

July 16, 2018

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

Re: Docket No. FDA-2017-N-6189, RIN 0910-AH86, Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

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) advanced notice of proposed rulemaking on developing a tobacco product standard to set the maximum nicotine level for combusted cigarettes. The AACR and ASCO are the preeminent scientific organizations for cancer researchers and physicians. The AACR, which has 40,000 members, is the world's oldest and largest professional organization dedicated to preventing and curing cancer through research, education, communication, and collaboration. ASCO represents nearly 45,000 oncology professionals who care for people living with cancer. Through research, education, and promotion of the highest-quality patient care, ASCO members are committed to ensuring that evidence-based practice for the prevention, diagnosis, and treatment of cancer is available to all Americans.

Tobacco use is the leading preventable cause of premature mortality in the United States and globally. In 2016, tobacco use caused over 7.1 million deaths worldwide due to active and secondhand smoking. In the United States, about a half million deaths from active and secondhand smoking occur every year, accounting for about 1 out of every 10 deaths. Tobacco use has a particularly profound impact on cancer incidence and mortality. Tobacco accounts for 30 percent of all cancer deaths and is causally associated with 18 different human cancers, including lung, head and neck, stomach, pancreas, colon, and cervical cancers. Continued smoking by cancer patients and survivors increases risk for overall mortality, cancer-related mortality, second primary cancer, and cancer treatment toxicity. Tobacco use in any form is one of the strongest threats to public health; therefore, to curb this epidemic, we must enforce existing laws and evidence-based policies with greater vigor, invest in more research to

understand nicotine addiction to inform effective control measures, and promote evidence-based policies to stem tobacco use.

The AACR and ASCO applaud the FDA for placing nicotine addiction at the center of the Agency's tobacco regulatory efforts. Most people who use tobacco regularly do so because they are addicted to nicotine, the major addictive component in tobacco. Although most users express a desire to reduce their use or stop entirely, overcoming nicotine addiction is difficult and can be supported by policy changes. We thank the Agency for taking this important step forward in improving public health and reducing the incidence of disease.

In response to the FDA's Federal Register announcement, the AACR and ASCO provide the following comments:

A. Scope

1. *If FDA were to propose a product standard setting a maximum nicotine level, should such a standard cover other combusted tobacco products in addition to cigarettes? If so, which other products? If FDA were to propose to include additional categories of combusted tobacco products in a nicotine tobacco product standard, should the standard be tailored to reflect differences in these products? What criteria should be used to determine whether, and which, products should be covered?*
 - a. *Combusted cigarettes (which FDA has previously interpreted to include kreteks and bidis),*
 - b. *Cigarette tobacco,*
 - c. *Roll-Your-Own (RYO) tobacco,*
 - d. *Cigars (some or all categories; i.e., small cigars, large cigars, cigarillos, and/or so-called premium cigars),*
 - e. *Pipe tobacco, and*
 - f. *Waterpipe tobacco.*

Benowitz and Henningfield, who proposed a nicotine threshold for cigarettes in a 1994 New England Journal of Medicine paper,¹ stated in a subsequent article that

¹ Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N Engl J Med.* 1994;331(2):123-125. DOI 10.1056/NEJM199407143310212, <https://www.ncbi.nlm.nih.gov/pubmed/7818638>

a reduced nicotine standard should apply to all the nicotine products listed above.² It is the AACR and ASCO's belief that when deciding the scope of a nicotine product standard, the FDA should consider the abuse liability, toxicity, and pattern of use of the product. Additionally, the FDA should consider the extent to which the products will substitute for cigarette smoking. Of particular concern are little cigars and cigarillos, as these products have similar product design, pharmacokinetics,³ and toxicity⁴ as combusted cigarettes and are likely to have higher abuse liability relative to reduced nicotine content cigarettes if they are not similarly covered by a reduced nicotine standard. Furthermore, as cigarette taxes increased, little cigar sales increased, suggesting that smokers are likely to substitute cigarettes for little cigars⁵ Although no large study has been conducted on the choice of products if cigarettes were reduced to minimally addictive levels, one pilot study demonstrated an increasing uptake of other combusted products, such as little cigars, when smokers were randomized to a very low nicotine content cigarette condition.⁶

2. Some suggest that large cigars and those cigars typically referred to as “premium” cigars should be regulated differently from other cigars, asserting that they are used primarily by adults and their patterns of use are different from those of regular cigars (81 FR 28973 at 29024). FDA requests information and data on whether large and/or so-called premium cigars should be excluded from a possible nicotine tobacco product standard based on asserted different patterns of use, and whether large and/or so-called premium cigars would be migration (or dual use) candidates if FDA were to issue a nicotine tobacco product standard that excluded premium cigars from its scope. FDA also requests data and information on whether and how there is a way that, if FDA were to exclude premium cigars from the scope of a nicotine tobacco product standard, FDA could define “premium cigar” to

² Benowitz NL, Henningfield JE *Reducing the nicotine content to make cigarettes less addictive* Tobacco Control 2013;22:i14-i17.

³ Pickworth, W.B., Z.R. Rosenberry, and B. Koszowski, *Toxicant exposure from smoking a little cigar: further support for product regulation*. Tob Control, 2017. **26**(3): p. 269-276.

⁴ Pickworth, W.B., et al., *Cigarillo and Little Cigar Mainstream Smoke Constituents from Replicated Human Smoking*. Chem Res Toxicol, 2018. **31**(4): p. 251-258.

⁵ Gammon DG, Loomis BR, Dench DL, King BA, Fulmer EB, Rogers T. Effect of price changes in little cigars and cigarettes on little cigar sales: USA, Q4 2011-Q4 2013. *Tob Control*. 2016;25(5):538-544. DOI 10.1136/tobaccocontrol-2015-052343, PMCID #: PMC4903936. <https://www.ncbi.nlm.nih.gov/pubmed/26357952>

⁶ Hatsukami DK, Luo X, Dick L, Kangkum M, Allen SS, Murphy SE, Hecht SS, Shields PG, al'Absi M. Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. *Addiction*. 2017;112(1):156-167. DOI 10.1111/add.13603, PMCID #: PMC5249662. <https://www.ncbi.nlm.nih.gov/pubmed/27614097>

include only unlikely migration or dual use products and thereby minimize such consequences.

The impact of reducing nicotine in combustible cigarettes on the uptake of cigar smoking is unclear at this time. We do know that exclusive premium cigar smokers generally exhibit a different pattern of use. Based on what we know about current use patterns, premium cigars may not be relevant substitutes for smokers who are seeking nicotine to replace the levels that were attained from higher nicotine content cigarettes. One important difference is that cigars, and especially premium cigars, tend to have a relatively higher pH which makes the smoke harsh and more difficult to inhale⁷ We suggest that, in addition to other factors defining cigars as “premium” (e.g. manufacturing processes, cost, etc.), the FDA consider setting a limit on the pH of premium cigars, e.g. premium cigars tend to have a high pH (~ 6.0). A justification for this pH standard is that the tobacco industry may try to label something with a lower pH (i.e. lower than 6.0) as a “premium cigar” but it may have a greater abuse liability relative to the other premium cigar (higher pH) products. If a pH threshold (e.g., ≥ 6.5) is considered by the FDA, the toxicity, abuse liability and pattern of use of associated with this standard would need to be determined.

3. *Should waterpipe tobacco products, which are different from regular pipe tobacco, be included in such a standard? Are there data showing different use topographies or that they are not likely to be migration substitutes or dual use candidates? If FDA were to issue a nicotine tobacco product standard that did not include waterpipe tobacco products within the scope, what would be the likelihood that former smokers would switch to waterpipe tobacco to maintain their nicotine addiction? What are the relative risk consequences of switching to waterpipe tobacco?*

Unfortunately, there is very little research to help us understand how to regulate waterpipes as the pattern of waterpipe use is different from that of other tobacco products. There is evidence that in the U.S., these products are typically used in social situations, contain a robust nicotine level, and are used for longer durations of time relative to combusted cigarettes.⁸ A recent study demonstrated that waterpipe smoking comprised half the volume of tobacco smoke consumed by

⁷ Lawler, TS et al., Surveillance of Nicotine and pH in Cigarettes and Cigar Filler, Tobacco Regulatory Science, 2107, April; Suppl. 1, 101-116.

⁸ Primack BA, Shensa A, Sidani JE, et al

Comparison of toxicant load from waterpipe and cigarette tobacco smoking among young adults in the USA
Tobacco Control Published Online First: 16 May 2018. doi:10.1136/tobaccocontrol-2017-054226

young adults in the United States. Furthermore, there is evidence that patterns of waterpipe use in younger cohorts are changing. We suggest that the FDA conduct research to determine the substitutability of waterpipes for very low nicotine content cigarettes and whether the pattern of use might change as a result of the reduced nicotine product standard. Although empirical evidence is sparse, it is not unreasonable to think that some smokers might switch to home use of waterpipes and portable waterpipes. We also recommend active and timely surveillance of waterpipes to assess the potential of a shift from combustible cigarette to waterpipe use so that rapid regulatory action could be taken if such a shift does indeed occur.

B. Maximum Nicotine Level

1. *The Tobacco Control Act prohibits FDA from reducing nicotine yields in any combusted tobacco product to zero (section 907(d)(3) of the FD&C Act). If FDA were to propose a maximum nicotine level for cigarettes, what should be the maximum level to ensure that the product is minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health? Rather than establishing a nicotine target to make products “minimally addictive” or “nonaddictive,” should FDA consider a different threshold (e.g., less addictive than current products on the market)? How should the maximum level be measured (e.g., nicotine yield, nicotine in cigarette filler, something else)? What would be the potential health impacts of requiring a maximum nicotine level such as 0.4 mg nicotine/g of tobacco filler? FDA is interested in public health impacts of requiring different maximum nicotine levels, such as 0.3, 0.4, and 0.5 mg nicotine/gram of tobacco filler, as well as other maximum nicotine levels and solicits comments about the potential health impacts of different maximum levels.*

The lower the dose of nicotine in combustibles, the less reinforcing the drug would be in promoting and sustaining addiction. The majority of studies that are now being conducted have assessed a level of 0.4 mg nicotine per gram of tobacco because this is the lowest dose available to researchers. Based on existing peer-reviewed and published research that demonstrates reduced smoking, nicotine, and toxicant exposure, dependence *and* increased quit attempts with the 0.4 mg nicotine/g tobacco dose,⁹ we recommend a maximum nicotine level no greater than 0.4 mg nicotine/g tobacco. The 0.4 mg nicotine/g tobacco level has been

⁹ World Health Organization. Advisory Note: Global Nicotine Reduction Strategy. *WHO Study Group on Tobacco Product Regulation (TobReg)*. Geneva, Switzerland: World Health Organization; 2015.

demonstrated to be less reinforcing than normal nicotine content cigarettes in the general population of smokers¹⁰ and in vulnerable populations such as smokers with psychiatric co-morbidities or who are of lower socioeconomic status. Furthermore, the 0.4 mg nicotine/g tobacco dose has been shown to be less reinforcing than typical nicotine content cigarettes in young adults¹¹ and youth.¹²

2. *FDA lists four types of studies to estimate the threshold of nicotine addiction (i.e., indirect estimates; findings of increased cessation for VLNC cigarettes; subjective effects, craving, and withdrawal associated with VLNC cigarettes; and lower nAChR occupancy and cerebral response from the use of VLNC cigarettes). Should FDA rely on some or all of these types of studies? Why or why not? Is there a different method that FDA should investigate or use to determine the threshold for nicotine addiction?*

The primary outcome criteria for whether a nicotine product standard should be pursued are its impact on behaviors (i.e., smoking cessation and reducing progressing from experimentation to dependence). To this end, clinical trials are one of the best ways to determine a product's effect on behavior. Examining the effects of a product standard on craving, withdrawal symptoms, or other unintended consequences is also important to identify ways to mitigate some of these untoward effects. Studies on brain response and other physiological responses can also provide information on potential behavioral changes.

Because some studies cannot ethically be conducted on tobacco naïve adolescents or adults, non-human animal studies can help to identify potential behavioral effects (e.g. establishment of regular nicotine-seeking behaviors). Observations on

¹⁰ Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobos DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized trial of reduced-nicotine standards for cigarettes. *N Engl J Med.* 2015;373(14):1340-

¹¹ Cassidy RN, Tidey JW, Cao Q, Colby SM, McClernon FJ, Koopmeiners JS, Hatsukami D, Donny EC. Age moderates smokers' subjective response to very low nicotine content cigarettes: evidence from a randomized controlled trial. *Nicotine Tob Res.* 2018;Epub ahead of print April 28, 2018. DOI 10.1093/ntr/nty079, <https://www.ncbi.nlm.nih.gov/pubmed/29718460>

¹² Cassidy RN, Colby SM, Tidey JW, Jackson KM, Cioe PA, Krishnan-Sarin S, Hatsukami D. Adolescent smokers' response to reducing the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations. *Drug Alcohol Depend.* 2018;188:153-160. DOI 10.1016/j.drugalcdep.2018.04.006, <https://www.ncbi.nlm.nih.gov/pubmed/29775959>

the effects of reduced nicotine dose in animals¹³ are remarkably similar to observations in humans.¹⁰ Furthermore, determination of abuse liability of a product has been demonstrated using animal models.¹⁴ In addition to animal studies, examining of nAChR occupancy can help to infer the possible effects in a tobacco naïve individual.

Thus, while the ultimate focus is behavioral changes in humans, additional types of studies should be included and can provide valuable supporting information on lowering levels of nicotine in cigarettes. In addition, information can be drawn from multiple data sources including relevant tobacco industry documents.

3. *In addition to nicotine, minor tobacco alkaloids (including nornicotine, cotinine, anabasine, anatabine, and myosamine) and tobacco smoke aldehydes (such as acetaldehyde) are pharmacologically active and may contribute to addiction (see, e.g., Refs. 98 and 99). Researchers have investigated the abuse potential of nornicotine, cotinine, anabasine, and acetaldehyde in animals (Ref. 100). However, many of these compounds are only present in tobacco smoke at low levels and are likely less potent than nicotine in mediating pharmacological response and, therefore, reinforcement (Refs. 101 and 102). In addition to setting a maximum nicotine level, should the product standard also set maximum levels of other constituents (e.g., nornicotine, acetaldehyde, anabasine) that may have the potential to produce dependence and be addictive? If so, at what levels?*

Minor alkaloids could contribute to the abuse liability of a product, but generally only in higher doses.¹⁵¹⁶ In particular, monoamine oxidase inhibitors (MAO) inhibitors appear to enhance nicotine self-administration¹⁶ Because of the potential contributions of these constituents to addiction, the FDA should consider ensuring

¹³ Smith TT, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Low-dose nicotine self-administration is reduced in adult male rats naïve to high doses of nicotine: implications for nicotine product standards. *Experimental and Clinical Psychopharmacology*. 22: 453-9. PMID 24999867 DOI: 10.1037/a0037396

¹⁴ Tracy T Smith, Laura E Rupprecht, Rachel L Denlinger-Apte, Jillian J Weeks, Rachel S Panas, Eric C Donny, Alan F Sved; Animal Research on Nicotine Reduction: Current Evidence and Research Gaps, *Nicotine & Tobacco Research*, Volume 19, Issue 9, 1 September 2017, Pages 1005–1015, <https://doi.org/10.1093/ntr/ntx077>

¹⁵ Smith TT, Rupprecht LE, Denlinger-Apte RL, Weeks JJ, Panas RS, Donny EC, Sved AF. Animal research on nicotine reduction: current evidence and research gaps. *Nicotine Tob Res*. 2017;19(9):1005-1015. DOI 10.1093/ntr/ntx077, PMID #: PMC5896531. <https://www.ncbi.nlm.nih.gov/pubmed/28379511>

¹⁶ Smith TT, Rupprecht LE, Cwalina SN, Onimus MJ, Murphy SE, Donny EC, Sved AF. Effects of monoamine oxidase inhibition on the reinforcing properties of low-dose nicotine. *Neuropsychopharmacology*. 2016;41(9):2335-2343. DOI 10.1038/npp.2016.36, PMID #: PMC4946064. <https://www.ncbi.nlm.nih.gov/pubmed/26955970>

the levels of these components are no higher than in products currently on the market.

Sugars are converted to aldehydes which then can be converted to harman or norharman,¹⁷ which inhibit MAO;¹⁸ therefore, the FDA may also want to consider the contributions of sugars on the appeal and addictiveness of a product. The FDA should also anticipate possible introduction of nicotine analogues with similar addictive properties to nicotine. In any new product application, a company should be required to demonstrate that the abuse liability of the combusted products is no greater than that of existing VLNC cigarettes.

4. *If FDA were to finalize a nicotine tobacco product standard, what is the potential that adults and adolescents would perceive these VLNC cigarettes as “safe” -- and how could youth and adult risk perceptions of these cigarettes impact initiation, use, and cessation habits of combusted tobacco products?*

Studies have shown that smokers perceive VLNC cigarettes to be safer than conventional cigarettes because of the reduced levels of nicotine (Smith). Therefore, it is critical to proactively educate consumers with information that reducing nicotine decreases the addictive potential but that, because the harm to health is caused primarily by other components of cigarettes, lowering nicotine levels does not equate to reducing the substantial harms of smoking combusted cigarettes. In addition, companies should not be permitted to give the impression, in either marketing or labeling, that VLNC products are less harmful to health than other nicotine products.

C. Implementation (Single Target vs. Stepped-Down Approach)

1. *What data are available to demonstrate that a single target approach to reach a maximum nicotine level would or would not result in any unintended consequences?*

Unpublished data shows that a single target approach leads to more rapid reduction in exposure to toxicants, reduced dependence, and increased cigarette-free days

¹⁷ Talhout, R., A. Opperhuizen, and J.G. van Amsterdam, *Role of acetaldehyde in tobacco smoke addiction*. Eur Neuropsychopharmacol, 2007. **17**(10): p. 627-36.

¹⁸ Herraiz, T. and C. Chaparro, *Human monoamine oxidase is inhibited by tobacco smoke: beta-carboline alkaloids act as potent and reversible inhibitors*. Biochem Biophys Res Commun, 2005. **326**(2): p. 378-86.

compared to a more gradual approach.¹⁹ However, a single target date is likely to lead to greater severity of withdrawal and discomfort and could potentially lead to seeking alternative sources of nicotine (e.g., medicinal nicotine, products such as electronic nicotine delivery system, or illegal market products). Therefore, with the single target approach, it is essential that less harmful alternative nicotine products are available and accessible to smokers, especially FDA-approved nicotine replacement therapies and behavioral cessation therapies.

2. *In the alternative, what data are available to demonstrate that a stepped-down approach involving a sequence of incremental levels and implementation dates to reach a proposed nicotine level would or would not result in any unintended consequences?*

The stepped down approach is likely to lead to potentially greater exposure to toxicants at moderate doses of nicotine during the step-down time period^{20,21,22}) and prolonged exposure to toxicants. Furthermore, the extent to which smokers adapt to reduced nicotine if nicotine is gradually reduced is unknown and a stepped-down approach could lead to less overall cessation. A step-down approach would also prolong the period of time that products with high or moderate addiction are on the market, a time at which many nicotine naïve individuals, especially youth, could initiate habit-forming use.

3. *If FDA were to select a stepped-down approach for a nicotine tobacco product standard, what scientific evidence exists to support particular interim nicotine levels and the appropriate number of steps that would be needed to reach the target level?*

¹⁹ Hatsukami DK. Approaches to reducing nicotine in cigarettes. Presidential Symposium at the SRNT 24th Annual Meeting;

February 21-24, 2018; Baltimore, MD. Copy of abstract attached.

²⁰ Mercincavage M, Souprontchouk V, Tang KZ, et al. A randomized controlled trial of progressively reduced nicotine content cigarettes on smoking behaviors, biomarkers of exposure, and subjective ratings. *Cancer Epidemiol Biomarkers Prev.* 2016;25(7):1125-1133.

²¹ Hatsukami DK, Kotlyar M, Hertsgaard LA, et al. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction.* 2010;105(2):343-355.

²² Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, et al. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiology Biomarkers & Prevention.* 2012;21:761-9.

We do not recommend a stepped down approach. Please see our response to question C2.

4. *Would a single target and a stepped-down approach for implementation result in comparable quit rates or reduced initiation rates?*

A greater number of cigarette-free days were observed over time with the single targeted reduction approach compared to the gradual nicotine reduction approach.¹⁹ As such, a single targeted reduction would lead to more rapid public health benefit. Furthermore, it is not clear whether gradual reduction would lead to greater adaptation to VLNC cigarettes and lower long-term cessation rates.

5. *What would be the likely implementation differences, including implementation timelines and transition costs, between a single target approach or a stepped-down approach involving a sequence of incremental levels and implementation dates?*

The single target approach involves a single timeline and a single transition and will therefore be more straightforward to industry and the general public compared with the stepped-down approach. The one-time transition is likely to result in less costly manufacturing costs for industry and less confusing for the general public.

D. ^[01]Possible Countervailing Effects

1. *In addition to a nicotine tobacco product standard, should FDA consider any additional regulatory action to address the possibility of migration to, or dual use with, other tobacco products?*

The FDA should first and foremost actively encourage cessation with FDA-approved nicotine replacement therapies and evidence-based behavioral cessation therapies. For those unable or unwilling to give up nicotine, migration of smokers to regulated non-combusted products should include FDA regulating the toxicity of these products and informing the public of their relative harms. It is important to allow a sufficient level of nicotine for some products so that cigarettes are relatively devalued in terms of reinforcement compared to the alternative nicotine products with lower toxicity. The FDA should allow for more innovation with medicinal nicotine products per the suggestions made in a February 2018 AACR

comment letter to the FDA.²³ Finally, FDA should strongly regulate characteristics of all combusted and non-combusted products to minimize appeal and uptake in nicotine naïve individuals, especially youth.

2. *If FDA were to issue a product standard setting a maximum nicotine content for cigarettes, would smokers seek to add liquid nicotine to their VLNC cigarettes? Therefore, should such a regulation include provisions prohibiting the sale or distribution of any tobacco product designed for the purposes of supplementing the nicotine content of a combusted tobacco product (or any product where the reasonably foreseeable use is to supplement this nicotine content)? How could such a provision be structured to efficiently and effectively achieve this purpose? Should FDA consider other means to prevent supplementing the nicotine content of a combusted tobacco product subject to a nicotine tobacco product standard?*

We recommend that the FDA consider prohibiting the sale or distribution of any product designed for the purposes of supplementing the nicotine content of combusted tobacco products. These could include filters that contain nicotine, nicotine sprays for cigarettes, etc. Research should be conducted (e.g. focus groups and/or surveys) to assess how smokers might seek to enhance their cigarettes to increase their nicotine levels. Finally, companies should be prohibited from developing nicotine analogs.

3. *Would a nicotine tobacco product standard affect the current illicit trade market, and, if so, to what extent? How would users obtain their sources of tobacco in an illicit market? How would manufacturers distribute their illicit products and develop consumer awareness of such products? How would such sales take place?*

The AACR and ASCO do not have the expertise to provide detailed comments on this question. However, we speculate that some number of illicit products could potentially be distributed via internet sales and social media.

²³ American Association of Cancer Research. (2018, February 15). AACR 2018 Comments to FDA on NRT. Retrieved from [https://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/2018 Comments to FDA on NRT_Final.pdf](https://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/2018%20Comments%20to%20FDA%20on%20NRT_Final.pdf)

4. *FDA hypothesizes that, based on currently available research, nicotine levels like those levels that FDA would consider with a possible nicotine tobacco product standard would be self-limiting (i.e., smokers would be unable to obtain their nicotine dose from cigarettes no matter how they smoke them and eventually would stop trying to do so). Do any peer-reviewed studies demonstrate that lowering the nicotine content of cigarettes to minimally addictive levels might encourage consumers to smoke more VLNC cigarettes to achieve the higher nicotine doses currently delivered by NNC cigarettes?*

To date, no study has demonstrated significant compensatory smoking occurring with VLNC cigarette,^{24,25} even among intermittent smokers. The likelihood of being able to obtain similar amounts of nicotine as normal nicotine content (NNC) cigarettes is slim if the cigarettes were 97-98% lower in nicotine content than NNC cigarettes. Obtaining a similar amount of nicotine from VLNC cigarettes as from NNC cigarettes would entail an impractical level of cigarette consumption in terms of cost and time needed for smoking, significantly minimizing the likelihood that compensatory smoking would be occur.

5. *If a nicotine tobacco product standard were in effect, the following outcomes could occur: (1) smokers could continue to smoke but use the low nicotine products; (2) smokers could completely switch to, or dual use low nicotine products with, other legal tobacco or nicotine products; (3) smokers could quit using any nicotine or tobacco product; or (4) smokers could seek to buy illegal cigarettes in an illicit market. Are there data that would provide information on which of these outcomes is most likely? Is there some other outcome that could occur?*

Data are limited, but we speculate based on the data available that the most likely outcome would be smokers obtaining nicotine from other sources. In one study, about 40% of smokers assigned to VLNC cigarettes used an alternative nicotine

²⁴ Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobles DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized trial of reduced-nicotine standards for cigarettes. *N Engl J Med*. 2015;373(14):1340-1349. DOI 10.1056/NEJMsa1502403, PMID #: PMC4642683. <https://www.ncbi.nlm.nih.gov/pubmed/26422724>

²⁵ Hatsukami, D.K., Donny, E.C., Koopmeiners, J.S., Benowitz, N.L. (2015) Compensatory smoking from gradual and immediate reduction in cigarette nicotine content. *Cancer Epidemiology, Biomarkers & Prevention*, 24(2):472-476. Epub 2014/12/18. doi: 10.1158/1055-9965.EPI-14-0739. PubMed PMID: 25515551; PMID: PMC4324025

delivery system (ANDS), predominantly ENDS.²⁶ There will likely be an illegal market, but the extent and strength of this market will depend on the policies that are developed and enforced to monitor illicit product, and penalize manufacturers, distributors, and retailers for selling NNC cigarettes.²⁷ The extent and strength of the illegal market would also depend on the availability of cessation options and access to less harmful ANDS.

F. Other Considerations

- a. *What data may be helpful to assess the universe of tobacco products that are currently available to consumers and their relevant characteristics, such as nicotine levels? How can available sources of information, such as manufacturer registrations and/or product listings with FDA, be used in this assessment?*

Helpful data would include: constituents in a given tobacco product, nicotine level, pH, and other constituents that may be associated with or enhance addiction potential (e.g. nicotine flux).²⁸

- b. *How should potential consumer surplus or utility loss from the removal of nicotine in cigarettes be considered, given the availability of other sources of nicotine such as ENDS and the continued availability of combustible tobacco products?*

If market forces decreased consumer demand for combusted tobacco cigarettes and increased consumer demand for other sources of nicotine such as ENDS, with static or lower total nicotine consumption levels, this would result in significant overall public health gains. As clearly delineated in the 2018 NASEM report entitled “The Public Health Consequences of E-Cigarettes,” while the health risks caused by e-cigarettes remain to be precisely characterized, the risks are almost certainly significantly less than the risks of smoking combusted cigarettes.

²⁶ Hatsukami DK, Luo X, Dick L, Kangkum M, Allen SS, Murphy SE, Hecht SS, Shields PG, al'Absi M. Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. *Addiction*. 2017;112(1):156-167. DOI 10.1111/add.13603, PMID #: PMC5249662. <https://www.ncbi.nlm.nih.gov/pubmed/27614097>

²⁷ Institute of Medicine. 2013. *Reducing Tobacco-Related Cancer Incidence and Mortality: Workshop Summary*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/13495>.

²⁸ Shihadeh, A., & Eissenberg, T. (2015). Electronic Cigarette Effectiveness and Abuse Liability: Predicting and Regulating Nicotine Flux. *Nicotine & Tobacco Research*, 17(2), 158–162. <http://doi.org/10.1093/ntr/ntu175>

- c. *What sources of information could be used to estimate the change in demand for VLNC cigarettes? What factors should we consider in estimating the changes in demand for other tobacco products?*

Sources of information could include national surveys (such as the Population Assessment of Tobacco and Health survey) and retail sales data. A more rapid response system that includes a panel/cohort of smokers and nonsmokers could be established. Additionally, use of electronic medical records to assess health outcomes could be established.

- d. *What factors should be considered in estimating changes in experimentation and initiation that may occur as a result of a potential nicotine tobacco product standard?*

One issue to carefully monitor is that a nicotine product standard could conceivably lead to an increased prevalence of smoking initiation. High levels of nicotine are a primary reason for symptoms, such as nausea, that sometimes discourage first-time smokers from continued use. Lower levels of nicotine could potentially ease this transition and increase the likelihood of progressing toward heavier smoking. However, given that lower doses of nicotine in combustibles would be less reinforcing and have lower addictive potential, the likelihood of long-term and heavy use associated with the most damaging health outcomes would be lower. To ensure monitoring, national surveys should be considered to determine the number of people who have ever tried and the number who eventually become dependent or use cigarettes daily.

- e. *In what ways might a change in nicotine levels in cigarettes spur innovation in the market for both combusted and non-combusted tobacco products?*

If other combusted products were also low in nicotine, it could spur innovation in non-combusted products including medicinal nicotine products.

- f. *What factors should be considered in estimating the impacts of externalities that might exist for VLNC cigarettes, such as secondhand smoke, litter, and pollution? How could the impact of externalities for VLNC cigarettes be compared to the impacts from NNC cigarettes?*

Secondhand smoke contains nicotine, which can sensitize nonsmokers to nicotine and facilitate the transition to smoking once a nonsmoker tries smoking. VLNC cigarettes would minimize this specific impact of secondhand smoke exposure because the lowered nicotine levels would minimize the sensitization of the nonsmoker to nicotine. If smoking prevalence is decreased, this might also reduce litter and pollution.

- g. *What factors should we consider in estimating the impact of changes in demand for other tobacco products?*

Factors include the effects of migration of smokers to other products on health and dependence. The effectiveness of a product in delivering nicotine to the user is of paramount importance. Based on the importance of a product's effectiveness in delivering nicotine to the user, VLNCs would be anticipated to lose market share to more effective nicotine delivery systems. Given that combusted tobacco cigarettes have by far the greatest health risks, shifts to alternative forms of nicotine delivery would be expected to result in significant public health gains with regard to current smokers and those exposed to secondhand smoke.

- h. *If FDA were to finalize a nicotine tobacco product standard, what might be the costs to current smokers?*

Costs would include removing availability of something pleasurable from smokers and possible stress and physical discomfort due to withdrawal symptoms. These consumers may be able to substitute other products to ameliorate these costs.

- i. *Are there any other relevant comments or information that would be helpful for FDA to consider in analyzing the economic impacts of a proposed nicotine tobacco product standard?*

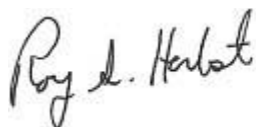
Estimating the economic impacts needs to account for the fact that cigarette smoking is the leading cause of morbidity and premature mortality in the United States today. The healthcare and lost productivity costs of smoking are well documented and should be considered in terms of the overall economic impact.²⁹

²⁹ National Cancer Institute. (n.d.). Monograph 21: The Economics of Tobacco and Tobacco Control. Retrieved from <https://cancercontrol.cancer.gov/brp/tcrb/monographs/21/>

A decrease in the prevalence of cigarette smoking resulting from a lower nicotine tobacco product standard resulting would result in significant health improvements in the U.S. population as well as substantial positive economic benefits.

In conclusion, the AACR and ASCO commend the FDA on their comprehensive plan that places nicotine addiction at the center of the Agency's tobacco regulatory efforts. Thank you very much for considering our input on this important issue. These comments are based on careful discussion and evaluation of the extant literature on tobacco treatment by the AACR's Tobacco and Cancer Subcommittee (roster attached), ASCO's Tobacco Cessation and Control Subcommittee (roster attached), and are approved by the AACR's CEO and Chairs of the Tobacco and Cancer Subcommittee and Science Policy and Government Affairs Committee, and ASCO's President. If we can provide any additional information or assistance to the FDA, please do not hesitate to contact Nicole Boschi, PhD, AACR Senior Science Policy Analyst, at 215-446-7275 or nicole.boschi@aacr.org.

Sincerely,



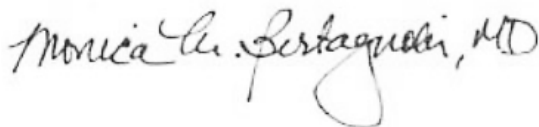
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