enough to ensure ease of readability.

G. Premarket Review Timelines

The AACR and ASCO support shortening the period for submitting premarket and substantial equivalence applications for new products to one year from the date the deeming rule becomes final. We encourage the FDA to take steps to avoid undue delay in resolving these applications. In addition, as a condition of allowing newly deemed products to remain on the market until the applications are reviewed, FDA should place sales and marketing restrictions on these products, require product manufacturers to submit ingredient information within 90 days of the final rule, and require manufacturers to meet standards for good manufacturing practices.

H. Possible Exemptions for Small Manufacturers

The tobacco products made by small manufacturers are no less harmful or addictive than the products made by large manufacturers. Given the adverse impact that tobacco products have on public health, the FDA should not exempt manufacturers of deemed products from tobacco product regulations based on the size of the manufacturer.

I. Discounting Benefits from Smoking Cessation in Regulatory Impact Analyses

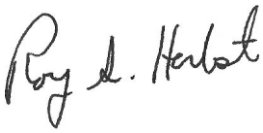
The AACR and ASCO strongly encourage the FDA to drop the consumer surplus discount from its regulatory impact analysis of the proposed deeming rule, and all subsequent rules related to tobacco. The consumer surplus discount should only be applied when consumer buying decisions are based on rational and fully informed choices. However, as FDA acknowledges in the proposed rule, the vast majority of smokers begin smoking and become addicted while they are still underage, and at a time of life when their decision to begin smoking is neither fully-informed nor rational. Moreover, once a tobacco user becomes addicted, the decision to continue buying tobacco products is no longer rational. The vast majority of smokers indicate that they regret taking up smoking.[16] Moreover, research demonstrates that smoking cessation is beneficial,[17] and these benefits extend beyond physical health. Smokers report greater stress, poorer mood, and lower health–related and overall quality of life than nonsmokers,[18,19] and quitting smoking seems to improve these dimensions in the longer term.[20,21,22,23,24] For most smokers, addiction is an unwelcome burden, imposing enormous psychological and physical costs from the inability to quit. It is therefore perverse to consider the satisfaction of an addiction to smoking as a "pleasure."

J. Timing of Implementation

The AACR and ASCO urge FDA to implement the final rule by April 25, 2015, which is one year following the issuance of the proposed rule.

Thank you for very much for considering our input on this important issue. If the AACR or ASCO can provide any additional information or assistance to the FDA, please do not hesitate to contact Jennifer A. Hobin, PhD, Director of Government Relations for AACR at (202) 898-6499 or jennifer.hobin@aacr.org, or Courtney Tyne, MPH, Health Policy Manager for ASCO at (571) 483-1667 or courtney.tyne@asco.org.

Sincerely,



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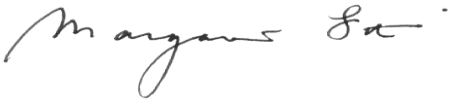

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Appendix 1

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Appendix 2

Summary of Current Research on Electronic Nicotine Delivery Systems (ENDS)

ENDS toxicity

Known toxicants (including those causing respiratory and heart distress) and carcinogens have been identified in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions. One study found the levels of the toxicants in e-cigarettes to be significantly lower than in cigarette smoke and, in many cases, comparable with trace amounts found in a medicinal nicotine inhaler.[25] It remains unclear what effects these toxicants might have on ENDS users after chronic and frequent use of the devices, and there are several unanswered health questions with regard to ENDS use, such as the pulmonary effects of propylene glycol, glycerin, and other constituents of ENDS.

Nicotine is a known potentially lethal toxin. Some users reported experiencing side-effects such as mouth and throat irritation, which may be caused by exposure to nicotine, nicotine solvents, or toxicants found in the ENDS aerosol.[26,27] Given the relatively low doses of nicotine that ENDS deliver, and users' ability to titrate the desired dose, serious overdose from ENDS aerosol inhalation is unlikely. In contrast, concentrated nicotine in the liquid reservoirs of tank-based e-cigarettes can be toxic if it is inadvertently ingested or absorbed through the skin, and data from the Centers for Disease Control and Prevention showed a significant increase in e-cigarette-related calls to poison centers.[28]

Studies have found that e-cigarettes emit ultrafine particles, traces of carbonyls, volatile organic compounds, polyaromatic hydrocarbons, tobacco-specific nitrosamines, and glycols into the indoor air,[29,30] but these emissions have been show to fall below OSHA exposure limits.[31] Studies have shown that e-cigarettes may expose non-users to nicotine from secondhand exposure,[32,33] but it has been estimated that secondhand exposure to nicotine from e-cigarettes is on average 10 times less than from tobacco smoke, and the level of exposure depends on the brand.[34] There are no current data to suggest that second-hand exposure to ENDS has any health effects.

Although there are no data to show ENDS emissions negatively impact health, the effects of second hand exposure to ENDS vapor on an individual's desire to smoke is important to consider. One study found that exposing young adult daily smokers to e-cigarette use by others in an experimental setting increased their desire to smoke both combustible and e-cigarettes.[35] There are no published studies evaluating third-hand exposure to ENDS aerosol.

Abuse liability

Although some ENDS do not contain nicotine, surveys show that 97% of respondents who use e-cigarettes use products containing nicotine.[36] Variation among products in composition and use patterns makes research on abuse liability difficult. In addition to variable nicotine delivery within and across brands,[37,38] nicotine delivery varies by the user's level of experience with these products, with more experienced users obtaining

levels of nicotine comparable to that achieved by cigarette smokers.[39,40,41] Research has shown the rate of absorption, an important factor contributing to the abuse liability of a drug, may be slower for e-cigarettes compared to conventional cigarettes,[42] which may lessen the abuse potential of e-cigarettes compared to combustible cigarettes.

The sensory aspects of ENDS use may also affect abuse liability. For example, Eissenberg[43] observed that despite the minimal increase in plasma nicotine from the e-cigarettes, there was a significant decrease in craving with the use of these products. Another study showed a reduction in self-reported stages of addiction whether or not the e-cigarettes contained nicotine.[44] To date, no study has been conducted that carefully investigated the effect of e-cigarettes with different nicotine doses to determine participant preference and effect.

Patterns of ENDS Use

ENDS initiation by nonsmokers—including former smokers—is a cause for concern. Data on patterns of use are rapidly evolving, and current data are summarized below.

Youth

A 2011 study of adolescents males reported low use of e-cigarettes (<1%). Approximately 18% of participants were willing to try e-cigarettes, and smokers were more willing to try them than non-smokers.[45] The National Youth Tobacco Survey (NYTS) reported that in 2011 and 2012,[46] ever use of e-cigarettes (tried at least once) among middle and high school students increased from 3.3% to 6.8%, whereas current use (within the last 30 days) increased from 1.1% to 2.1%. Among high school students specifically, current use rose from 1.5% to 2.8%. However, of the ever-users in high school, 80.5% reported current use of combustible cigarettes in 2012, suggestive that e-cigarettes are primarily attractive to current smokers. Another analysis of NYTS data from the same time period confirmed that current e-cigarette users were much more likely to be current smokers.[47] Reasons for youth e-cigarette use are not well-known at this time. Though absolute prevalence rates of e-cigarette use by youth are low, the proportional increase in current use is concerning.

Adults

Current data show that overall use of ENDS by adults is low, with less than 2% reporting using every day or some days in 2012-2013 compared to 18% who report using cigarettes.[48] The vast majority of e-cigarette users are smokers,[49] with only about 1% lifetime prevalence among never smokers.[50] At least 20-35% of current smokers have tried e-cigarettes,[51,52,53] with the proportion increasing rapidly. Low-income individuals appear more likely to have used e-cigarettes, but there appear to be no differences in prevalence according to sex, race/ethnicity, or age.[54] Adults primarily report use of e-cigarettes to quit or reduce smoking, as e-cigarettes are perceived to be safer than combustible cigarettes.[55] Moreover, users tend to report high satisfaction with the product.[56]

Overall, patterns suggest that e-cigarettes are used primarily by combustible cigarette smokers, but ever-use by never smokers is higher among youth, raising concerns that this product may serve as an introduction to tobacco use among adolescents. Indeed, e-cigarette initiation by either youth or adult nonsmokers—including former smokers—is a cause for concern. Dual-use patterns appear to be common, and adults tend to report harm-

reduction motivations for using e-cigarettes. However, existing data are rapidly evolving and are insufficient to clarify patterns of or motivations for ENDS use by youth or adults.

Using ENDS for smoking cessation

Few studies have been conducted to determine the efficacy of ENDS for smoking cessation, and data are currently inconclusive to support or refute the use of ENDS as smoking cessation aids. The major surveys are summarized here.

- An online survey of 3,587 found that 92% of e-cigarette users who were current smokers reported e-cigarettes helped them to reduce smoking, and 96% of former smokers reported the product helped them to quit smoking. About 79% used e-cigarettes to deal with craving and 67% to deal with tobacco withdrawal symptoms.[57]
- In a survey of nearly 6,000 adults in the United Kingdom who tried to quit smoking at least once in the past year, respondents who used e-cigarettes had a higher quit rate (20%) than those who used nicotine replacement therapy (NRT) (10%) or no smoking cessation aids (15%).[58]
- A four country survey of 5,939 current and/or former smokers conducted under the International Tobacco Control Policy Evaluation Project (ITC) reported that 85% of current e-cigarette users reported using e-cigarettes to quit smoking; however, only 11% reported having quit. There were no significant differences in quit rates between e-cigarette users and nonusers.[59]
- Another trial that randomized 657 adult smokers to nicotine containing e-cigarettes, nicotine patches, or non-nicotine containing patches found no difference in abstinence rates among groups at six months. Quit rates in this trial were lower than expected for NRT, but the authors concluded that the trial was not sufficiently powered to make conclusions on the effectiveness of e-cigarettes.[60]

Using ENDS to reduce use of combustible cigarettes

Many ENDS users use these products in combination with combustible cigarettes. Studies have found that ENDS use by combustible cigarette smokers can reduce the number of cigarettes smoked.[61,62,63,64] Although ENDS may deliver fewer toxic compounds compared with combustible cigarettes, the extent to which reducing exposure to these compounds would lead to meaningful reductions in adverse health effects is unknown. One study demonstrated that in order to achieve a 42% reduction in exposure to carcinogens, about a 90% reduction in cigarettes smoked must occur.[65] This result demonstrates that smokers trying to reduce the number of cigarettes they smoke tend to smoke each cigarette more intensely. The increased intensity occurred even when smokers were provided NRTs. E-cigarette studies have shown that only 1-15% of those who continued to smoke reduced their usual brand smoking intake by around 90%.[66,67]

ENDS research gaps

The evidence regarding the risks and benefits of ENDS is difficult to interpret since the marketplace of ENDS products is evolving rapidly and data on the long-term consequences of ENDS use are not yet available. Additional studies are needed to inform FDA regulation of ENDS and guide the decisions of consumers and healthcare providers related to ENDS

use. In addition to developing a standardized system for testing ENDS, research is needed to understand:

- how different design features affect abuse liability and health effects of ENDS;
- the health effects of acute and chronic ENDS product use, including the health effects of second- and third-hand exposure;
- whether transition from smoking to ENDS confers a health benefit;
- the abuse potential of different types of ENDS;
- how ENDS are being used by youth and adults;
- how ENDS use affects combustible tobacco product use;
- the effects of flavorants on the appeal and use of ENDS products and on the use of combustible tobacco products;
- how the marketing and availability of ENDS affect perception and use of ENDS as well as other tobacco products;
- how tobacco control policies impact the pattern of ENDS use;
- the potential role of ENDS for smoking cessation.

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