

VIA ELECTRONIC SUBMISSION

June 30, 2015

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

RE: Docket No. FDA-2014-N-1936-0001, Electronic Cigarettes and the Public Health

To Whom It May Concern:

The American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) are the preeminent scientific organizations for cancer physicians and researchers. AACR, which has 34,000 members, is the world's first and largest professional organization dedicated to preventing and curing cancer through research, education, communication, and collaboration. 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.

Electronic Nicotine Delivery Systems (ENDS), which include electronic cigarettes, are devices capable of delivering nicotine in an aerosolized form. As the leading professional societies for researchers and clinicians in the field of oncology, both with a focus that includes preventing and curing cancer, ENDS are of particular interest because of the new nicotine delivery technology with the unknown, but potentially significant, ability to alter patterns of tobacco use and its attendant health consequences. AACR and ASCO recently published a joint statement on ENDS which may be viewed in its entirety here:

<http://clincancerres.aacrjournals.org/content/early/2015/01/04/1078-0432.CCR-14-2544.full.pdf+html>

The AACR and ASCO would like the FDA to consider comments and recommendations from its 2015 joint policy statement on ENDS concerning e-cigarettes and the public health.

Toxicological Considerations

Roles of nonclinical models and human clinical studies

The AACR and ASCO recommend the use of in vitro, in vivo and clinical studies to develop biologic and clinical models of physiologic effects of the aerosol exposure received through ENDS. Studies should examine the efficacy and safety in the general population and specifically in patients with cancer treated with surgery, chemotherapy, and radiotherapy; and how ENDS potentially interact with cytotoxic cancer therapies. The effect of ENDS use on treatment adverse effects, complications, response and cancer recurrence also need to be examined. Relevant ENDS user

outcomes should be examined relative to those individuals who continue to smoke, those who quit smoking, and those who use FDA-approved NRT products.

Impact of local and systemic exposure of e-liquid and aerosol

Concerns have been raised that ENDS can harm their users by delivering toxic nicotine levels. Studies have shown that some ENDS users experience adverse effects such as mouth and throat irritation, which may be caused by exposure to the nicotine itself, nicotine solvents, or toxicants found in the aerosol. However serious overdose from ENDS aerosol inhalation is unlikely. In contrast, the concentrated nicotine in ENDS solutions can be toxic if it is inadvertently ingested or absorbed through the skin. Data from the CDC showed a significant increase in e-cigarette related calls to poison centers; the number of calls rose from one per month in September 2010 to 215 per month in February 2014, with more than half of the calls involving young children.

There are no current data to suggest that secondhand exposure to ENDS has any health effects; however, secondhand exposure to ENDS vapor is possible. Although no sidestream aerosol is generated from ENDS between puffs, some of the aerosol is exhaled by the user, and e-cigarettes may expose nonusers to nicotine from secondhand exposure. It has also been reported that e-cigarettes emit ultrafine particles, trace amounts of carbonyls, volatile organic compounds, polyaromatic hydrocarbons, tobacco-specific nitrosamines, and glycols into the indoor air. However, other studies have found levels of dangerous substances that fall below OSHA exposure limits. The estimated exposure to nicotine from e-cigarettes is on average 10 times less than the exposure from tobacco smoke, but the level of exposure depends on the brand.

There are no published studies evaluating third hand exposure to ENDS aerosol in indoor environments, although preliminary data suggest nicotine from ENDS can stick to surfaces.

Levels of toxicant exposure from e-cigarettes compared to those in users of other tobacco or nicotine containing products

At this time it remains unclear how effectively various ENDS deliver nicotine. Furthermore, some ENDS contain no nicotine or virtually no nicotine. There are at least four factors that affect the amount of nicotine from ENDS absorbed into the bloodstream and reaching the nicotine receptors in the brain: 1) the nicotine content in a product; 2) how effectively the vaporization process transfers nicotine from the reservoir into the aerosol; 3) additives that may facilitate nicotine absorption; 4) use habits (such as frequency and depth of inhalation) that may affect the bioavailability of nicotine.

Toxicological concerns associated with long-term inhalation of aerosols containing propylene glycol, glycerin and flavorings

A review released by the FDA in May 2014¹ reported that various chemical substances and ultrafine particles known to be toxic or carcinogenic and/or to cause respiratory and heart distress have been identified in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions. Additional research should allow comparisons of ENDS aerosol and traditional smoke constituent levels to inform an evaluation of the toxicity potential of ENDS.

¹ Cheng T: Chemical evaluation of electronic cigarettes. *Tob Control* 23:ii11-ii17, 2014 (suppl 2)

Clinical Pharmacology and Abuse Liability

Reinforcing effects of e-cigarettes

Patterns suggest that e-cigarettes are used primarily by combustible cigarette smokers, but use by never-before smokers is higher among youth, raising concerns that this product may serve as an introduction to tobacco use among adolescents. Dual-use patterns seem to be common, and adults tend to report harm-reduction motivations for using e-cigarettes.

Some experts believe that the availability of flavored ENDS may encourage adult smokers to switch from combustible products to ENDS, prevent youth from transitioning to combustible products from ENDS, and enhance the efficacy of ENDS as cessation aids. At the present time, the impact of flavored ENDS on patterns of use and smoking cessation is unknown.

Enhancement of the abuse liability of e-cigarettes through flavorings

Research shows that flavored tobacco is particularly appealing to youth, and some flavored combustible products potentiate continued use and addition. There is concern that flavored ENDS may have a similar effect on youth.

Unique abuse liability risks for e-cigarette users in specific subpopulations

Knowledge about the abuse liability of ENDS is important to determine the potential for continued and persistent use of these products, the extent to which they can substitute for cigarettes, and how difficult it will be for ENDS users to stop using these devices after initiation of regular use. Research on the abuse liability of ENDS is complicated by variation among product composition and use patterns. In addition to variable nicotine delivery within and across brands, nicotine delivery varies by the user's level of experience with the products, with more experienced users obtaining levels of nicotine comparable to those achieved by cigarette smoking. The rate of absorption, however, may be slower for e-cigarettes compared with conventional cigarettes, which may lessen the abuse potential of e-cigarettes compared to combustible cigarettes. The sensory aspects of ENDS use may also affect abuse liability.

Research is needed to determine the addictive potential of ENDS as related to nicotine content and product design. Studies should examine how variability in the nicotine concentration of ENDS liquid, the amount of nicotine vaporized, and ENDS topography affects delivery of nicotine to users and how this compares with nicotine delivered by combustible cigarettes and FDA-approved NRTs. Studies should also assess other factors that contribute to potential abuse liability of ENDS, including non-nicotine additives and the sensory aspects of smoking.

Impact of e-cigarette use on nicotine addiction

Recently, data have been emerging from large population-level analyses suggesting a benefit of ENDS on smoking cessation, although findings are not yet conclusive. Among smokers, controlled clinical trials are needed to determine whether ENDS facilitate or hinder short- and long-term smoking cessation, as well as whether use of ENDS in addition to combustible cigarettes undermines cessation efforts or increases nicotine addiction/dependence. Studies should consider outcomes for both smokers interested and not interested in quitting smoking. Currently, there is insufficient evidence regarding potential benefits or harms of ENDS use among patients with cancer. Well-controlled trials examining the safety and efficacy of ENDS for treating tobacco dependence are needed to guide oncology practice guidelines.

Health Effects in Users

Evaluation of known short and long-term health effects of e-cigarettes in experienced users, and potential other short and long-term health effects of e-cigarettes in users

It is currently impossible to draw firm conclusions about the health risks of these products as a whole because there are more than 460 ENDS brands available, thousands of e-liquid alternatives on the market, and considerable variability in the product design and performance. A standardized system for testing ENDS products and performance is needed.

Considerations for Health Effects in Specific User Populations

Populations of users may be at lower or higher risk of adverse effects

Currently, there is insufficient evidence regarding potential benefits or harms of ENDS use among patients with cancer. Well-controlled trials examining the safety and efficacy of ENDS for treating tobacco dependence are needed to guide oncology practice guidelines.

Factors to be considered in the evaluation of risk in vulnerable populations

Studies should examine the efficacy and safety of ENDS in the general population and in cancer patients treated with surgery, chemotherapy, and radiotherapy, and should examine how ENDS potentially interact with cytotoxic cancer therapies. The effect of ENDS use on treatment adverse effects, complications, response and cancer recurrence also need to be examined. Relevant ENDS user outcomes should be examined relative to those individuals who continue to smoke, those who quit smoking, and those who use FDA-approved NRT products.

Health effects in dual users

There is no consensus that ENDS should be used as a substitute for smoking among those who experience difficulty quitting or do not want to quit. Further, a report published by the World Health Organization in 2012 raised concerns that ENDS may in fact normalize the use of combustible cigarettes. More evidence is needed to understand patterns of use and to determine if dual use with reductions in smoking is a path toward abstinence from cigarette smoking.

Unique issues for evaluation of the short and long-term health effects in users of e-cigarettes in combination with traditional cigarettes, other combusted products, and smokeless tobacco

Many ENDS users are dually using these products with combustible cigarettes, and studies find that ENDS use by cigarette smokers can reduce the number of cigarettes smoked. Although ENDS may deliver fewer toxic compounds compared to combustible cigarettes, the extent to which reducing exposure to these compounds would lead to meaningful reductions in adverse health effects is unknown.

Unique health effects of concern for users with underlying disease

Studies should examine the efficacy and safety of ENDS in the general population and in cancer patients treated with surgery, chemotherapy, and radiotherapy, and examine how ENDS potentially interact with cytotoxic cancer therapies. The effect of ENDS use on treatment adverse effects, complications, response and cancer recurrence also need to be examined. Relevant ENDS user outcomes should be examined relative to those individuals who continue to smoke, those who quit smoking, and those who use FDA-approved NRT products.

Human Factors

Adverse events associated with e-cigarette use

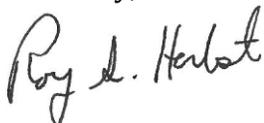
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Information needed by consumers to adequately understand the product and mitigate risk

ENDS manufacturers should be required to report all product and ingredient listings, including harmful and potential harmful components, as well as the nicotine concentration in the ENDS solution. AACR and ASCO encourage FDA to exercise its regulatory authority to require health warning and safety labels in addition to its proposed nicotine warning on e-cigarette packaging and advertising as appropriate to protect the public health.

The AACR and ASCO appreciate the opportunity to comment on e-cigarettes and the public health, and we look forward to working closely with the FDA on this issue in the future. If the AACR or ASCO can provide any additional information or assistance, please do not hesitate to contact Shimere Sherwood, PhD, Associate Director of Science Policy for AACR at (202) 898-6499 or shimere.sherwood@aacr.org, or Janette Merrill, MS CHES, Program Manager, Health Policy for ASCO at (571) 483-1629 or janette.merrill@asco.org.

Sincerely,



Roy S. Herbst, MD, PhD
Chair, Tobacco and Cancer Subcommittee
American Association for Cancer Research



Margaret Foti, PhD, MD (h.c.)
Chief Executive Officer
American Association for Cancer Research



Graham Warren, MD, PhD
Chair Tobacco Control Subcommittee
American Society of Clinical Oncology



Julie M. Vose, MD, MBA, FASCO
President
American Society of Clinical Oncology