A SCIENCE AND EVIDENCE BASED NICOTINE TOBACCO PRODUCT STANDARD

Donna Smith

Senior Principal Scientist

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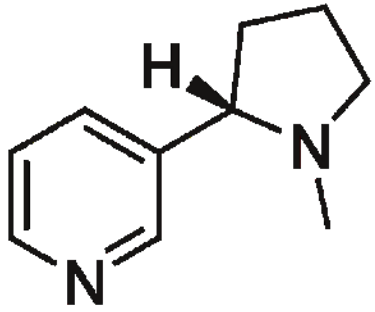
FDA's 2017 Policy Shift

- Endorsement of harm reduction and the continuum of risk
- Policy: encourage cigarette smokers to switch to less risky products
- Drastically reduce nicotine to minimal levels to force the migration of cigarette smokers and reduce initiation



FDA Published ANPRM on Nicotine Content

11818 Federal Register / Vol. 83, No. 52 / Friday, March 16, 2018 / Proposed Rules

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 1130

[Docket No. FDA–2017–N–6189]

RIN 0910–AH86

Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing this advance notice of proposed rulemaking (ANPRM) to obtain information for consideration in developing a tobacco product standard to set the maximum nicotine level for cigarettes. Because tobacco-related harms ultimately result from addiction to the nicotine in such products, causing repeated use and exposure to toxicants, FDA is considering taking this action to reduce the level of nicotine in these products so they are minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health. FDA is using the term "nonaddictive" in this document specifically in the context of a potentially nonaddictive cigarette. We acknowledge the highly addictive potential of nicotine itself depending upon the route of delivery. As discussed elsewhere in this document, questions remain with respect to the precise level of nicotine in cigarettes that might render them either minimally addictive or nonaddictive for specific members or segments of the population. We envision the potential circumstance where nicotine levels in cigarettes do not spur or sustain addiction for some portion of potential smokers. This could give addicted users the choice and ability to quit more easily, and it could help to prevent experimenters (mainly youth) from initiating regular use and becoming regular smokers. The scope of products covered by any potential product standard will be one issue for comment in the ANPRM. Any additional scientific data and research relevant to the empirical basis for regulatory decisions related to a nicotine tobacco product standard is another issue for comment in the ANPRM.

DATES: Submit either electronic or written comments on the ANPRM by June 14, 2018.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before June 14, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of June 14, 2018. Comments received by mail/hand delivery/courier (for written/paper submission) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA–2017–N–6189 for "Tobacco Product Standard for Nicotine Level of Certain Tobacco Products." Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Gerie Voss, Center for Tobacco Products, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 1–877–CTP–1373, *gerie.voss@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

Table of Contents

"FDA is particularly interested in comments about the merits of nicotine levels like 0.3, 0.4 and 0.5 mg nicotine/g of tobacco filler, as well as other levels of nicotine."

Source: Fed. Reg. Vol 83, No. 52/11820

FDA U.S. FOOD & DRUG ADMINISTRATION

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ANPRM Nicotine Content Focus

- "A 2013 survey paper noted that researchers initially estimated that reducing the total nicotine content of cigarettes to 0.5 milligrams (mg) per rod would minimize addictiveness and that a 'more recent analysis suggests that the maximum allowable nicotine content per cigarette that minimizes … addiction may be lower.'"

Source: Fed. Reg. Vol 83, No. 52/11819

- "We specifically request comment regarding this paper's conclusions..."

Source: Fed. Reg. Vol 83, No. 52/11819

me proposal

I ACCESS

Reducing the nicotine content to make cigarettes less addictive

Neal L Benowitz,[1] Jack E Henningfield[2]

ABSTRACT

Nicotine is highly addictive and is primarily responsible for the maintenance of cigarette smoking. In 1994, Benowitz and Henningfield proposed the idea of federal regulation of the nicotine content of cigarettes such that the nicotine content of cigarettes would be reduced over time, resulting in lower intake of nicotine and a lower level of nicotine dependence. When nicotine levels get very low, cigarettes would be much less addictive. As a result, fewer young people who experiment with cigarettes would become addicted adult smokers and previously addicted smokers would find it easier to quit smoking when they attempt to do so. The regulatory authority to promulgate such a public health strategy was provided by the Family Smoking Prevention and Tobacco Control Act. Although it precludes 'reducing nicotine to zero', the act does not prohibit the Food and Drug Administration from setting standards for cigarette nicotine content that would prevent them from being capable of causing addiction. This paper reviews the assumptions implicit in a nicotine reduction strategy, examines the available data on the feasibility and safety of nicotine reduction, and discusses the public education, surveillance and support services that would be needed for the implementation of such a policy.

INTRODUCTION

Nicotine is the highly addictive tobacco constituent that is primarily responsible for the maintenance of cigarette smoking. Our society values personal freedom of choice; however, addiction undermines freedom of choice with respect to stopping or not stopping the use an addictive drug. When nicotine addiction develops, it is difficult to stop using tobacco products. Furthermore, while adolescents and young adults may have a general awareness of the risks of cigarette smoking, they underestimate the harm and the addictive nature of cigarette smoking.[1 2]

RATIONALE

The general aim of a nicotine reduction policy is to make cigarettes non-addictive, so that novice smokers will not transition from experimental or occasional smoking to addiction and so that the smoker can be truly free to consider the benefits versus risks of smoking or not smoking and to then act on their decision to quit if that is their choice. The idea is to reduce the nicotine content of cigarettes over time, resulting in a lower intake of nicotine and a lower level of nicotine dependence until the dosage is reached at which the cigarettes do not produce reinforcing and other effects that sustain addiction. Such a policy is consistent with WHO's Framework Convention on Tobacco Control (the

'Tobacco Treaty') that has been ratified b countries but not the USA[3]. Article 9 Tobacco Treaty addresses the need to guidelines for testing, measuring, and re the contents and emissions of tobacco prod contribute to a regulatory framework to red dependence potential of tobacco products.[3]

Tobacco company documents suppo concept of nicotine reduction to reduce ence: 'To reduce the nicotine per cigarette as possible and thus satisfy the trend of co demand … might end in destroying the habit in a large number of consumers and it ever being acquired by new smokers.' additional documents describe various app to ensuring that nicotine levels—and the f form of nicotine in particular—is optim maintain tobacco product addictiveness."

THE NATURE OF REDUCED NICOTINE CIGARETTES

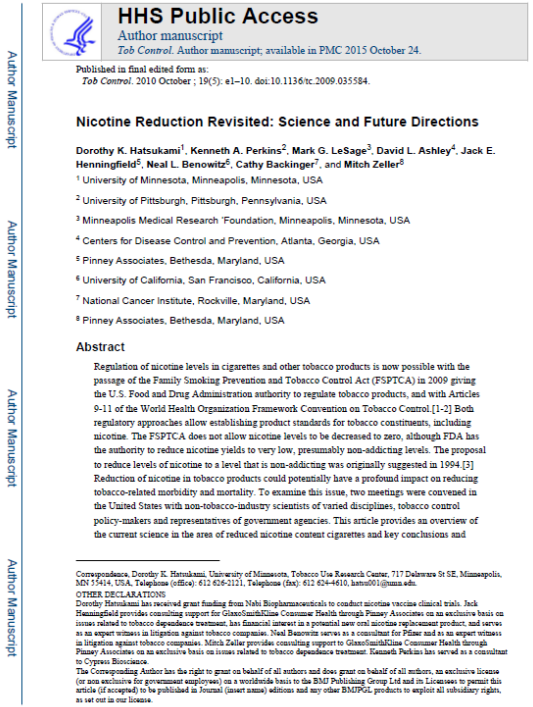
Lowering the nicotine content of cigarette ferent from designing cigarettes that have lo tine delivery as tested by cigarette s machines. The latter types of cigarette, once tised as 'low tar and nicotine' or 'light' ci generate low yields in machine tests due to features such as a faster rate of cigarett increased ventilation and other factors, but involve reducing the nicotine content of th ette tobacco.[2 7] Smokers of such purport yield cigarettes are easily able to compen these low-yield cigarettes by taking bigg more frequent puffs, blocking the ventilatio with their fingers or lips and/or smokin cigarettes per day.[2 7] Reduced nicotine cigarettes can be designed similarly to regul ettes, except for the lower nicotine content nicotine content is decreased in cigarette tob would be extremely difficult or impos absorb substantial levels of nicotine by s cigarettes more intensively (ie, by compe smoking[8 9]).

THE REDUCED NICOTINE CONTENT CIGA PROPOSAL

A gradual reduction of nicotine levels of ci was proposed by Benowitz and Henning 1994.[10] Whereas this proposal envisioned tion to non-addicting nicotine dosage level decade or longer, recent research studie reduced nicotine content cigarettes to aid s cessation have raised the possibility that mo lowering of nicotine content might be eq more effective.[11] A reduced nicotine policy would have to apply to all manuf

Benowitz NL, et al. Tob Control 2013;22:14–17. doi:10.1136/tobaccocontrol-201

The More Recent Analysis



HHS Public Access

Author manuscript

Tob Control. Author manuscript; available in PMC 2015 October 24.

Published in final edited form as:

Tob Control. 2010 October ; 19(5): e1–10. doi:10.1136/tc.2009.035584.

Nicotine Reduction Revisited: Science and Future Directions

Dorothy K. Hatsukami[1], **Kenneth A. Perkins**[2], **Mark G. LeSage**[3], **David L. Ashley**[4], **Jack E. Henningfield**[5], **Neal L. Benowitz**[6], **Cathy Backinger**[7], and **Mitch Zeller**[8]

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[2] University of Pittsburgh, Pittsburgh, Pennsylvania, USA

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[5] Pinney Associates, Bethesda, Maryland, USA

[6] University of California, San Francisco, California, USA

[7] National Cancer Institute, Rockville, Maryland, USA

[8] Pinney Associates, Bethesda, Maryland, USA

Abstract

Regulation of nicotine levels in cigarettes and other tobacco products is now possible with the passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) in 2009 giving the U.S. Food and Drug Administration authority to regulate tobacco products, and with Articles 9-11 of the World Health Organization Framework Convention on Tobacco Control.[1-2] Both regulatory approaches allow establishing product standards for tobacco constituents, including nicotine. The FSPTCA does not allow nicotine levels to be decreased to zero, although FDA has the authority to reduce nicotine yields to very low, presumably non-addicting levels. The proposal to reduce levels of nicotine to a level that is non-addicting was originally suggested in 1994.[3] Reduction of nicotine in tobacco products could potentially have a profound impact on reducing tobacco-related morbidity and mortality. To examine this issue, two meetings were convened in the United States with non-tobacco-industry scientists of varied disciplines, tobacco control policy-makers and representatives of government agencies. This article provides an overview of the current science in the area of reduced nicotine content cigarettes and key conclusions and

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OTHER DECLARATIONS

Dorothy Hatsukami has received grant funding from Nabi Biopharmaceuticals to conduct nicotine vaccine clinical trials. Jack Henningfield provides consulting support for GlaxoSmithKline Consumer Health through Pinney Associates on an exclusive basis on issues related to tobacco dependence treatment, has financial interest in a potential new oral nicotine replacement product, and serves as an expert witness in litigation against tobacco companies. Neal Benowitz serves as a consultant for Pfizer and as an expert witness in litigation against tobacco companies. Mitch Zeller provides consulting support to GlaxoSmithKline Consumer Health through Pinney Associates on an exclusive basis on issues related to tobacco dependence treatment. Kenneth Perkins has served as a consultant to Cypress Bioscience.

- The paper makes no attempt to identify a nicotine threshold of addiction.
- Expressed optimism that a threshold level “will eventually be identified.”
- Recognized that “developing practical, scientifically supported recommendations about nicotine levels in tobacco products involves filling gaps in knowledge in diverse areas…”

Where Did 0.3, 0.4, or 0.5 Originate?

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JACK E. HENNINGFIELD, PH.D.

ESTABLISHING A NICOTINE THRESHOLD FOR ADDICTION

most smokers is well established.[4] Once a person is addicted to nicotine, quitting smoking is difficult, and more than 90 percent of the smokers who try to quit

"an absolute limit of 0.4 to 0.5 mg of nicotine per cigarette should be adequate to prevent or limit the development of addiction in most young people"

cigarette should be conceived not as a product but as a package. The product is nicotine. . . . Smoke is beyond question the most optimized vehicle of nicotine

IS THERE A THRESHOLD LEVEL OF NICOTINE INTAKE ASSOCIATED WITH ADDICTION?

We define addiction according to the Surgeon Gen-

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Where Did 0.3, 0.4, or 0.5 Originate?

- Based analysis on work by Shiffman 1989 & 1990
- Assumed “chippers” are not addicted thus implicitly assumed a threshold of addiction
- Normalized biomarkers of exposure of chippers (5 mg nicotine/day) to a daily measurement for daily cigarette smokers
- Assumed 30 cigarettes per day
- Assumed 40% “bioavailability” (yield)

$$\frac{5\ mg\ nicotine}{day}\ X\ \frac{day}{30\ cigarettes} \div 40\%\ yield = \frac{0.42\ mg\ nicotine}{cigarette}$$

$$\frac{0.42\ mg\ nicotine}{cigarette}\ X\ \frac{1\ cigarette}{0.7\ g\ tobacco} = \frac{0.6\ mg\ nicotine}{g\ tobacco}$$

A More Realistic Calculation

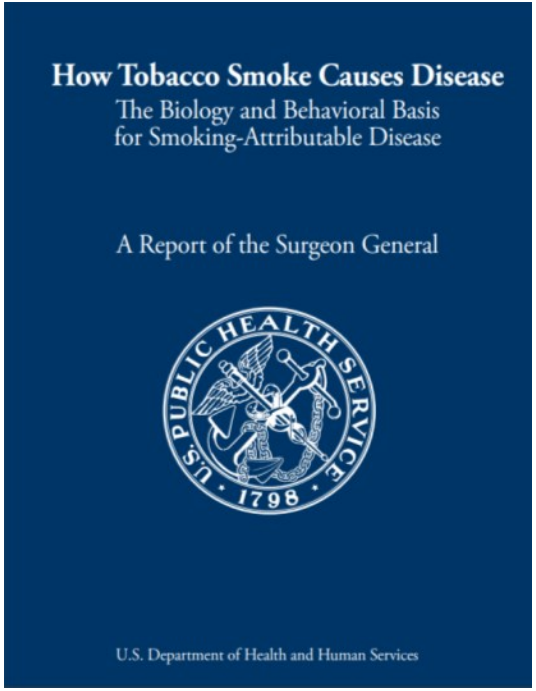
- Accept the chipper hypothesis at face value
- 14.1 cigarettes per day on average (MMWR, 2016)
- 20% nicotine yield – HCl (Ding et al., 2017)

$$\frac{5\ mg\ nicotine}{day}\ X\ \frac{day}{14.1\ cigarettes} \div 20\%\ yield = \frac{1.78\ mg\ nicotine}{cigarette}$$

$$\frac{1.78\ mg\ nicotine}{cigarette}\ \mathrm{X}\ \frac{1\ cigarette}{0.7\ g\ tobacco} = \frac{2.5\ mg\ nicotine}{g\ tobacco}$$

There Are No Consensus Criteria for Diagnosing Nicotine Addiction

- Surgeon General (2010)
  - "The crux of understanding the pathophysiology of tobacco addiction and its measurement … continues to evolve, and significant gaps in research are evident."
  - "There is no established consensus on criteria for diagnosing nicotine addiction"



Source: Centers for Disease Control & Prevention, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General* (2010)

ANPRM Treats Donny et al. as the Pivotal Study on VLNC Cigarettes

- Authors' Conclusions:
  - "In this 6-week study, participants assigned to cigarettes with 2.4 mg of nicotine or less per gram smoked 23 – 30% fewer cigarettes per day at week 6 than did participants assigned to cigarettes with 15.8 mg per gram."
  - "The cigarettes with the lowest nicotine content (0.4 mg per gram) reduced dependence according to both measures used in this study."

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Randomized Trial of Reduced-Nicotine Standards for Cigarettes

Eric C. Donny, Ph.D., Rachel L. Denlinger, B.S., Jennifer W. Tidey, Ph.D., Joseph S. Koopmeiners, Ph.D., Neal L. Benowitz, M.D., Ryan G. Vandrey, Ph.D., Mustafa al'Absi, Ph.D., Steven G. Carmella, B.A., Paul M. Cinciripini, Ph.D., Sarah S. Dermody, M.S., David J. Drobes, Ph.D., Stephen S. Hecht, Ph.D., Joni Jensen, M.P.H., Tonya Lane, M.Ed., Chap T. Le, Ph.D., F. Joseph McClernon, Ph.D., Ivan D. Montoya, M.D., M.P.H., Sharon E. Murphy, Ph.D., Jason D. Robinson, Ph.D., Maxine L. Stitzer, Ph.D., Andrew A. Strasser, Ph.D., Hilary Tindle, M.D., M.P.H., and Dorothy K. Hatsukami, Ph.D.

ABSTRACT

BACKGROUND
The Food and Drug Administration can set standards that reduce the nicotine content of cigarettes.

METHODS
We conducted a double-blind, parallel, randomized clinical trial between June 2013 and July 2014 at 10 sites. Eligibility criteria included an age of 18 years or older, smoking of five or more cigarettes per day, and no current interest in quitting smoking. Participants were randomly assigned to smoke for 6 weeks either their usual brand of cigarettes or one of six types of investigational cigarettes, provided free. The investigational cigarettes had nicotine content ranging from 15.8 mg per gram of tobacco (typical of commercial brands) to 0.4 mg per gram. The primary outcome was the number of cigarettes smoked per day during week 6.

RESULTS
A total of 840 participants underwent randomization, and 780 completed the 6-week study. During week 6, the average number of cigarettes smoked per day was lower for participants randomly assigned to cigarettes containing 2.4, 1.3, or 0.4 mg of nicotine per gram of tobacco (16.5, 16.3, and 14.9 cigarettes, respectively) than for participants randomly assigned to their usual brand or to cigarettes containing 15.8 mg per gram (22.2 and 21.3 cigarettes, respectively; P<0.001). Participants assigned to cigarettes with 5.2 mg per gram smoked an average of 20.8 cigarettes per day, which did not differ significantly from the average number among those who smoked control cigarettes. Cigarettes with lower nicotine content, as compared with control cigarettes, reduced exposure to and dependence on nicotine, as well as craving during abstinence from smoking, without significantly increasing the expired carbon monoxide level or total puff volume, suggesting minimal compensation. Adverse events were generally mild and similar among groups.

CONCLUSIONS
In this 6-week study, reduced-nicotine cigarettes versus standard-nicotine cigarettes reduced nicotine exposure and dependence and the number of cigarettes smoked. (Funded by the National Institute on Drug Abuse and the Food and Drug Administration Center for Tobacco Products; ClinicalTrials.gov number, NCT01681875.)

How the ANPRM cites Donny et al. (2015)

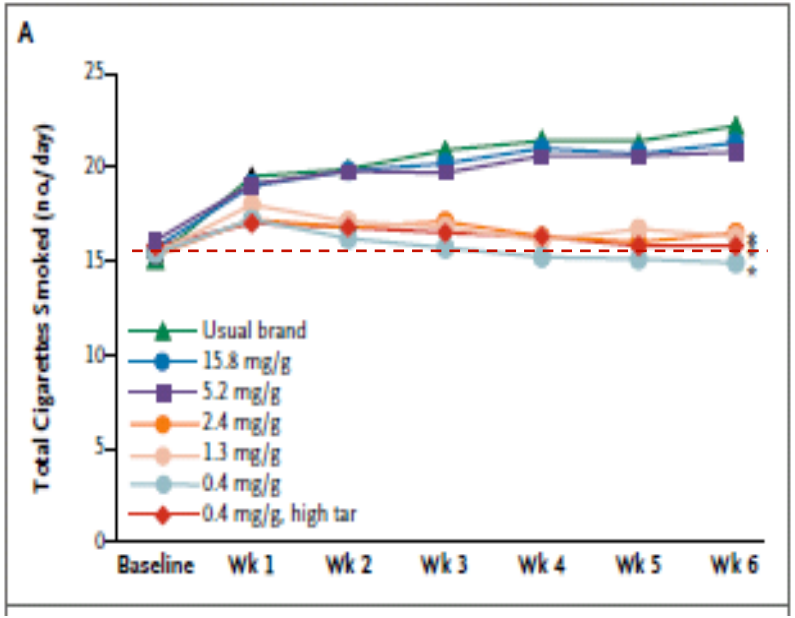
- "During the sixth week of the study, the average number of cigarettes smoked per day was lower for participants randomly assigned to cigarettes containing 2.4, 1.3 or 0.4 mg of nicotine per gram of tobacco … than for those assigned to their usual cigarette brand or those cigarettes containing 5.2 or 15.8 mg/gram …"

- "Those participants using cigarettes with the lowest nicotine content (0.4 mg per gram nicotine/gram of tobacco filler), demonstrated reduced dependence, and use of reduced nicotine cigarettes, including the VLNC cigarettes, with minimal evidence of withdrawal-related discomfort or safety concerns."

Important Caveats

- One primary outcome – Cigarettes per Day at week 6
- According to protocol, study is sufficiently powered to detect differences in cotinine, FTND and withdrawal – based on results from Hatsukami 2010
- All comparisons made in relation to test cigarettes NOT participants' own brand (except CPD).
- QSU was administered in relation to the research cigarettes instead of the participants' own brand (e.g., craving for test cigarette).
- Nardone (2016) reported a 78% incidence of noncompliance

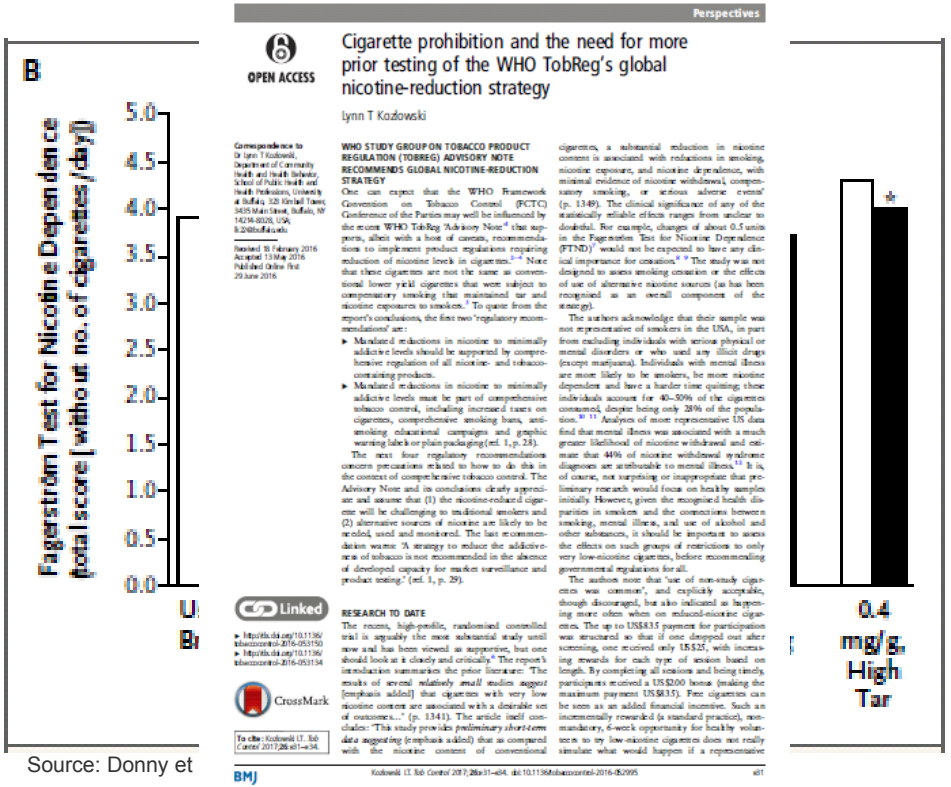
There Are No Differences Between Any Nicotine Content Groups and Baseline in CPD



Source: Donny et al. 2015

A Closer Look At Dependence Measures

- The authors report a “significant” difference between the lowest nicotine delivery cigarettes and the higher models.
- They do NOT assign any clinical relevance to these statistical differences.
- “[c]hanges of about 0.5 units in the [FTND] would not be expected to have any clinical importance for cessation.”



Perspectives

OPEN ACCESS

Cigarette prohibition and the need for more prior testing of the WHO TobReg's global nicotine-reduction strategy

Lynn T Kozlowski

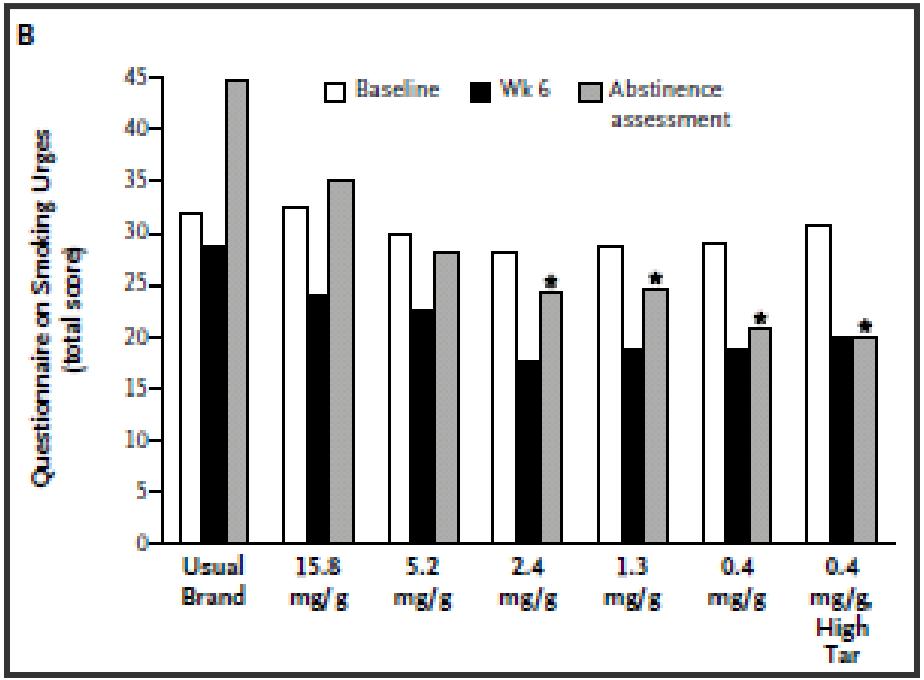
Linked

CrossMark

BMJ

Source: Donny et

A Closer Look At Withdrawal Measures



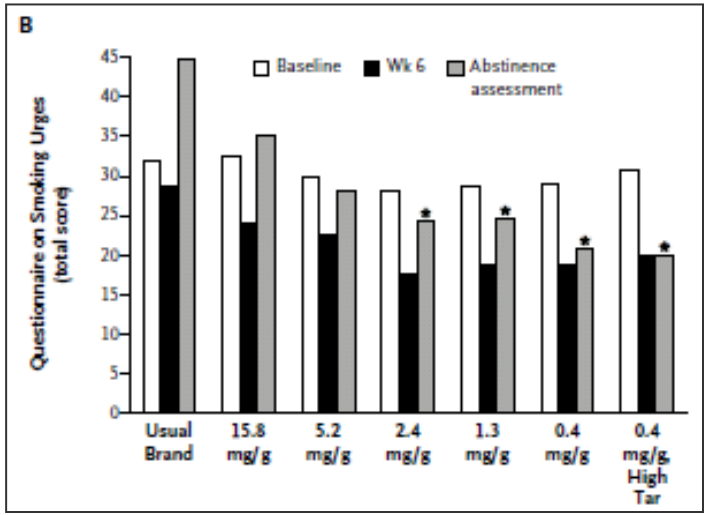
Source: Donny et al. 2015.

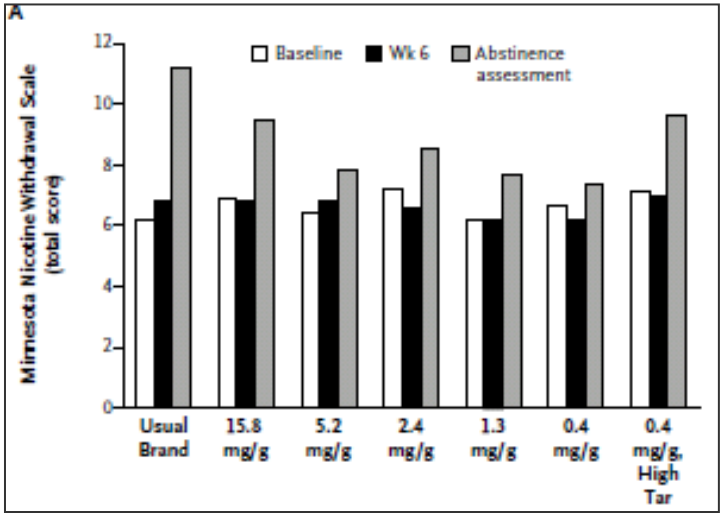
- QSU administered in relation to 15.8 mg nicotine/g research cigarette NOT Usual Brand
- Every single SPECTRUM® model is significantly different from participants' own brand

Source: Tables S31-S33 of Supplemental Materials to Donny et al. 2015.

A Closer Look At Withdrawal Measures

- Typically, the QSU and MNWS co-vary
- No differences in MNWS were observed between research cigarettes





Source: Donny et al. 2015

Analysis of Recent VLNC Cigarette Literature

- This analysis demonstrates that, in most measures, across multiple studies 2.4 mg/g is not different than 0.4 mg/g.

			NRC102	NRC200	NRC300	NRC400	NRC600
			Nicotine content (mg/g)				
Study	Measure	Area	0.4	1.3	2.4	5.2	15.8
Donny 2015	Total CPD at week 6	CPD					
Donny 2015	Total CPD at week 6 - menthol	CPD					
Donny 2016	Total CPD at week 6 - non-menthol	CPD					
Donny 2015	Study Cig CPD at week 6	CPD					
Donny 2015	Nonstudy cig use						
Donny 2015	Quit attempt 30 day follow-up	Quit					
Donny 2015	CPD 30 day follow-up	CPD					
Donny 2015	Urinary total NE	Exposure					
Donny 2015	Urinary NNAL	Exposure					
Donny 2015	Expired CO at week 6	Exposure					
Donny 2015	CO boost after 1 cigarette	Exposure					
Donny 2015	Total puff volume	Topography					
Donny 2015	Perceived nicotine level	Subjective					
Donny 2015	CPD @$6/pack	Behavior					
Donny 2015	WISDM – week 6	Dependence					
Donny 2015	Fagerstrom – week 6	Dependence					
Donny 2015	MNWS – week 6 (total & max)	Dependence					
Donny 2015	QSU (total)–wk6	Dependence					
Donny 2015	QSU (total)–wk6 - abstinence	Dependence					
Donny 2015	QSU(factor 1)–wk6 - abstinence	Dependence					
Donny 2015	QSU(factor 2)–wk6 - abstinence	Dependence					
Smith 2017	Estimated CPD @$4, $10/pack	Behavior					
Smith 2017	Estimated CPD @$20/pack	Behavior					
Smith 2017	Smoke 0 CPD @>$0/pack	Behavior					
Smith 2017	Quit in 1 year if only product option	Behavior					
Smith 2017	Omax (max $/day will spend)	Behavior					
Smith 2017	Intensity (CDP if free)	Behavior					
Smith 2017	Breakpoint (lowest price to 0 CPD)	Behavior					
Smith 2017	Breakpoint after 24h abstinence	Behavior					
Rupprecht	Weight gain-wk6, compliant	Weight					
Perkins 2016	Nicotine discrimination (Smokers)	Threshold					
Perkins 2017	Nicotine discrimination (S vs NS)	Threshold					
Perkins 2017a	Nicotine discrimination - Menthol	Threshold					
Perkins 2017a	Nicotine discrimination - Non-	Threshold					
Higgins 2017	MNWS (Total)	Dependence					
Higgins 2017	MNWS (Desire)	Dependence					
Higgins 2017	QSU (Factor 1)	Dependence					
Higgins 2017	QSU (Factor 2)	Dependence					
Higgins 2017	Breakpoint	Behavior					
Higgins 2017	Direct test of preference	Behavior					
Faulkner 2017	Craving and withdrawal reduction	Dependence					
Faulkner 2017	Positive or negative affect	Dependence					
Faulkner 2017	Sustained attention	Performance					
Faulkner 2017	Liking	Dependence					

Source: ALCS Comments to FDA's ANPRM on Nicotine

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Comments to the ANPRM Docket from Donny

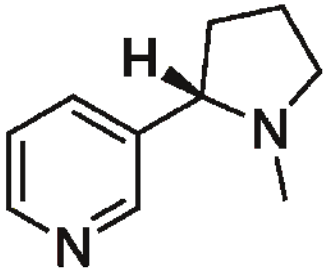
- "Available data suggest that nicotine should be reduced to a maximum of 2.4 mg/g and that there are likely to be additional benefits to decreasing content to ≤0.4 mg/g."
- "Similarly, although most smokers cannot discriminate between cigarettes with 2.4 and 0.4 mg/g, some can, suggesting that reducing nicotine content to ≤0.4 mg/g may impact more smokers."
- "Reducing nicotine content to ≤0.4 mg/g of tobacco will likely maximize the net benefits to the population"
- "These data suggest additional benefits to public health for establishing a standard of ≤0.4 mg/g"
- "To minimize the likelihood of compensation…FDA should reduce nicotine as low as possible"

Dr. Eric Donny
Professor
Department of Physiology & Pharmacology
Social Science & Health Policy
Wake Forest School of Medicine
Comments to FDA's ANPRM on Nicotine, July 13, 2018

FDA Minimizes Unintended Consequences

- Compensation
  - "According to studies involving very low nicotine cigarettes … researchers expect there would be little or no compensatory smoking."
    Source: Fed. Reg. Vol 83, No. 52/11829
  - "FDA expects … the nicotine level in cigarettes would be self-limiting (e.g., 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, making it easier for smokers to make more successful quit attempts..."
    Source: Fed. Reg. Vol 83, No. 52/11824

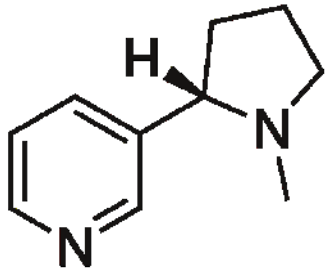
FDA U.S. FOOD & DRUG ADMINISTRATION



FDA Minimizes Unintended Consequences

- Consumer Impact
  - Will consumers believe VLNC cigarettes are safer?
  - What are the consequences of withdrawal effects on a population level?

FDA U.S. FOOD & DRUG ADMINISTRATION



ANPRM Suggests that the Agency Should Rely on "Best Available Science"

11818 Federal Register / Vol. 83, No. 52 / Friday, March 16, 2018 / Proposed Rules

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 1130

[Docket No. FDA–2017–N–6189]

RIN 0910–AH86

Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing this advance notice of proposed rulemaking (ANPRM) to obtain information for consideration in developing a tobacco product standard to set the maximum nicotine level for cigarettes. Because tobacco-related harms ultimately result from addiction to the nicotine in such products, causing repeated use and exposure to toxicants, FDA is considering taking this action to reduce the level of nicotine in these products so they are minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health. FDA is using the term "nonaddictive" in this document specifically in the context of a potentially nonaddictive cigarette. We acknowledge the highly addictive potential of nicotine itself depending upon the route of delivery. As discussed elsewhere in this document, questions remain with respect to the precise level of nicotine in cigarettes that might render them either minimally addictive or nonaddictive for specific members or segments of the population. We envision the potential circumstance where nicotine levels in cigarettes do not spur or sustain addiction for some portion of potential smokers. This could give addicted users the choice and ability to quit more easily, and it could help to prevent experimenters (mainly youth) from initiating regular use and becoming regular smokers. The scope of products covered by any potential product standard will be one issue for comment in the ANPRM. Any additional scientific data and research relevant to the empirical basis for regulatory decisions related to a nicotine tobacco product standard is another issue for comment in the ANPRM.

DATES: Submit either electronic or written comments on the ANPRM by June 14, 2018.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before June 14, 2018. The https://www.regulations.gov electronic filing system will accept comments until midnight Eastern Time at the end of June 14, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA–2017–N–6189 for "Tobacco Product Standard for Nicotine Level of Certain Tobacco Products." Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Gerie Voss, Center for Tobacco Products, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 1–877–CTP–1373, *gerie.voss@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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"Therefore, FDA hypothesizes that making cigarettes minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health, would significantly reduce the morbidity and mortality caused by smoking."

Source: Fed. Reg. Vol 83, No. 52/11821

FDA U.S. FOOD & DRUG ADMINISTRATION

Best Available Science?

- Studies referenced in ANPRM are from a small group of researchers and none involve a nationally representative cohort of smokers
- Significant scientific gaps exist within these studies
- Full data sets and original protocols are unavailable to date
- No access to research cigarettes
- Dozens of clinical studies are currently being conducted

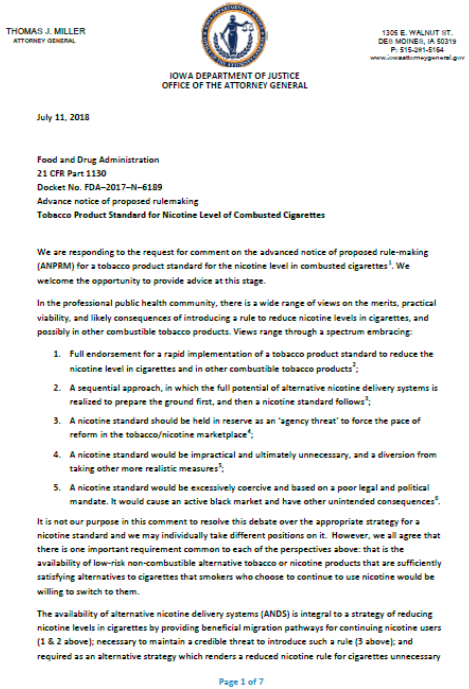
On What Science Should the Agency Rely?

- Weight of Evidence analysis of well-conducted studies by multiple stakeholders

- Analyses in real-world conditions
  - Illicit products
  - Availability of sensorially acceptable VLNC products
  - Long term effects
  - Nationally representative

- Studies using the continuum of risk and FDA framework in their design

Policy On Which Everyone Can Agree



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IOWA DEPARTMENT OF JUSTICE
OFFICE OF THE ATTORNEY GENERAL

July 11, 2018

Food and Drug Administration
21 CFR Part 1130
Docket No. FDA–2017–N–6189
Advance notice of proposed rulemaking
Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

We are responding to the request for comment on the advanced notice of proposed rule-making (ANPRM) for a tobacco product standard for the nicotine level in combusted cigarettes[1]. We welcome the opportunity to provide advice at this stage.

In the professional public health community, there is a wide range of views on the merits, practical viability, and likely consequences of introducing a rule to reduce nicotine levels in cigarettes, and possibly in other combustible tobacco products. Views range through a spectrum embracing:

1. Full endorsement for a rapid implementation of a tobacco product standard to reduce the nicotine level in cigarettes and in other combustible tobacco products[2];
2. A sequential approach, in which the full potential of alternative nicotine delivery systems is realized to prepare the ground first, and then a nicotine standard follows[3];
3. A nicotine standard should be held in reserve as an 'agency threat' to force the pace of reform in the tobacco/nicotine marketplace[4];
4. A nicotine standard would be impractical and ultimately unnecessary, and a diversion from taking other more realistic measures[5];
5. A nicotine standard would be excessively coercive and based on a poor legal and political mandate. It would cause an active black market and have other unintended consequences[6].

It is not our purpose in this comment to resolve this debate over the appropriate strategy for a nicotine standard and we may individually take different positions on it. However, we all agree that there is one important requirement common to each of the perspectives above: that is the availability of low-risk non-combustible alternative tobacco or nicotine products that are sufficiently satisfying alternatives to cigarettes that smokers who choose to continue to use nicotine would be willing to switch to them.

The availability of alternative nicotine delivery systems (ANDS) is integral to a strategy of reducing nicotine levels in cigarettes by providing beneficial migration pathways for continuing nicotine users (1 & 2 above); necessary to maintain a credible threat to introduce such a rule (3 above); and required as an alternative strategy which renders a reduced nicotine rule for cigarettes unnecessary

Page 1 of 7

- Letter from the AG of Iowa in response to the nicotine ANPRM
- Signed by the AG and 17 Public Health scientists – including Eric Donny
- Comments focus on the availability of alternative nicotine-containing products as a more appropriate means of achieving public health goals