PHILIP MORRIS INTERNATIONAL

COMMENTS ON FDA ADVANCE NOTICE OF PROPOSED RULEMAKING: TOBACCO PRODUCT STANDARD FOR NICOTINE LEVEL OF COMBUSTED CIGARETTES

July 16, 2018

Via Electronic Submission

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-N-6189 (83 Fed. Reg. 11818, March 16, 2018)
Advance Notice of Proposed Rulemaking on Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

INTRODUCTION

A federally mandated ceiling on nicotine levels in cigarettes has been a topic of discussion for many years.[1] It would be a dramatic, sweeping, and irrevocable change to the entire U.S. cigarette market. But it is a change that FDA can mandate under, and subject to the criteria in, Subchapter IX of the Food, Drug, and Cosmetics Act (FDCA).

As is clear from the extensive background that the ANPRM provides, a product standard for nicotine levels requires careful consideration of many questions of science, of policy, and of law. Whether concrete or abstract, whether fuzzy or distinct, the questions invariably touch on the interests of the 40 million men and women in America who smoke cigarettes. How will they respond when cigarettes as they have always existed are no longer available? How best can the Agency design and implement a standard that is likely to yield the most socially desirable outcome?

[1] Tobacco Product Standard for Nicotine Level of Combusted Cigarettes (ANPRM), 83 Fed. Reg. 11818, 11827 (Mar. 16, 2018), available at https://www.gpo.gov/fdsys/pkg/FR-2018-03-16/pdf/2018-05345.pdf.

Which other agencies may contribute to the optimal solution? This is no easy inquiry, and the ANPRM will surely elicit many views and insights. For its part, Philip Morris International[2] (PMI) respectfully submits these comments, which we hope the Agency will find useful as the rulemaking process moves ahead.

ABOUT PHILIP MORRIS INTERNATIONAL

PMI is one of the world's leading tobacco companies. We do not currently operate in the U.S., but we follow with interest FDA's comprehensive regulatory plan for regulating tobacco products under FDCA and the Agency's determination to drive socially desirable innovation in tobacco products.[3] We therefore note Commissioner Gottlieb's precept that:

> [W]e need to envision a world where cigarettes lose their addictive potential through reduced nicotine levels. And a world where less harmful alternative forms, efficiently delivering satisfying levels of nicotine, are available for those adults who need or want them.[4]

At PMI, we operate according to a manifesto that, in calling for a smoke-free future, aligns remarkably well with the future state that the Commissioner describes. Indeed, our business strategy envisions a world in which cigarettes eventually disappear altogether. To that end, our organization is dedicating itself to developing, scientifically assessing, and commercializing a range of non-combustible alternatives to which adult smokers will switch completely.[5]

FOCUS OF PMI'S COMMENTS

We support the Agency's aims to make it easier for smokers to quit and to help "prevent experimenters (mainly youth and young adults) from initiating regular cigarette smoking."[6] The desired future state is clear and, especially given our own vision of a smoke-free world, one that PMI shares.

The ANPRM contemplates a product standard that would allow only non-addictive cigarettes on the market. From our perspective, and consistent with FDA's modeling, the success of the standard would largely depend on consumer access to and

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[2] Comments submitted by Philip Morris International Management S.A., which is an affiliate of Philip Morris International Inc. and Philip Morris Products S.A.

[3] FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (July 28, 2017), available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm.

[4] Gottlieb, S., Protecting American Families: Comprehensive Approach to Nicotine and Tobacco (July 28, 2017), available at https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm.

[5] Information about our vision for a smoke-free future is available on our corporate website, www.pmi.com. For detailed information on our research and development work, please visit www.pmiscienceusa.com.

[6] ANPRM, *supra* note 1, at 11819.

information about non-combustible alternatives to cigarettes. This includes the right regulatory framework (including appropriate measures such as differentiated label and labelling, marketing rules, and price and tax measures), which combined with significant commercial investment from manufacturers, can accelerate market movement to less harmful alternatives.

Our comments therefore focus on two areas. First, we share our views on the ways in which the market for tobacco products should develop before the Agency issues a standard for non-addictive cigarettes. Second, we address several points specific to a standard.

At the outset, we also call attention to terminology. For the sake of simplicity in these comments, PMI is using the phrase "non-addictive cigarettes" to describe products that comply with a standard for nicotine levels. We believe this terminology aligns with the discussion in the ANPRM.[7]

In discussing "less harmful alternatives" to cigarettes, we are referring to products that: 1) contain and deliver nicotine at levels smokers find satisfactory; and 2) support the Agency's stated objective of "ending the use of traditional cigarettes and switching to a non-combustible product made or derived from tobacco."[8] We are not referring to cessation or cessation aids.

U.S. TOBACCO POLICY AT A CROSSROADS

Through six major pieces of legislation from 1965 until 2008, Congress largely reserved to itself control of tobacco policy in the United States. Notably, federally mandated warnings, advertising restrictions, disclosures by manufacturers, federal excise tax, and reports by the Surgeon General have always been matters for Congress.[9]

A new era of tobacco policy under federal law began on June 22, 2009, when Congress amended FDCA to grant FDA jurisdiction over tobacco products. Under Subchapter IX of FDCA, which runs 102 pages in the U.S. Code, FDA has a broad spectrum of

[7] *See, e.g.,* ANPRM, *supra* note 1, at 11819 ("Through this ANPRM, FDA indicates that it is considering the issuance of a product standard to set a maximum nicotine level in cigarettes so that 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.").

[8] Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," (FDA Clarification) 82 Fed. Reg. 2193, 2214 (Jan. 9, 2017), available at https://www.gpo.gov/fdsys/pkg/FR-2017-01-09/pdf/2016-31950.pdf.

[9] *See generally* FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 148-156 (2000).

regulatory powers.[10] In the present rulemaking, two major components of the Agency's authority are in play.

PRE-MARKET REVIEW

First, FDA controls whether, and if so under what conditions, new tobacco products can reach the market. It acts as a gatekeeper of the pathways to market that Sections 387j and 387k create.[11] Those provisions empower the Agency to propel the flow of innovations that provide better choices for consumers while minimizing the risk of new products that are not appropriate for the protection of public health.[12]

PRODUCT STANDARDS

Second, and complementary to its *ex ante* control over new products, is FDA's statutory authority to mandate product standards under Section 387g. Such standards can cover a broad range of topics, from relatively narrow ones, such as provisions for product testing,[13] to far more dramatic measures such as the nicotine ceiling that the present ANPRM contemplates.[14]

CASE-BY-CASE VERSUS PRODUCT CATEGORY

There are many similarities in the statutory criteria that FDA applies when reviewing applications for new products and when setting product standards. In both instances, the Agency must assess whether the proposed action is appropriate for the protection of the public health. In turn, that assessment requires consideration of scientific evidence concerning risks and benefits to the population as a whole; the increased or decreased likelihood that existing users of tobacco products will stop using such products; and the increased or decreased likelihood that those who do not use tobacco products will start using such products.[15]

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[10] At the same time, Subchapter IX preserves the authority of the Federal Trade Commission, as well as State and local authority. *See* 21 U.S.C. §§ 387n, 387p (2009).

[11] *See, e.g.,* Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776, finding 44 (June 22, 2009) ("In connection with its mandate to promote health and reduce the risk of harm, the Food and Drug Administration routinely makes decisions about whether and how products may be marketed in the United States.").

[12] In fact, FDA's very mission is to take prompt, efficient, and appropriate actions with respect to regulated products, see 21 U.S.C. § 393(b) ("*Mission* The Administration shall— (1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner.").

[13] 21 U.S.C. § 387g(a)(4)(B)(ii).

[14] 21 U.S.C. § 387g(a)(4)(A)(i).

[15] 21 U.S.C. § Sec. 387g(a)(3)(B)(i)(I)-(III); *see also* 21 U.S.C. § 387j(c)(4)(PMTA) and 21 U.S.C. § 387k(g)(4)(B)-(C)(MRTP).

But there is also a major difference between the pathways for pre-market authorization and the conditions for product standards. A marketing order for a new product is specific to the product that is the subject of an application.[16] There is a careful review process that entails extensive scientific evidence, including clinical studies, behavioral assessments, and, in certain cases, scientific advisory committees. If the applicant is successful the product can get to market. Unless they meet the standard for substantial equivalence, subsequent products seeking authorization must pass through the Agency's gates. As further safeguards against Type I errors — *i.e.,* erroneous *go* decisions — FDCA requires post-market surveillance for Modified Risk Tobacco Products and empowers the Agency to withdraw marketing orders in light of subsequent evidence.

By contrast, and by its very nature, a product standard applies to an entire category of products. For example, the pending standard for levels of N-nitrosonornicotine (NNN) would apply to a broad range of smokeless tobacco products.[17] Similarly, a nicotine standard would apply to all cigarettes and such other combustible products that fall within the scope that the Agency might ultimately define.

To be sure, decisions to allow new products are immensely important. But a product standard can, in a single action, fundamentally and irrevocably, alter an entire category. Therefore, in our view, the evidence package that the Agency compiles in support of a product standard should be as thorough and of the same scientific rigor as applicants must proffer to bring a new product to market. In that regard, the ANPRM contemplates using "the best available science" to satisfy all of the statutory requirements for a product standard involving a maximum level of nicotine. As we suggest below, a comparably high standard should apply to all considerations, including consumer perceptions and market impact.

SYNTHESIZING POLICY APPROACHES

Taken together, Sections 387g, 387j, and 387k provide interrelated powers over which products can enter (*e.g.*, non-combustible products), which products must exit, the

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[16] *See, e.g.,* FDA Clarification, *supra* note 8, at 2213 ("We note that FDA currently interprets the standards in various medical and tobacco product premarket review pathways to refer to individual products rather than product categories."); FDA Final Rule: Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products (Deeming Rule), 81 Fed. Reg. at 28973, 28990 (May 10, 2016) ("Whether the marketing of a product is appropriate for the protection of the public health will be evaluated on a case-by-case basis...and with consideration of the continuum of risk of nicotine-delivering products."), available at https://www.gpo.gov/fdsys/pkg/FR-2016-05-10/pdf/2016-10685.pdf.

[17] Tobacco Product Standard for N-Nitrosonornicotine Level in Finished Smokeless Tobacco Products (Proposed NNN Standard), 82 Fed. Reg. 8004 (Jan. 23, 2017), available at https://www.gpo.gov/fdsys/pkg/FR-2017-01-23/pdf/2017-01030.pdf.

market (*e.g.*, today's cigarettes), and therefore indirectly over other market factors such as illicit trade. They also provide powers over the sequencing and timing of these market changes.

In PMI's view, the task at hand, and the corresponding opportunity, is to find the "sweet spot"[18] that optimizes outcomes from the exercise of the Agency's authority as the market's gatekeeper. In this role, FDA can authorize or remove products, enforce existing rules, and influence consumer and industry behavior. To that end, we find informative the views of Benowitz *et al.*, who urge against treating the policy approaches that focus, respectively, on market entry and exit "independently" or even "antithetically."[19] As they state in a 2016 article:

> Most studies of reduced nicotine content cigarettes have not provided access to alternative non-combusted nicotine products (ANDS). Conversely, the primary focus of those advocating using ANDS has been to provide smokers with products that could substitute for conventional cigarettes (harm reduction). We believe that the combination of these two approaches is likely to have the greatest impact upon public health.[20]

Put differently, and as Prof. Levy has written, "To be more effective, governments must combine policies that motivate behavior change with those that facilitate behavior change."[21]

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As the ANPRM demonstrates, there is a long list of details to work out within the four corners of a nicotine standard. Should a ceiling be at 0.4 or 0.5 mg or some other level? Should there be a single target or a step-down approach? These are surely core questions. But, in our view, a nicotine ceiling can only be assessed in conjunction with the effects of measures that facilitate adult smoker access to less harmful alternatives to cigarettes. We suggest that the right sequencing of a nicotine standard relative to the availability of alternative products is paramount and that a robust, credible marketplace of such products, both for consumers and manufacturers, is a necessary predicate to removing cigarettes as they now exist.

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[18] *See* Abrams, D. et al., *Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives*, 39 ANNU. REV. PUBLIC HEALTH, 193 (2018), available at https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-040617-013849.

[19] Benowitz, N. et al., *Reduced Nicotine Content Cigarettes, E-cigarettes and the Cigarette End Game*, 112 ADDICTION, 6, 6 (2016), *available at* https://onlinelibrary.wiley.com/doi/pdf/10.1111/add.13534.

[20] *Id*. ("The key to successful cigarette nicotine reduction is likely to lie with providing readily available, consumer-acceptable non-combusted forms of nicotine.").

[21] Levy, D. et al., *The Need for a Comprehensive Framework,* 112 ADDICTION 22, 23 (2017), available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/add.13600.

KEEPING AN OPEN MIND

The scope of FDA's mandate — and the many *go*/*no-go* decisions it must make — inevitably leads the Agency into controversy. People may criticize actions that are too slow…or too fast; too narrow…or too sweeping.[22] Despite an atmosphere of on-going point-counterpoint, "[a] common judgment call inside the agency is whether there are enough data to take regulatory action."[23]

Of all FDA-regulated products, tobacco is perhaps the most controversial. The "tobacco wars" date to at least the 1950s and have engendered entrenched ideologies and rigid positions. Commissioner Gottlieb described the state of play in his July 28, 2017, speech:

> Precious little progress has been made as competing camps dig in on the benefits and risks of a harm reductionist approach to this new technology. Both sides are convinced that they're right, but we've seen little progress, and virtually no common ground.[24]

But, more optimistically, the Commissioner added that "there's a pathway forward that reframes the debate around nicotine."[25] PMI shares that optimism and embraces the drive towards less harmful alternatives to cigarettes. As much as rigorous science, an open mind by all concerned is essential to reduce smoking prevalence in the U.S. To quote again Commissioner Gottlieb: "It's incumbent upon us as regulators to explore both the potential public health benefits and the risks of this new technology with an open mind."[26]

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[22] *See, e.g.,* Scharfstein, J., *The FDA—A Misunderstood Agency*, 306 JAMA 1250 (Sept. 21, 2011) ("Some claim the FDA is captive to manufacturers and too quick to approve new therapies; others assert the agency is safety obsessed and too slow to make treatments available. Some criticize the FDA for refusing to challenge advertising claims; others fault the agency for restricting reasonable avenues of marketing that could inform the public. Sometimes stories outlining conflicting perspectives appear on facing pages of the same newspaper."), available at https://jamanetwork.com/journals/jama/article-abstract/1104342. Or, as Director Zeller put it during the January 25, 2018 TPSAC hearing on PMI's MRTP application, "welcome to our world as regulators," available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM599235.pdf.

[23] Scharfstein, *supra* note 22.

[24] Gottlieb, *supra* note 4.

[25] *Id.*

[26] *Id.*; *see also* Hatsukami, D. et al., *Harm Reduction Approaches to Reducing Tobacco-Related Mortality*, 25 ANNU. REV. PUBLIC HEALTH 377, 390 (2004) ("It is the responsibility of the public health professionals to be open-minded about the possibility that reduced exposure products may potentially reduce death and disease."), available at https://www.annualreviews.org/doi/full/10.1146/annurev.publhealth.25.102802.124406.

ENABLING BETTER CHOICES TO REDUCE CIGARETTE SMOKING PREVALENCE

When Congress passed the Federal Cigarette Labeling and Advertising Act (FCLAA) in 1965,[27] smoking prevalence in the United States was more than 40%.[28] Prevalence declined over the ensuing decades and currently hovers around 15%.[29] Current tobacco control policies, which focus on reducing initiation and use of cigarettes, aim to see prevalence at 12% by 2020.[30]

The statistics on prevalence are encouraging. Nonetheless, as a result of population growth, roughly 40 million Americans smoke cigarettes. Our understanding is that most of those people will continue to smoke and, therefore, over time increase their risk of smoking-related harm and disease.[31]

THE OPPORTUNITY

Statistics on smoking prevalence provide a slice-in-time description on a population basis. A different measure, which looks at the public health opportunity from a consumer perspective, is cigarette pack-years. A cigarette pack year is calculated by multiplying the number of cigarette packs smoked per day by number of years smoked. For example, a one-pack per day smoker who has smoked for 10 years would have a 10 pack-year smoking history. A one-pack per day per smoker who smoked for 20 years would have a 20 pack-year smoking history.

The opportunity for adult smokers is to avoid additional pack-years — ideally, through cessation or, if not, by complete switching to a non-combustible alternative.[32] In so doing, these smokers reduce the likelihood of smoking-related harm and disease. According to the ANPRM:

> Former smokers that choose to switch completely to a potentially less harmful nicotine delivery product (*e.g.,* electronic nicotine delivery systems (ENDS)) to maintain their nicotine dose also would, to the

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[27] *See* 15 U.S.C. §§ 1331 et seq.

[28] Centers for Disease Control and Prevention (CDC), Trends in Current Cigarette Smoking Among High School Students and Adults, United States, 1965–2014, available at https://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/index.htm.

[29] CDC Fact Sheet: Current Cigarette Smoking Among Adults in the United States (2016), available at https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/.

[30] CDC Best Practices for Comprehensive Tobacco Control Programs (2014), available at https://www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2014/executive-summary.pdf.

[31] ANPRM, *supra* note 1, at 11823 ("For adult smokers who report quit attempts, many of these attempts are unsuccessful. For example, among the 19 million who reported attempting to quit in 2005, epidemiologic data suggest that only 4 to 7 percent were successful.").

[32] *Id.* at 11835 ("FDA expects that making cigarettes minimally addictive or nonaddictive would reduce tobacco-related harms by promoting smoking cessation or complete migration to alternative, potentially less harmful noncombusted products and by reducing initiation.").

> extent that those products result in less harm, significantly reduce their risk of tobacco-related death and disease.[33]

Similarly, the evidentiary basis for the proposed standard assumes, and relies on the existence of, less harmful non-combustible alternatives. The modeling by Apelberg *et al.* contemplates various categories of tobacco-use transitions, including complete switching and partial switching.[34] If those categories do not exist at all or if they are not sufficiently available or known to consumers, the choices remaining to adult smokers will ultimately come down to cessation, which is the optimal transition category, or to the worst category, continued smoking. All of which shows there is a significant risk of a missed opportunity (a Type II error) that flows from the increased likelihood that adult smokers who would otherwise switch completely to a non-combustible alternative will continue to smoke — and thereby increase their total cigarette pack-years.

If a nicotine standard comes into force before a market of non-combustible alternatives has fully emerged the situation becomes even more troubling. A regulatory standard cannot eliminate smokers' persistent demand for nicotine. That demand will seek a supply, including through illicit channels. Again, therefore, PMI's view is that strategic sequencing of a comprehensive policy framework — one that integrates and synchronizes the complementary approaches of authorizing new innovative products and product standards — is the key.

ALL TOBACCO PRODUCTS ARE NOT EQUALLY HARMFUL

The views we have expressed in the preceding paragraphs rest on the premise that different tobacco products might present different risks or, in other words, that all tobacco products are not the same with respect to the risks they present. That premise is indeed valid. Briefly stated:

First, there is uniform agreement among scientists and policy makers that cigarettes are the "worst" (or the most harmful) tobacco product. According to the ANPRM, for example,

> Cigarettes are the tobacco product category that causes the greatest burden of harm to public health as a result of the prevalence of cigarette use and the toxicity and addictiveness of these products.[35]

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[33] ANPRM, *supra* note 1, at 11824.
[34] Apelberg, B. et al., *Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States*, 378 N ENGL J MED 1725 (2018), available at https://www.nejm.org/doi/full/10.1056/NEJMsr1714617?query=featured_home.
[35] ANPRM, *supra* note 1, at 11825.

Phrases such as cigarettes are the *worst* or cigarettes present the *greatest* risk are comparative assertions. Logically, there is the "worst" only if there is something else that is less "bad" than the "worst."[36]

In any event:

> These consumers and potential consumers have a fundamental right (based on the principles of autonomy, health communication, and health literacy) to be well aware of the dramatic differential harms from the various products they are already or might consider using.[37]

Second, there is an enormous body of epidemiology that quantitatively describes, *e.g.,* using measures such as relative risk ("RR"), the correlation between different types of tobacco products and different diseases. For cigarette smoking, the RRs for major diseases are significantly higher than the RRs for those diseases among people who use non-combustible tobacco products. For example, among cigarette smokers the RR for continued smoking is estimated to be roughly 11.7,[38] whereas the RR for lung cancer among people who are exclusive users of snus is estimated to be roughly 1.1.[39]

Third, it may even be possible to reduce the risk of a particular tobacco product, which is the aim of FDA's proposed product standard for levels of NNN in finished smokeless tobacco. The Agency states that smokeless tobacco would be less harmful if there is a ceiling on NNN.[40] The proposed rule estimates significant benefits:

> In the 20 years following implementation of the proposed product standard, approximately 12,700 new cases of oral cancer and approximately 2,200 oral cancer deaths would be prevented in the United States because of this rule. Moreover, during that 20-year

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[36] *See also* Deeming Rule, *supra* note 16, at 29027 ("FDA agrees that a continuum of nicotine-delivering products does exist as demonstrated by the lower levels of toxicants in ENDS in comparison to cigarettes, and may warrant different requirements for products at different ends of this continuum.").

[37] Kozlowski, L. & Sweanor, D., *Young or Adult Users of Multiple Tobacco/Nicotine Products Urgently Need to be Informed of Meaningful Differences in Product Risks*, 76 ADDICTIVE BEHAVIORS 376, 376 (2018), available at https://www.sciencedirect.com/science/article/pii/S0306460317300539?via%3Dihub.

[38] Lee, P. et al., *Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer*, 12 BMC CANCER 385 (2012), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505152/.

[39] FDA, Recommendation on Swedish Match Premarket Tobacco Application (2015) ("There is no evidence that snus causes lung cancer and COPD, which together are estimated to account for over 50% of smoking-attributable mortality in the U.S. (CDC, 2008). This along suggest a difference between cigarette smoking and snus in overall risks to health."), available at https://www.fda.gov/downloads/tobaccoproducts/labeling/tobaccoproductreviewevaluation/ucm472123.pdf.

[40] Proposed NNN Standard, *supra* note 17, at 8006 ("FDA is using its authority to propose a standard that would reduce tobacco-related harms by establishing a limit of NNN in smokeless tobacco products.").

> period, approximately 15,200 life years would be gained in the United States as a result of the proposed standard.[29]

The Agency also estimates a reduction of risk on an individual basis as follows:

> Setting the proposed limit for NNN in finished smokeless tobacco products means that, on average, in a population of daily users of smokeless tobacco products, over their life time, there would be an approximately 65 percent reduction in ELCR, compared with lifetime daily use of a population that used smokeless tobacco products with NNN levels at the current level.[41]

Fourth, innovative, non-combustible tobacco products, such as heated tobacco, offer great potential as less harmful alternatives to continued smoking. As mentioned at the outset, this is the area of greatest interest to PMI and is the central focus in our efforts to deliver a smoke-free future.

To reiterate: tobacco products differ in the risk of harm they present, a fact that should guide the public and the private sector alike in driving people who will otherwise continue smoking from cigarettes to less harmful alternatives. And, the people who smoke cigarettes should know – indeed, have a right to know – about the benefits of cessation and about the continuum of risk for different tobacco products. Kiviniemi and Kozlowski make the point forcefully:

> Given the scientific consensus that cigarettes are the most deadly form of tobacco use, the public has a right to a clear understanding of this fact and efforts should be made to impart an understanding of the differential health risks for various tobacco/nicotine products.[42]

HEALTH LITERACY AMONG SMOKERS

As FDA pursues its comprehensive plan for tobacco, consumer perceptions, knowledge, beliefs, and so on will be increasingly important. In its proposed NNN rule, the Agency gives an example of how the information environment can function well:

> In addition, to the extent that cigarette smokers who cannot or will not quit smoking are motivated to switch completely to smokeless tobacco due to perceptions of lower risk, this complete switching could result

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[41] *Id.*

[42] Kiviniemi, M. & Kozlowski, L., *Deficiencies in Public Understanding About Tobacco Harm Reduction: Results from a United States National Survey*, 12 HARM REDUCTION JOURNAL 1, 2 (2015), available at https://harmreductionjournal.biomedcentral.com/articles/10.1186/s12954-015-0055-0.

> in additional benefits to public health through reduced risks to these individual users.[43]

Put negatively, the plan will miss many opportunities if people who smoke hold mistaken beliefs or misperceptions about cessation or non-combustible alternatives. Prof. Levy captured the point in a recent article:

> Not only is accurate information needed for tobacco users to make informed decisions, but misinformation can lead to unintended consequences, such as distrust, which can ultimately lead to behaviors inconsistent with the intended goals of tobacco control policy.[44]

PROTECTING THE INFORMATION ENVIRONMENT

Confusing or inaccurate information from all sorts of sources can easily pollute the information environment.[45] In our experience outside the U.S., we have seen that misperceptions about the risks of nicotine, among other things, appear to be driving significant confusion about the comparative risks of different tobacco and nicotine-containing products.

On February 6, 2018, Public Health England issued a report on e-cigarettes and heated tobacco products. The report zeroed in on misreporting of scientific studies by the media. After giving examples of headlines that did not reflect the facts, the report stated: "The consequences of this inaccurate or inadequate reporting are that the general public is misled. This could induce smokers to carry on smoking rather than switching."[46]

TRUSTED SOURCES OF INFORMATION

The U.S. Department of Health & Human Services (HHS) and FDA hold central, essential roles in providing quality information to the public. For example:

> It is HHS's goal to ensure and maximize the quality, objectivity, utility, and integrity of information that it disseminates to the public. We

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[43] Proposed NNN Standard, *supra* note 17, at 8026.

[44] Levy, D., *Communicating Accurate and Complete Information,* 76 ADDICTIVE BEHAVIORS 386, 387 (2018), available at https://www.sciencedirect.com/science/article/pii/S0306460317300552.

[45] *See, e.g.,* Kozlowski & Sweanor, *supra* note 37 ("Existing trends and patterns in tobacco product use are so corrupted by disinformation or error that they provide little indication of what might happen if accurate information were widely understood by the public.").

[46] Public Health England, Evidence review of e-cigarettes and heated tobacco products 2018 (2018), available at https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review.

> strive to provide information that is accurate, reliable, clear, complete, unbiased, and useful.[47]

According to FDA: "As part of our mission to protect the public health and safety, we provide the public with a wide variety of information on risk."[48] Further, FDA describes its mission as including "helping people protect their health through informed decisions about using FDA-regulated products."[49]

FDA recently produced a Strategic Plan for Risk Communication and Health Literacy. The plan touches on many points that are salient to these comments, such as:

- "FDA is uniquely positioned to conduct or fund research on risk communication and health literacy."
- "Risk communication and health literacy are ongoing concerns for FDA."
- "…clear communication is integral to FDA's mission…"[50]

We readily acknowledge the significant amount of information that FDA makes publicly available to U.S. consumers. At the same time, we reiterate the need to increase awareness and understanding of non-combustible alternatives. Moreover, in the midst of so much rhetoric and hostility, it is extremely hard to separate the signal from the noise. It is therefore helpful and reassuring for consumers to look to HHS and FDA as their trusted, expert sources of information.

BUILDING AN EVER-LARGER DATA SET

A well-functioning pathway to market for innovations should "incentivize development of tobacco products that pose less risk to human health by limiting market access for more-risky competitor products."[51] As the Agency has further explained, "since the 'appropriate for the protection of the public health' standard involves comparison to the general tobacco product market existing at the time of an application, FDA believes that, over time, the premarket authorities will move the market toward less-risky tobacco products."[52]

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[47] U.S. Department of Health & Human Services (HHS), *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public: A Summary of HHS Agency Guidelines* (Oct. 2002), available at https://aspe.hhs.gov/report/hhs-guidelines-ensuring-and-maximizing-quality-objectivity-utility-and-integrity-information-disseminated-public/summary-hhs-agency-guidelines.

[48] *Id.*

[49] FDA Strategic Plan for Risk Communication and Health Literacy 2017-2019 (Sept. 2017), available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM579719.pdf.

[50] *Id.* at 6, 11, 12.

[51] Deeming Rule, *supra* note 16, at 28999.

[52] *Id.*

Once a diverse market of non-combustible products is available to smokers, FDA will be able to collect and assess data on consumer perception and behavior toward those products, including switching rates. In turn, those real-world data will enhance the modeling that informs a possible standard for non-addictive cigarettes.

OBSERVATIONS ON THE STANDARD

Nicotine occurs naturally in tobacco. It has always been in cigarettes. It is integral to the smoking experience. To mandate that no cigarette can have more than a *de minimis* level of nicotine will necessarily and entirely alter both the consumer experience and the marketplace. In fact, in addition to reducing the level of nicotine, the taste of non-addictive cigarettes is likely to be significantly altered irrespective of the nicotine reduction technology used, while the negative effects of combustion will remain. Because it will result in a highly unsatisfactory proposition for the 40 million American smokers, amongst all the requirements and restrictions that are in FDA's armamentarium of regulatory tools, a nicotine ceiling is perhaps the most dramatic measure the Agency might take.

"DAY ZERO"

According to the ANPRM, a product standard for a nicotine ceiling could come into force through a stepped-down approach or through a single target. In either scenario, however, there will eventually be a "Day Zero," at which point the U.S. will move entirely to non-addictive cigarettes.[53] As we conceive it, "Day Zero" is when the Agency "flips the switch," a metaphor that conveys the on/off, binary nature of a market-wide standard.

It is common practice for consumer goods companies to use a test market for a new product before launching nationally or more broadly. This phased approach would be available for new tobacco products under Sections 387j and 387k. For example, the product might initially be available in three cities and expand geographically thereafter. By contrast, it does not seem feasible to use the equivalent of a test launch in the context of Section 387g. Instead, in all likelihood, on "Day Zero" the new, non-addictive products would be national.

A change as significant as a nicotine ceiling calls for advanced testing. Paradoxically, however, there seems to be an inverse relationship between the magnitude of the change under Section 387g and the ability to test it in whole or in part ahead of time. The ANPRM addresses this topic in a brief passage that perhaps understates the

[53] *See* ANPRM, *supra* note 1, at 11819 ("FDA intends that any nicotine tobacco product standard would cover all brands in a particular product category and, therefore, those products currently on the market and any new tobacco products would be expected to adhere to the standard.").

situation: "research studies cannot easily replicate the condition of a nationally enforced restriction on nicotine to minimally addictive levels in cigarettes."[54]

The many scenarios for "Day Zero" reinforce our suggestion that a robust, credible market for non-combustible alternatives precede a product standard for nicotine.

SEQUENCING AND TIMING OF "DAY ZERO"

Non-addictive cigarettes would essentially have no nicotine, have an unpleasant taste, and provide no satisfaction for U.S. smokers. But they will deliver all the negative health effects of combustion.

As the experience with denicotinized cigarettes has shown, nicotine contributes to sensory aspects of smoking. Cigarettes that comply with the standard will lack elements of flavor and satisfaction to which nicotine contributes. The difference in cigarettes before and after the standard will be readily and immediately apparent to smokers.[55]

It is impossible to know exactly how cigarette smokers will respond on "Day Zero" and thereafter.[56] But certain reactions are predictable if not, as a matter of logic, close to certain. Following "Day Zero," the vast majority of smokers who do not quit will switch to other available combustible products, including illicit products,[57] switch to non-combustible alternatives if the category is already sufficiently large and well-understood, or smoke non-addictive cigarettes as they are or add nicotine if available in the market.[58]

Under all circumstances, the market for non-addictive cigarettes will be transitional and limited in size and time. The time is likely to be measured in months not years. The transitional market size will be very difficult to quantify as it will depend on the

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[54] ANPRM, *supra* note 1, at 11838.

[55] The proposed NNN rule is a useful point of comparative reference. In that regard, the Agency has stated: "Methods used to reduce NNN levels as a result of this proposed rule may or may not produce changes that affect the sensory experiences of smokeless tobacco use." Proposed NNN Standard, *supra* note 17, at 8025. In sharp contrast to a ceiling on NNN in smokeless tobacco, a maximum level of nicotine in cigarettes will surely be noticeable to smokers.

[56] "While these results [of studies the ANPRM summarizes], taken together with other studies, are promising, FDA acknowledges the inherent limitations of the available research on changes in smoking as a function of VLNC cigarettes use." ANPRM, *supra* note 1, at 11828.

[57] Britton, J., *Denicotinised Cigarettes*, 392 THE LANCET 104, 105 (July 14, 2018) ("Among the wider population of nearly 40 million current smokers in the USA, the proportion seeking to obtain tobacco cigarettes will inevitably be higher and likely to generate demand for illicit tobacco. The FDA appears confident that this risk can be managed, and the hearts and minds of smokers sufficiently captured, for the benefits of denicotinisation to outweigh the risks. Time will tell."), available at https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31358-8/abstract.

[58] ANPRM, *supra* note 1, at 11833.

degree of availability, acceptability, and penetration of non-combustible alternatives, as well as access to illicit products. The question for manufacturers will then be whether such products are worth the investment in terms of costs and benefits.

However, a non-addictive cigarette standard, at the right time, for example when non-combustible alternatives represent a significant portion of the market (*e.g.*, 50%-70%), could provide a final incentive for the remaining smokers to switch out of combustible products or quit all together. For manufacturers, the prospect of a nicotine ceiling is certainly an incentive to accelerate the development, scientific assessment, and serious investment in the commercialization of less harmful non-combustible alternatives.

FDA, with the help of other agencies,[59] should develop the appropriate regulatory framework to accelerate the availability and consumer adoption of these alternatives. Such coordinated work is likely to render a cigarette nicotine ceiling, or other supply-side measures, much easier to implement or, ideally, unnecessary.

PUBLIC PERCEPTIONS

A "nationally enforced restriction on nicotine"[60] would raise unusual challenges with respect to public perception and consumer understanding. In our view, therefore, it would be essential to accompany the product standard with a highly effective communications strategy.

Many authorities on tobacco control have described misperceptions and gaps in understanding among the general public with respect to nicotine. In particular, there are "mistaken public beliefs that nicotine is the cause of disease risk and cancer, rather than the smoke from combustion."[61] Those "mistaken public beliefs" could lead to faulty reasoning along the following lines:

1. FDA has ordered nearly all nicotine out of cigarettes.
2. Nicotine is bad, and FDA requiring nicotine ceilings for cigarettes confirms this.
3. Cigarettes now on the market are better or less bad.
4. Non-combustible products still contain nicotine so they must also be bad.

A communications strategy would also need to anticipate questions such as: Are non-addictive cigarettes FDA approved? Are they "safer?" Are they "better" than the

[59] *See, e.g.*, 21 U.S.C. § 387g(a)(6).
[60] ANPRM, *supra* note 1, at 11838.
[61] Abrams, *supra* note 18, at 205; *see also* Kiviniemi and Kozlowski, *supra* note 42, at 4 ("Clearly, the public does not show an expert understanding of tobacco/nicotine harm reduction. These limitations in the public's understanding have the potential to lead to both individual and public health harms.").

cigarettes that FDA has ordered off the market? Or alternatively, if nicotine is "bad," why are the nicotine-containing non-combustible alternatives better? And so on.

As noted earlier, we respect and do not doubt FDA's expertise and credibility to inform and educate the public, to correct misperceptions, and to address misplaced concerns. We encourage FDA to develop a scenario-based communications strategy that would be part of the rulemaking process. The strategy should cover the time period leading up to, and extend well-beyond, "Day Zero" to prepare the market for the impending change.

SCOPE OF A STANDARD

If implemented, a nicotine standard should apply to combustible cigarettes. We suggest the scope also extend to combustible tobacco products that are substitutes for cigarettes, such as roll-your-own tobacco.

FDA has made it clear that a cigarette nicotine standard should not apply to non-combustible products. As Commissioner Gottlieb has acknowledged, less harmful alternatives to cigarettes need to satisfy smokers:

> FDA is committed to the proper development of products that can allow adults who still need or want to enjoy satisfying levels of nicotine to get it through products that don't have all of the risks associated with the combustion of tobacco.[62]

Critical to that satisfaction is nicotine delivery, which depends on non-combustible products having pharmacokinetic and pharmacodynamic profiles that are similar to (but do not exceed) those of today's cigarettes. In this respect, we find instructive the comments of Prof. Fagerström and Prof. Eissenberg about the potential of products that deliver satisfying levels of nicotine:

> If a particular product is far from cigarettes and close to [NRT] on the continuum of harm and at the same time closer to cigarettes than [NRT] on the continuum of dependence, this product may have considerable success in reducing the public health costs associated with cigarette use.[63]

In setting the scope of a standard, the Agency should also address the possible interplay between definitions in FDCA and FCLAA. In particular, certain non-

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[62] Gottlieb, S., et al., *Advancing Medicinal Nicotine Replacement Therapies as New Drugs – A new step in FDA's comprehensive approach to tobacco and nicotine* (Nov. 28, 2017), available at https://blogs.fda.gov/fdavoice/index.php/tag/nicotine-replacement-therapy/.

[63] Fagerström, K. & Eissenberg T., *Dependence on Tobacco and Nicotine Products: A Case for Product-Specific Assessment*, 14 NICOTINE & TOBACCO RESEARCH 1382, 1386 (March 29, 2012), available at https://academic.oup.com/ntr/article/14/11/1382/1096943.

combustible products could fall within the definition of "cigarette" under FCLAA, which defines cigarettes as "any roll of tobacco wrapped in paper or in any substance not containing tobacco."[64] This definition could capture a variety of novel products that heat tobacco rather than burning it.

Therefore, if FDA concludes that a cigarette nicotine standard would be "appropriate for the protection of public health," it should draft the standard in a way that ensures that non-combustible products are not covered by the standard even if they meet the FCLAA definition of cigarettes. One way to make such a distinction would be to define the products that are subject to the cigarette nicotine standard as only those intended to be combusted.

CONCLUSION

We welcome and appreciate the opportunity to submit these comments, including those in the Annex that follows.

A cigarette nicotine ceiling would be a dramatic, sweeping, and irrevocable change to the entire U.S. cigarette market – a much more drastic change than authorizing non-combustible alternatives on a case-by-case basis. With the many open questions surrounding a cigarette nicotine ceiling, it is incumbent upon the agency to compile the same rigorous scientific evidence that is required for pre-market product authorization.

Consistent with FDA's comprehensive regulatory plan, the success of any cigarette nicotine ceiling would largely depend on consumer access to and information about non-combustible alternatives to cigarettes. A non-addictive cigarette standard, at the right time, for example when non-combustible alternatives represent a significant portion of the market, could provide a final incentive for the remaining smokers to switch out of combustible products or quit all together.

FDCA provides the agency with comprehensive powers to propel the flow of innovations that provide better choices for consumers while minimizing the risk of new products that are not appropriate for the protection of public health. By thoughtfully exercising its authority to authorize new products and regulate them appropriately, FDA can support the development of a sufficiently large and well-understood category of non-combustible alternatives, at which time a cigarette nicotine ceiling, or other supply-side measures, may become unnecessary.

The 40 million Americans who smoke are indeed at a crossroads — as are FDA, tobacco companies, and the public health community. Reasonable minds will differ on many

[64] 15 U.S.C. § 1332(1)(a).

details, but there should be a collective will to move beyond yesterday's battles;[65] to step out of today's pitched camps; and, to the benefit of people who smoke and those around them, to seize the tremendous opportunities that lie right before us.

[65] Levy, *supra* note 21, at 23 ("To facilitate individual and population-level behavior change, we need policies based on science, not those based on speculation, fear and bias.").

ANNEX

Technical Achievability

FDA seeks information about the technical achievability of combusted cigarettes with a maximum nicotine content of 0.5 mg per gram of tobacco, or lower (very low nicotine tobacco). In the ANPRM, FDA identifies the two main methods for removing nicotine from tobacco – chemical extraction and genetic engineering. While it is possible to produce very low nicotine tobacco on a small scale using either method, it is not clear whether and at what cost it is possible to produce very low nicotine tobacco on a commercial scale. PMI is conducting research using both methods. However, at this time, we cannot predict with certainty whether this research will yield commercially viable very low nicotine tobacco.

Chemical extraction

Chemical extraction should be thought of as a two-part process. In the first step, a solvent (*e.g.*, water or super-critical carbon dioxide) is used to remove nicotine from the tobacco. However, when the nicotine is removed, other elements, such as flavors, are removed as well. In a second step nicotine must be separated from the rest of the extract, and the remaining extract must be added back to the tobacco. There have been experimental attempts to improve chemical extraction processes to reduce the impact on taste, for example through fractional distillation. Today, these new technologies are untested and not sufficiently developed to allow the production of very low nicotine tobacco on a commercial scale. Therefore, consideration of technical achievability via the chemical extraction route requires both an assessment of available technology to remove nicotine from tobacco, as well as an assessment of technology available to separate nicotine from other elements of the tobacco that have been removed during the extraction process and need to be added back to the tobacco substrate.

Past attempts to market non-addictive cigarettes produced using chemical extraction failed because smokers did not accept them.[66] For example, PM USA launched NEXT brand cigarettes in 1989, which were produced via chemical extraction without adding back the extracted flavors. Consumers rejected the product because of the taste and lack of satisfaction, and NEXT was withdrawn from the market in 1993.

[66] Dunsby, J. & Bero, L., *A Nicotine Delivery Device Without the Nicotine? Tobacco Industry Development of Low Nicotine Cigarettes*, 13 TOBACCO CONTROL 362 (2004), available at https://tobaccocontrol.bmj.com/content/13/4/362.

Furthermore, much of the existing technology is subject to patents owned by specific manufacturers, which may limit other manufacturers' ability to use these technologies to produce very low nicotine tobacco. At the same time, these technologies are costly, and can be resource-intensive. For example, water-based extraction technology requires large quantities of water to extract the nicotine, as well as more energy to dry the tobacco following extraction. Super-critical carbon-dioxide extraction is done under high pressure (2,000 psi), which requires greater upfront investments from manufacturers and requires additional safety measures.

Given the current state of the available technology, PMI's best estimate is that it would take between four and six years to assess if it is technically feasible to commercially produce very low nicotine tobacco using the chemical extraction methods. This estimate is subject to the inherent uncertainty of all research and development activities.

Seed technologies

Selective breeding and genetic engineering, which involve modifying the genetic code of a tobacco plant, either by transgenesis or gene editing, have been researched as potential methods to achieve plants with a lower nicotine content.[67] To date, selective breeding and genetic engineering alone are not sufficient to produce very low nicotine tobacco.[68] These techniques must be combined with agronomic practices, such as lowering fertilization and selecting leaves from certain stalk positions that naturally contain less nicotine compared to other stalk positions, to try to reach the levels proposed in the ANPRM.

Furthermore, growing low-nicotine tobacco plants could present additional hurdles to commercial scale production. Because the tobacco plant metabolism is naturally geared towards alkaloid production, changing the natural metabolism is likely to negatively impact farm profitability (approximately 20% to 30% loss in cash return)[69]

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[67] Regulatory frameworks for Genetically Modified Organisms (GMO) could impact the feasibility of genetic engineering for the purpose of reducing nicotine levels in tobacco. For countries focusing regulating the final product, such as the US, plants that are gene-edited for loss of function are not considered GMO. In some other countries, where regulation extend to plant line development processes, a strict interpretation of the rules would classify most gene-edited plant lines as GMOs. Furthermore, all new crop variants must be registered with the authorities, which in itself will add an additional burden to manufacturers and farmers. Additional complexities may arise from differences within GMO legislative frameworks in various countries. Some countries have limitations in place that ban or limit the growing of GMO or GM-derived tobacco in addition to the disparate definitions of the GMO classification.

[68] Lewis, R., *Potential Mandated Lowering of Nicotine Levels in Cigarettes: A Plant Perspective*, NICOTINE & TOBACCO RESEARCH, 1, 5 (2018), available at https://www.ncbi.nlm.nih.gov/pubmed/29401309.

[69] *Id*.

because of lower yields and/or leaf quality.[70] Alteration of this important alkaloid metabolic flux in tobacco might also affect the plant's overall chemical composition.[71] It is not clear whether current agronomic practices will support the commercial scale production of very low nicotine tobacco via the selective breeding or genetic engineering routes.

In addition, the existing genetic engineering technologies are subject to patents owned by specific manufacturers, which may limit access to very low nicotine tobacco seeds by some farmers, as well as other manufacturers' ability to use these technologies to produce very low nicotine tobacco.

Reports state variable efficiencies in nicotine reduction (90% to 97%) for selective breeding or genetic engineering.[72] None of the reported seed technologies have been deployed as commercial seeds and tested at a large agronomic scale consistent with commercial tobacco production. Development and deployment of numerous varieties of Virginia, Burley, or Oriental tobaccos grown around the world to cover different agronomic and quality needs would take six to eight years to first crop, plus an additional two years to build the inventory necessary to replace the existing cigarette market with non-addictive cigarettes. Again, this estimate is subject to the inherent uncertainty of all research and development activities, and ultimately the production of very low nicotine tobacco using genetic engineering methods may not be commercially feasible.

Finally, we expect that commercial deployment of any of the current reported seed technologies would not consistently lower average nicotine levels to below 0.5 mg per gram of tobacco on a dry weight basis. Based on current knowledge and technology, no single strategy alone would be sufficient to meet the standards proposed in the ANPRM. One or more genetic engineering strategies would have to be applied in combination with agronomic practices to further reduce nicotine levels in tobacco.

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[70] Chaplin, J. & Weeks, W., *Association Between Percent Total Alkaloids and Other Traits in Flue-cured Tobacco*, 16 CROP SCIENCE 416 (1976), available at https://dl.sciencesocieties.org/publications/cs/abstracts/16/3/CS0160030416?access=0&view=pdf.

[71] Dalton, H. et al., *Effects of Down-Regulating Ornithine Decarboxylase upon Putrescine-Associated Metabolism and Growth in Nicotiana tabacum*, 67 L. J EXP BOT 113367 (2016), available at https://academic.oup.com/jxb/article/67/11/3367/2197681; Wang P. et al., *Silencing of PMT Expression Caused a Surge of Anatabine Accumulation in Tobacco*, 36 MOLECULAR BIOLOGY REPORTS 2285 (2009), available at https://link.springer.com/article/10.1007%2Fs11033-009-9446-1.

[72] Lewis, *supra* note 68.

Agronomic practices

Agronomic practices can reduce the level of nicotine in tobacco. For example, reducing the amount of fertilizer used, harvesting tobacco earlier in the season, or not topping tobacco plants have all been shown to reduce nicotine levels, as has increasing plant density, because it causes the plants to compete for resources.[73] None of these techniques, on their own, would be sufficient to produce tobacco that meets the nicotine levels specified in the ANPRM.

Other relevant information

Developing very low nicotine tobacco to meet the standards suggested in the ANPRM would require a supply chain designed specifically to achieve low nicotine targets. Growing very low nicotine tobacco would also require the development and implementation of nicotine content testing at each stage of the production process from farm to factory floor. Farmers growing tobacco for export or for non-combustible products would have to segregate very low nicotine varieties from other varieties in order to avoid cross-contamination.

Given the commercial failure of non-addictive cigarettes in the past, and the risk of a small or no market for their crops, farmers may be unwilling to make the investments necessary to grow very low nicotine tobacco. This could lead to a lack of supply necessary to support the conversion of the entire U.S. cigarette market.

Environmental Considerations

In accordance with the National Environmental Policy Act and 21 CFR Part 25.20, FDA will evaluate the environmental impact of a nationally enforced nicotine standard.

Unlike the Agency's Tobacco Product Standard for NNN reduction in finished smokeless tobacco products where there was no finding of a significant impact on the human environment,[74] the environmental assessment of the proposed nicotine standard may be more complex because of the breadth and depth of changes required throughout the industry. The Agency's assessment will be further complicated by the fact that it lacks authority over tobacco leaf not in the possession of manufacturers,

[73] Weybrew, G. et al., *Factors Affecting the Nicotine Content of Flue-Cured Tobacco.* NORTH CAROLINA STATE AGRICULTURAL EXPERIMENT STATION RESEARCH REPORT, NCSU D.H. Hill Library (1953), available at https://repository.lib.ncsu.edu/handle/1840.4/1441.

[74] *See, e.g.*, FDA Environmental Assessment of the Tobacco Product Standard for Establishing the Level of N'-Nitrosonornicotine in Finished Smokeless Tobacco Products (January 2017).

or over the producers of tobacco leaf, including tobacco growers, tobacco warehouses, and tobacco grower cooperatives.[75]

There is no question that the proposed nicotine standard for cigarettes will affect every aspect of the industry, starting from the tobacco seed through to the finished product sold to adult smokers in the U.S. The dramatic changes required to achieve the low levels of nicotine proposed will present new and different environmental impacts involving people, chemicals and pesticides, land, waste, water, and energy.

For example, tobacco growers, tobacco warehouses, and tobacco grower cooperatives will be immediately affected because manufacturers must find sources in the U.S. and internationally to produce non-addictive cigarettes on a commercial scale. These operators would have to segregate practices, equipment, and very low nicotine tobacco from regular tobacco production to avoid cross-contamination.

There are various methods tobacco growers could employ to partially reduce natural nicotine content in tobacco leaves. For example, some studies show that reducing nitrogen fertilization rate can decrease nicotine levels, but this may require more land dedicated to tobacco crops. Similarly, very low nicotine tobacco may be more susceptible to insect damage because nicotine in tobacco plants serves as a natural insect repellant.[76] As a result, growers may need to apply more insecticides more frequently. Because estimates suggest that the vast majority of insecticides used in commercial farming reach a destination other than their target and move into the environment, this suggests potential for environmental damage.[77]

Selective breeding and genetic engineering routes would require new agronomic practices, such as reducing the quantity of nitrogen fertilizers, resulting in lower tobacco yields, as well as increased use of pesticides to protect the plants. At the manufacturer level, extraction technology is resource intensive. For example, water based extraction requires large amounts of water and energy to extract the nicotine and dry the tobacco leaf.

There could be many more direct and indirect environmental effects to consider. The Agency's careful analysis of the significance of these impacts, possible alternatives,

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[75] 21 U.S.C. § 387a(c)(2) (limiting authority and ability to enter a tobacco leaf farm without written consent).

[76] Steppuhn, A. et al*., Nicotine's Defensive Function in Nature*, 2 PLoS BIOLOGY 1074 (2004), available at http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0020217.

[77] Pimentel, D. et al., *Amounts of Pesticides Reaching Target Pests: Environmental Impacts and Ethics*, 8 JOURNAL OF AGRICULTURE AND ENVIRONMENTAL ETHICS 17 (1995), available at https://link.springer.com/article/10.1007/BF02286399).

and plans for mitigation and monitoring will be critical for the entire international supply chain and successful implementation.