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Public Interest Comment¹ on
The U.S. Food & Drug Administration’s Advanced Notice of Proposed Rulemaking
Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

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The George Washington University Regulatory Studies Center improves regulatory policy through research, education, and outreach. As part of its mission, the Center conducts careful and independent analyses to assess rulemaking proposals from the perspective of the public interest. This comment on the U.S. Food & Drug Administration’s “Advance Notice of Proposed Rulemaking, Tobacco Product Standard for Nicotine Level of Combusted Cigarettes” does not represent the views of any particular affected party or special interest, but it is designed to evaluate the effect of the FDA plan on overall consumer welfare.

Introduction

FDA’s plan to restrict nicotine to very low levels in combusted cigarettes in order to reduce smokers’ addiction to cigarettes is a novel and creative approach to promote public health. Although such an approach was suggested decades ago,³ it has not been implemented in any other country. And the plan is creative because, rather than attempting to regulate the hazards out of a

¹ This comment reflects the views of the author, and does not represent an official position of the GW Regulatory Studies Center or the George Washington University. The Center’s policy on research integrity is available at <http://regulatorystudies.columbian.gwu.edu/policy-research-integrity>.

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³ Neal L. Benowitz and Jack E. Henningfield, “[Establishing a Nicotine Threshold for Addiction -- The Implications for Tobacco Regulation](#),” *New England Journal of Medicine* 1994; 331:123-125.

product that some consumers demand, the policy would reduce the appeal of a product that is laden with hazards. However, the plan is speculative and unproven, and some tests of its underlying hypothesis cast some doubt on its likelihood of success.

FDA's plan is also incomplete as it addresses only removing access to combustible sources of nicotine. That will work only if people have access to noncombustible sources of nicotine.⁴ But FDA's proposed plan makes no definitive statements about any plans the agency might have for noncombustible sources of nicotine.

After briefly describing the issues raised in the advanced notice of proposed rulemaking (ANPRM) and the relationship of nicotine to combustible cigarettes, this comment addresses some of FDA's questions regarding the scope of future rulemaking, analytical testing method, technical achievability, possible countervailing effects, and other considerations.

FDA's Advanced Notice of Proposed Rulemaking

On March 16, 2018, FDA published an ANPRM to invite comments and submissions of information for it to consider as it plans to develop a maximum nicotine level for cigarettes.⁵ FDA is considering whether it should reduce the level of nicotine in tobacco products so that they are less addictive, or even nonaddictive, and how it might achieve that goal by establishing a new standard for nicotine levels. FDA is looking for input on the best available science to determine a nicotine level in tobacco products that will protect public health. The agency hopes to establish a standard for nicotine levels in cigarettes so that they do not initiate or perpetuate addiction to cigarettes for some portion of potential smokers. If successful, this standard may make it easier for some cigarette smokers to quit smoking, and it may also keep people from becoming regular tobacco users if they experiment with tobacco.

Because this is an ANPRM, FDA's document does not offer a draft of a rule with a detailed proposal for specific requirements on specific tobacco products. Instead, FDA requests comments, evidence, and other information on the following issues.

- **Scope:** Although, the title of the notice identifies cigarettes as the regulated product, FDA has requested comments on the scope of products covered by any potential product standard. FDA is seeking comment on whether the standard should cover any or all of the

⁴ Neal L. Benowitz, "Comprehensive Nicotine Regulation to End the Combustible Tobacco Epidemic," *Annals of Internal Medicine*; 167(10):736-737 and Tracy T. Smith, et al., "[Whether to Push or Pull? Nicotine Reduction and Non-Combusted Alternatives - Two Strategies for Reducing Smoking and Improving Public Health](#)," *Preventive Medicine*, in press, available online 29 March 2018.

⁵ Department of Health and Human Services, Food and Drug Administration, "[Tobacco Product Standard for Nicotine Level of Combusted Cigarettes](#)," 83 *Federal Register* 11818, March 16, 2018.

following products: combusted cigarettes, cigarette tobacco, roll-your-own tobacco, some or all cigars, pipe tobacco, and waterpipe tobacco.

- **Maximum Nicotine Level:** Setting a maximum nicotine level of 0.3 mg nicotine/g of tobacco filler or other levels. FDA has also requested data and research on specific subpopulations which are more sensitive to nicotine than the general population.
- **Implementation:** Whether a maximum nicotine level for cigarettes should be phased-in in a stepped-down approach or implemented all at once.
- **Analytical Testing Method:** Whether FDA should define a specific analytical method for testing the level of nicotine in tobacco.
- **Technical Achievability:** Issues relating to technical achievability, including:
 - The feasibility of using known techniques to reduce the nicotine in cigarettes, and the feasibility of using those techniques to reduce nicotine in non-cigarette tobacco products.
 - The effect on farmers' growing and/or curing practices of a maximum nicotine standard.
 - The appropriate effective date of a rule implementing a maximum nicotine standard.
 - The potential impact on characteristics of cigarettes (flavor, taste, aroma, etc.) and user experience of reducing the nicotine content in cigarettes.
- **Possible Countervailing Effects:** Issues relating to possible countervailing effects of a rule, including:
 - The degree to which cigarette smokers would switch to other tobacco products.
 - The degree to which cigarette smokers would attempt to add nicotine to cigarettes that have very low levels of nicotine.
 - The degree to which a black market in cigarettes containing normal levels of nicotine would develop.
 - The degree to which smokers of very low nicotine cigarettes will smoke more cigarettes in an effort to consume the same amount of nicotine.
- **Other Considerations:** Issues primarily related to quantifying the costs and benefits of a rule that established a maximum nicotine level for cigarettes.

Nicotine or Cigarettes

Nicotine occurs naturally in a number of plants, but tobacco contains far and away the largest concentrations.⁶ Inhaling tobacco smoke is the simplest, most efficient way of making nicotine

⁶ Edward F. Domino, et al., "The Nicotine Content of Common Vegetables" *New England Journal of Medicine* 1993; 329:437.

available to the human body.⁷ However, inhaling tobacco smoke is also a simple, efficient way of delivering many toxic substances to the human body in addition to nicotine. Nicotine is highly addictive,⁸ but, by itself, at the levels commonly derived from smoking tobacco, nicotine has little if any adverse health effect on adults.⁹ In fact, “Nicotine induces pleasure and reduces stress and anxiety.”¹⁰ Therefore, it is believed that smokers are addicted to smoking tobacco only because the tobacco contains nicotine.¹¹ By not conflating nicotine addiction with tobacco smoking, as has often been done,¹² a possibility to promote an improvement in public health presents itself. Reducing the nicotine content of tobacco would reduce some of the satisfaction that smokers derive from tobacco and may make it easier for tobacco smokers to successfully quit smoking, thereby reducing the public health consequences of smoking tobacco.

However, as FDA notes, the success of this strategy is not assured. Some research found that smokers of very low nicotine (0.4 mg nicotine per gram of tobacco) cigarettes smoked about one-third fewer cigarettes than if they smoked their regular brand.¹³ But other research has found that quit rates were low and almost identical for smokers of regular cigarettes and of very low nicotine content cigarettes after two years of study.¹⁴ Even FDA’s preliminary estimate of benefits of the policy suggests that 12% of smokers per year will quit smoking if the FDA plan is implemented. Although that is more than double the percentage of smokers who successfully quit smoking according to the latest statistics,¹⁵ it means that a large percentage of smokers can smoke very low nicotine cigarettes for an extended period of time without quitting.

Given the hopeful but unproven approach of FDA’s plan, FDA should continue to study the conditions under which a maximum nicotine standard is most likely to reduce smoking, develop a

⁷ Edward F. Domino, et al., “Regional Cerebral Blood Flow and Plasma Nicotine After Smoking Tobacco Cigarettes” *Progress in Neuro-Psychopharmacology and Biological Psychiatry* Volume 28, Issue 2, March 2004, Pages 319-327.

⁸ Jack E. Henningfield, “Is Nicotine More Addictive Than Cocaine?” *Addiction* Volume 86, Issue 5, May 1991, Pages 565-569.

⁹ Neal L. Benowitz, et al., “[Nicotine Absorption and Cardiovascular Effects with Smokeless Tobacco Use: Comparison with Cigarettes and Nicotine Gum](#)” *Clinical Pharmacology & Therapeutics* Volume 44, Issue 1, July 1988, Pages 23-28.

¹⁰ Neal L. Benowitz, “[Nicotine Addiction](#),” *New England Journal of Medicine*. 2010 June 17; 362(24): 2295–2303.

¹¹ Neal L. Benowitz and Jack E. Henningfield, “[Reducing the Nicotine Content to Make Cigarettes Less Addictive](#),” *Tobacco Control* 2013;22:i14–i17.

¹² For an example of FDA conflating the two, see David A. Kessler. “Nicotine Addiction in Young People,” *New England Journal of Medicine*, 1995 July 20; 333(3), 186-189.

¹³ Eric C. Donny, et al., “[Randomized Trial of Reduced-Nicotine Standards for Cigarettes](#),” *New England Journal of Medicine* 2015; 373:1340-1349.

¹⁴ Neal L. Benowitz, et al. “[Effect of Reducing the Nicotine Content of Cigarettes on Cigarette Smoking Behavior and Tobacco Smoke Toxicant Exposure: Two Year Follow Up](#).” *Addiction* 110.10 (2015): 1667–1675.

¹⁵ Shu-Hong Zhu, et al. “[E-Cigarette Use and Associated Changes in Population Smoking Cessation: Evidence from US Current Population Surveys](#),” *British Medical Journal* 2017; 358: j3262.

broad nicotine-access policy that will provide a robust set of alternatives to combustible products, and possibly propose a limited rule to try the effectiveness of the strategy. This comment offers information on some of the issues relating to scope, analytical testing, technical achievability, possible countervailing effects, and other considerations.

Scope: Initially Cover Only Combustible Cigarettes

Given the very large costs of compliance with a maximum nicotine standard that would require the complete reformulation of whatever combustible tobacco products to which it applies, FDA should proceed only with a rule that matches the scientific evidence. Therefore, an FDA rule should initially only cover combustible cigarettes. The only very low nicotine products that have been produced and tested are combustible cigarettes. Although all combustible tobacco products increase the risk of death (i.e., have hazard ratios greater than 1), the elevated risk for exclusive current cigarette smokers is about 5 times greater than it is for exclusive current smokers of cigars or pipes,¹⁶ and people are far more likely to smoke cigarettes than other combustible tobacco products. By initially covering only combustible cigarettes, FDA would follow the evidence and address the bulk of the public health risk.

If a rule is finalized for combustible cigarettes, then FDA will have the opportunity to learn by experience (rather than research projections) the answers to many of the questions that it poses in the notice.

Retrospective Review

Any rule issuing from this new FDA policy would be perfectly suited to benefit from retrospective review. It is impossible accurately to anticipate and evaluate the impact of every response to a nicotine reduction standard. FDA could begin with a well-crafted rule focused on combustible cigarettes that has a reasonable potential to significantly improve public health, and then a few years after implementation, FDA could use retrospective review to transparently analyze the effectiveness of the rule, and how it might be improved and expanded given any indications of significant countervailing effects. Executive Order 13563 directs agencies to conduct retrospective analyses of rules:

that may be outmoded, ineffective, insufficient, or excessively burdensome, and to modify, streamline, expand, or repeal them in accordance with what has been learned. Such retrospective analyses, including supporting data, should be released online whenever possible.¹⁷

¹⁶ Carol H. Christensen, et al., “Association of Cigarette, Cigar, and Pipe Use with Mortality Risk in the US Population,” *JAMA Internal Medicine*. 2018;178(4):469–476.

¹⁷ 76 *Federal Register* 3821, January 21, 2011.

If FDA publishes a proposed nicotine standard for tobacco products, FDA should include in the proposal (and request comment on) a proposed plan for retrospective review of such a rule. The retrospective review plan should include some of the issues that FDA has raised in the present notice, such as the effectiveness of the level of nicotine chosen, the extent of countervailing effects, and the scope of the rule. The retrospective review plan should also identify under what conditions FDA would admit that the plan failed and that the maximum nicotine standard should be removed.

Analytical Testing: Establish One Method FDA Will Use for Enforcement

Any FDA rule should be designed to minimize costs that do not improve public health. If FDA issues a proposed rule, it should propose to establish one validated method that it will use to determine compliance with the nicotine standard and what degree of variation it will accept from the standard. Beyond that, FDA should allow manufacturers to use whatever testing method they wish for their own internal purposes. However, the only analytical method that will matter is the one that FDA uses for enforcement. All of FDA's food standards, which are analogous to the nicotine standards, are written in this manner.

FDA should not go down the road of requiring manufacturers to execute batch or lot or periodic testing and accompanying recordkeeping. That is expensive and, especially in the case of tobacco products, pointless. The tobacco industry has a history of not being trustworthy with data.¹⁸ It is hard to imagine that FDA would ever rely upon whatever evidence the industry provides to it. FDA will and should do all of its own enforcement testing. This renders industry testing and reporting irrelevant and unnecessary. Additionally, establishing one method that FDA will use for enforcement reduces the potential for debates over differential results by different methods.

Technical Achievability: Potentially Exists Only for Combustible Cigarettes

Within the area of technical achievability, FDA has identified two distinct but equally important issues: 1) can very low nicotine cigarettes be created? and 2) are the very low nicotine cigarettes that can be created acceptable to smokers apart from the missing effect of nicotine?

Very low nicotine cigarettes at the level of 0.4 mg per gram of tobacco are only possible using genetic engineering or chemical extraction. Presently, very low nicotine cigarettes are the only very low nicotine combustible tobacco products that are being produced. Those cigarettes are produced by only one very small manufacturer, 22nd Century Group, using genetic engineering of tobacco plants.¹⁹ All very low nicotine cigarettes used for research purposes are produced by the company, doing so under its SPECTRUM brand of government research cigarettes. That brand is

¹⁸ United States v. Philip Morris USA, Inc., [449 F. Supp. 2d 1](#) (D.D.C. 2006).

¹⁹ 22nd Century Group, [SPECTRUM Government Research Cigarettes](#).

not sold commercially, but the existence of the brand and the fact that it can be used by research subjects for weeks and months at a time proves that it is physically possible to create very low nicotine cigarettes.

What is not clear is whether the company's cigarettes provide a combustible cigarette experience that could compete with other cigarettes, were it not for the fact that the cigarettes do not deliver the nicotine experience to smokers. Only outside of the United States does the company sell its brands other than the SPECTRUM Government Research Cigarettes. The 22nd Century Group website reveals that it has high, average, and low nicotine cigarettes available for sale outside of the United States. From the company's latest quarterly filing with the Securities and Exchange Commission, we can discern that about half of the company's \$6.1 million total revenue for the first quarter of 2018 was from sales outside of the United States.²⁰ For context, the total U.S. market for cigarettes is almost \$8.5 billion on a quarterly basis. The company's promotional materials claim that its Magic brand of very low nicotine cigarettes offers "A rich satisfying smoke with 95% less nicotine."²¹ However, with such small sales of all of their products, it is extremely difficult to say that the very low nicotine cigarettes are acceptable to smokers except for the fact that they do not deliver the satisfaction derived from nicotine.

Additionally, it is indisputable that, other than cigarettes, there are no very low nicotine combustible tobacco products. Therefore, while it may be possible to make products that fit the technical definition of a very low nicotine combustible cigarette, it is not possible, with the very few products that are currently marketed, to say that manufacturers can achieve a commercially viable product that anyone other than government researchers will buy. This should not be a complete surprise. Any smoker will tell you that different brands and varieties of cigarettes taste different regardless of the amount of nicotine in them. Different brands use different tobacco cultivars (the North Carolina Crop Improvement Association lists 49 different varieties of the tobacco plant certified in that state alone²²), different curing methods, different additives, and different processing techniques. Consequently, the different brands have different flavor profiles. One cigarette brand does not taste like another. The FDA does not recognize the smoker experience and discusses cigarettes only as homogeneous carriers of nicotine derived from the tobacco plant. FDA should design a policy not from the perspective of what control it can impose upon the tobacco industry, but instead, from the perspective of how typical smokers relate to the combustible tobacco products that they purchase. The advantage of a consumer-centric approach becomes especially clear when considering possible countervailing effects of a maximum nicotine standard.

²⁰ 22nd Century Group, [Quarterly Report Pursuant to Section 13 Or 15\(D\) of the Securities Exchange Act of 1934 for the Quarterly Period Ended March 31, 2018](#).

²¹ [Magic Cigarettes](#).

²² National Crop Improvement Association, [Tobacco Varieties](#).

Possible Countervailing Effects: Minimized with Liberal Access to Noncombustible Sources of Nicotine

FDA's ANPRM devotes much attention and expresses much concern about possible countervailing effects of a nicotine reduction policy for combustible tobacco and how countervailing effects might be avoided. The best way to avoid countervailing effects is for FDA to do what the present notice fails to do – articulate a broad policy for making nicotine easily available in consumer-friendly, noncombustible forms. For smokers, combustible cigarettes are legal, convenient, efficient ways to get nicotine in a way that they find satisfying. If FDA's thesis behind its nicotine standard is correct, then, as smokers attempt to quit smoking, they will still crave nicotine, preferably in a form that is legal, convenient, efficient, and satisfying. Electronic nicotine delivery systems (e-cigarettes) offer all of that for smokers of combustible cigarettes who are trying to quit smoking. On the other hand, black markets, smuggled cigarettes, liquid-nicotine solutions to soak into very low nicotine cigarettes, and roll-your-own cigarettes do not meet these same standards for consumers.

Scientists have noted that the evidence from the most recent statistics on quit rates²³ and from the limited success at enabling quitting using very low nicotine cigarettes alone in some tests²⁴ point to the ways in which electronic nicotine delivery systems make quitting easier. Instead of trying to control and regulate countervailing effects away, FDA should focus on finding ways to reduce barriers to noncombustible sources of nicotine.

Other Considerations: Prioritize Transparency

FDA requests comment on how to estimate the benefits of a rule that imposes a maximum nicotine standard. FDA has demonstrated its competence to estimate benefits for a number of tobacco rules,²⁵ and the Department of Health and Human Services has described a few acceptable methods suited to the purpose.²⁶ In the notice, FDA has included an estimate of the public health benefits that could result from one way that a rule could be structured. The agency has published the

²³ Shu-Hong Zhu, et al., "[E-Cigarette Use and Associated Changes in Population Smoking Cessation: Evidence from US Current Population Surveys](#)," *British Medical Journal* 2017; 358: j3262.

²⁴ Neal L. Benowitz, "Comprehensive Nicotine Regulation to End the Combustible Tobacco Epidemic," *Annals of Internal Medicine*; 167(10):736-737 and Tracy T. Smith, et al., "[Whether to Push or Pull? Nicotine Reduction and Non-Combusted Alternatives - Two Strategies for Reducing Smoking and Improving Public Health](#)," *Preventive Medicine*, in press, available online 29 March 2018.

²⁵ Elizabeth M. Ashley, et al., "Estimating the Benefits of Public Health Policies that Reduce Harmful Consumption." *Health Economics* 2015; 24(5):617.

²⁶ David M. Cutler, et al., "[Economic Approaches to Estimating Benefits of Regulations Affecting Addictive Goods](#)," *American Journal of Preventive Medicine* 2016;50(5S1): S20–S26.

underlying research for that estimate in two articles in science and medical journals.²⁷ Accompanying those articles in supplementary material are the data needed to replicate the results.²⁸ Many research papers have been published relating to nicotine and tobacco since the research underlying those two papers was conducted in 2015 and 2016. Any future proposed rule must take into account the significant body of research that has been published since 2015; some of these are referenced in FDA's notice and some of the others are referenced in this comment.

The agency's transparency relating to those two pieces of research is exemplary. All regulatory agencies should follow the approach for all significant regulatory actions. That is consistent with the transparency initiative of the previous administration, and with the recommendation of the Administrative Conference of the United States:

To the extent practicable and permitted by law and applicable policies, each agency should identify and make publicly available (on the agency website or some other widely available forum) references to the scientific literature, underlying data, models, and research results that it considered... Consistent with the limitations in the Information Quality Act (IQA) guidelines issued by the Office of Management and Budget and its own IQA guidelines, each agency should ensure that members of the public have access to the information necessary to reproduce or assess the agency's technical or scientific conclusions.²⁹

However, FDA has funded hundreds of research projects relating to nicotine and smoking.³⁰ FDA should work with its contractors and grant recipients to make the taxpayer-funded data publicly available. As instructed by the Director of the Office of Science and Technology Policy, "digitally formatted scientific data resulting from unclassified research supported wholly or in part by Federal funding should be stored and publicly accessible to search, retrieve, and analyze."³¹ FDA's unwritten policy of posting data only if it receives 3 or more FOIA requests for the data is completely unworkable for regulatory matters when public comment periods are only 60 to 90 days, and successful FOIA requests take about that much time for the delivery of the requested information.

²⁷ Benjamin J. Apelberg, et al., "Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States," *New England Journal of Medicine* 2018; 378:1725-1733 and Eric D. Vugrin, et al., "[Modeling the Potential Effects of New Tobacco Products and Policies: A Dynamic Population Model for Multiple Product Use and Harm](#)," *PLOS One*, March 27, 2015.

²⁸ See https://www.nejm.org/doi/suppl/10.1056/NEJMSr1714617/suppl_file/nejmsr1714617_appendix.pdf for the *NEJM* article and <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0121008#sec024> for the *PLOS One* article.

²⁹ [78 Federal Register 41358](#), July 10, 2013.

³⁰ [CTP-Supported Tobacco Regulatory Research Projects](#).

³¹ John P. Holdren, "[Memorandum for the Heads of Executive Departments and Agencies: Increasing Access to the Results of Federally Funded Scientific Research](#)," February 22, 2013.

Any proposal that FDA makes should be based only on scientific research for which the data and models needed to replicate the research are publicly posted. If FDA determines that it must rely on research where the data for replication cannot be made available, then FDA should explicitly describe the steps taken to attempt to make the data available and the reason why the agency must trust that specific piece of irreplicable research.³² FDA must anticipate that any rulemaking associated with this policy will be contentious. FDA should be careful to avoid providing opponents with grounds for suspicion about the agency's policy choices, as has been the case for the unavailable taxpayer-funded data underlying Environmental Protection Agency's National Ambient Air Quality Standards.³³

Conclusion

FDA's advanced notice of proposed rulemaking to establish a maximum nicotine standard for combustible cigarettes identifies an important opportunity to potentially make a significant long-term improvement in public health. Nicotine is the addictive agent in tobacco. Reducing nicotine in cigarettes to nonaddictive levels could make it much easier for smokers to successfully quit smoking. However, the policy has never been implemented anywhere and some research indicates that it may not be as successful as would be hoped. In light of both the potential benefits and the potential limitations and countervailing effects, FDA should:

1. Initially only cover combustible cigarettes as those are the only very low nicotine products that have been produced and tested in research.
2. Include in any rule a proposed plan for retrospective review and use the retrospective review to improve the rule as needed based on the experience with combustible cigarettes.
3. Propose to establish one validated method that it will use to determine compliance with the nicotine standard and what degree of variation it will accept from the standard.
4. Focus on reducing barriers to noncombustible sources of nicotine and develop a broad nicotine-access policy that will provide a robust set of alternatives to combustible products so that smokers of very low nicotine cigarettes are not driven to initiate countervailing effects.
5. Make the taxpayer-funded data from FDA-sponsored tobacco research publicly available.
6. Base any proposal only on scientific research for which the data and models needed to replicate the research are publicly posted.

³² Randall Lutter and David Zorn, [On the Benefits and Costs of Public Access to Data Used to Support Federal Policy Making](#), September 2016.

³³ Gina McCarthy, [letter to Lamar Smith](#), March 7, 2014.