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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I. Executive Summary

A. Purpose of the ANPRM

Tobacco use causes a tremendous toll of death and disease every year, and these effects are ultimately the result of addiction to the nicotine in combustible cigarettes which causes repeated use of such products, thus repeatedly exposing users and non-users to toxicants. This nicotine addiction causes users to engage in compulsive tobacco use, makes quitting less likely, and, thus, repeatedly exposes them to thousands of toxicants in combusted tobacco products. This is especially true with respect to cigarette smoking. 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. The Agency seeks information and comment on a number of issues associated with such a potential product standard. Greatly reducing or eliminating the addictiveness of cigarettes would have significant benefits for youth, young adults, and adults. More than half of adult cigarette smokers make a serious quit attempt each year (quit for at least a day), many of whom do not succeed due to the addictive nature of these products (Ref. 1). The establishment of a maximum nicotine level in cigarettes not only could increase the likelihood of successful quit attempts, but it also could help prevent experimenters (mainly youth and young adults) from initiating regular cigarette smoking. Therefore, rendering cigarettes minimally addictive or nonaddictive (however that were achieved) could help current users quit and prevent future users from becoming addicted and escalating to regular use.

B. Summary of the Major Issues Raised in the ANPRM

In this ANPRM, FDA is seeking information on a variety of issues regarding the development of a tobacco product standard that would limit the amount of nicotine in cigarettes. Specifically, FDA is seeking your comments, evidence, and other information supporting your responses to questions on the following topics:

- *Scope*—Cigarettes are the tobacco product category that causes the greatest burden of harm to public health given the prevalence of cigarette use, including among youth, and the toxicity and addictiveness of these products and the resulting tobacco-related disease and death across the population, including among non-users. If FDA were to establish a nicotine tobacco product standard that covered only cigarettes, some number of addicted smokers could migrate to other similar combusted tobacco products to maintain their nicotine dose (or engage in dual use with other combusted tobacco products), potentially reducing the positive public health impact of such a rule. Because the scope would impact the potential public health benefits of a nicotine tobacco product standard, FDA is seeking comment on whether the standard should cover any or all of the following products: Combusted cigarettes (which FDA has previously interpreted to include kreteks and bidis), cigarette tobacco, roll-your-own (RYO) tobacco, some or all cigars, pipe tobacco, and waterpipe tobacco. 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.
- *Maximum Nicotine Level*—FDA has considered the existing peer-reviewed studies regarding very low nicotine content (VLNC) cigarettes and the likely effects of reducing nicotine in combusted tobacco products (*i.e.,* cigarettes, cigars, pipe tobacco, roll-your-own tobacco, and waterpipe tobacco). 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 the risk of central nervous system effects contributing to addiction may be lower'' (Ref. 2). The study authors concluded that ''[p]reventing children from becom[ing] addicted smokers and giving people greater freedom to stop smoking when they decide to quit by reducing the addictiveness of cigarettes is a policy that increasingly appears to be feasible and warranted'' (id.). We specifically request comment regarding this paper's conclusions and the possible impact of higher or lower maximum nicotine levels in a potential nicotine tobacco product standard. If FDA were to pursue a nicotine tobacco product standard, it would be important for FDA to consider what maximum nicotine level for such standard would be appropriate, how this maximum nicotine level should be measured (*e.g.,* nicotine yield, nicotine in tobacco filler, something else), and how the threshold of nicotine addiction should be measured, using the best available science to determine a level that is appropriate for the protection of the public health. FDA seeks comment on a potential maximum nicotine level that would be appropriate for the protection of the public health, in light of scientific evidence about the addictive properties of nicotine in cigarettes. 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. FDA is also requesting any information on additional scientific data and research which would provide information about specific groups within the general population which may have an increased sensitivity to nicotine's reinforcing effects, or who may have otherwise not been captured in the literature on VLNC cigarettes. In addition, FDA is considering and requesting information on additional scientific data and research relevant to the empirical basis for regulatory decisions related to a potential nicotine product standard.
- *Implementation*—If FDA were to issue a product standard establishing a maximum nicotine level for cigarettes, such a standard could propose either a single target (where the nicotine is reduced all at once) or a stepped-down approach (where the nicotine is reduced gradually over time through a sequence of incremental levels and implementation dates) to reach the desired maximum nicotine level.
- *Analytical Testing Method*—As part of its consideration regarding a potential nicotine tobacco product standard, FDA is also considering whether such a product standard should specify a method for manufacturers to use to

detect the level of nicotine in their products. FDA believes that the results of any test to measure the nicotine in such products should be comparable across different accredited testing facilities and products. It is critical that the results from the test method used demonstrate a high level of specificity, accuracy, and precision in measuring a range of nicotine levels across a wide variety of tobacco blends and products. FDA is aware of a variety of methods being developed that quantify nicotine in tobacco or tobacco product filler for various products.

- *Technical Achievability*—If FDA were to move forward in this area and proceed to the next step of issuing a proposed rule, section 907(b)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387g(b)(1) would require that FDA consider information submitted in connection with that proposed product standard regarding technical achievability of compliance. FDA continues to analyze the technical achievability of a maximum nicotine level for cigarettes as part of its broader assessment of how best to exercise its regulatory authority in this area. Significant nicotine reductions in cigarettes and other combusted tobacco products can be achieved principally through tobacco blending and cross-breeding plants, genetic engineering, and chemical extraction. Agricultural practices (*e.g.,* controlled growing conditions, fertilization, and harvest) as well as more recent, novel techniques also can help to reduce nicotine levels. FDA is considering the feasibility of the current nicotine reduction techniques—for cigarette and other combusted tobacco product manufacturers of all sizes—to significantly reduce nicotine levels to levels similar to those in existing VLNC cigarettes. FDA also is considering the proper timeframe for implementation of a possible nicotine tobacco product standard to allow adequate time for industry to comply. In addition, FDA is seeking data and information regarding the potential costs, including possible costs to farmers, to implement such a standard.
- *Possible Countervailing Effects*—There may be possible countervailing effects that could diminish the population health benefits expected as a result of a nicotine tobacco product standard. As part of any subsequent rulemaking, FDA would need to assess these effects in comparison to the expected benefits, including among population subgroups. One possible countervailing effect is continued combusted tobacco product use. Current smokers of tobacco products subject to a nicotine tobacco product standard could turn to other combusted tobacco products to maintain their nicotine dependence, both in combination with cigarettes (*i.e.,* dual use) or in place of cigarettes (*i.e.,* switching). Coverage of other combusted tobacco products, as FDA is considering, is one way to significantly limit this product migration or transition to dual use with other combusted tobacco products.

  Another possible countervailing effect is the potential for increased harm due to continued VLNC smoking with altered smoking behaviors (*e.g.,* increase in number of cigarettes smoked, increased depth of inhalation). Some studies of VLNC cigarettes with nicotine levels similar to what FDA may consider including in a nicotine tobacco product standard have not resulted in compensatory smoking and have demonstrated reductions in cigarettes smoked per day and in exposure to harmful constituents (*e.g.,* Ref. 3; Ref. 4; Ref. 5).

  Another possible countervailing effect of setting a maximum nicotine level for cigarettes could be users seeking to add nicotine in liquid or other form to their combusted tobacco product. Therefore, FDA is considering whether any action it might take to reduce nicotine in cigarettes should be paired with a provision that would prohibit the sale or distribution of any tobacco product designed for the purposes of supplementing the nicotine content of the combusted tobacco product (or where the reasonably foreseeable use of the product is for the purposes of supplementing the nicotine content). FDA is also considering other regulatory options to address this concern.

  FDA is also considering whether illicit trade could occur as a result of a nicotine tobacco product standard and how that could impact the marketplace. In addition, FDA is considering how, if FDA were to issue a nicotine tobacco product standard that prompted an increase in the illicit market, comprehensive interventions could reduce the size of the illicit tobacco market through enforcement mechanisms and collaborations across jurisdictions.
- *Other Considerations*—FDA also recognizes that, if FDA were to proceed to the stage of proposing a rule in this area, potential costs and benefits from a possible nicotine tobacco product standard would be estimated and considered in an accompanying preliminary impact analysis, including the potential impacts on growers of tobacco and current users of potentially regulated products. Thus, FDA is also seeking comments, data, research results, and other information regarding economic impacts of a potential nicotine tobacco product standard.

Further, this ANPRM briefly describes the potential public health benefits that could result from the increased cessation from and decreased initiation to regular use of cigarettes that FDA expects could occur with a nicotine tobacco product standard. FDA references findings from a population-based simulation model that projects the potential public health impact of enacting a regulation lowering nicotine levels in cigarettes and certain other combusted tobacco products to minimally addictive levels, utilizing inputs derived from empirical evidence and expert opinion (eight subject matter experts provided quantitative estimates for the potential outcomes of the policy on smoking cessation, initiation, switching, and dual use rates). Based on the experts' determinations that the reduction in nicotine levels in combusted tobacco products would create substantial reductions in smoking prevalence due to increased smoking cessation and reduced initiation of regular smoking, the model calculates that by the year 2100, more than 33 million youth and young adults who would have otherwise initiated regular smoking would not start as a result of a nicotine tobacco product standard. The model also projected that approximately 5 million additional smokers would quit smoking 1 year after implementation of the product standard, compared to the baseline scenario, which would increase to approximately 13 million additional former smokers within 5 years after policy implementation.

II. Background

A. Purpose

On July 28, 2017, FDA announced a comprehensive approach to the regulation of nicotine that includes the Agency's plan to begin a public dialogue about lowering nicotine levels in combustible cigarettes to minimally addictive or nonaddictive levels through achievable product standards, including the issuance of an ANPRM to seek input on the potential public health benefits and any possible adverse effects of lowering nicotine in cigarettes. Tobacco use causes a tremendous toll of death and disease every year, and these effects are ultimately the result of addiction to the nicotine contained in combustible cigarettes, leading to repeated exposure to toxicants from such cigarettes. This nicotine addiction causes users to engage in compulsive use, makes quitting less likely and, therefore,

repeatedly exposes them (and others) to thousands of toxicants in combusted tobacco products. This is especially true with respect to cigarette smoking. Researchers have found that the mortality rate from any cause of death at any given age is 2 to 3 times higher among current cigarette smokers, compared to individuals who never smoked (Ref. 6).[1] 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.[2] The Agency seeks information and comment on a number of issues associated with such a potential product standard. Greatly reducing the addictiveness of cigarettes would have significant benefits for youth, young adults, and adults.[3] More than half of adult smokers make a serious quit attempt each year (quit for at least a day), many of whom are not able to succeed due to the addictive nature of these products (Ref. 1). The establishment of a maximum nicotine level in cigarettes not only could increase the likelihood of successful quit attempts, but it also could help prevent experimenters (mainly youth) from initiating regular use. 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.

Preventing nonsmokers, particularly youth and young adults, from becoming regular smokers due to nicotine addiction would allow them to avoid the severe adverse health consequences of smoking and would result in substantial public health benefits. In 2014, the Surgeon General estimated that, unless this trajectory is changed dramatically, 5.6 million youth aged 0 to 17 years alive today will die prematurely from a smoking-related disease (Ref. 7 at table 12.2.2). In 2009, Congress estimated that a 50 percent reduction in youth smoking would also result in approximately $75 billion in savings[4] attributable to reduced health care costs (see section 2(14) of the Family Smoking Prevention and Tobacco Control Act; 21 U.S.C. 387 note). As further explained in this ANPRM, if cigarettes were minimally addictive or nonaddictive, it is expected that many fewer youth and young adults would be subjected to the impacts of nicotine (which has a significantly stronger effect on the developing brains of youth (*e.g.,* Refs. 8 and 9)) from cigarettes, nor would they suffer from the health and mortality effects of cigarette use.

Nicotine is powerfully addictive. The Surgeon General has reported that 87 percent of adult smokers start smoking before the age of 18 and half of adult smokers become addicted before the age of 18, which is before the age at which they can legally buy a pack of cigarettes (Ref. 7). Nearly all smokers begin before the age of 25, which is the approximate age at which the brain has completed development (Ref. 8). Generally, those who begin smoking before the age of 18 are not aware of the degree of addictiveness and the full extent of the consequences of smoking when they begin experimenting with tobacco use (see, *e.g.,* Ref. 10). Although youth generally believe they will be able to quit when they want, in actuality they have low success rates when making a quit attempt. For example, more than 60 percent of high school aged daily smokers have tried to quit but less than 13 percent were successful at quitting for 30 days or more (Ref. 11). In addition, one study found that 3 percent of 12th grade daily smokers estimated that they would ''definitely'' still be smoking in 5 years, while in reality 63 percent of this population is still smoking 7 to 9 years later (Ref. 12). Another survey revealed that ''nearly 60 percent of adolescents believe that they could smoke for a few years and then quit'' (Ref. 13).

Because it is such a powerful addiction, addiction to nicotine is often lifelong (Ref. 14). Among adolescent tobacco users in 2012, over half (52.2 percent) reported experiencing at least one symptom of tobacco dependence (Ref. 15). FDA expects that making cigarettes minimally addictive or nonaddictive (however that were achieved) may have significant benefits for youth by reducing the risk that youth experimenters progress to regular use of cigarettes as a result of nicotine dependence.

The adolescent brain is more vulnerable to developing nicotine dependence than the adult brain; there are also data from animal studies that indicate that brain changes induced by nicotine may have long-term consequences (*i.e.,* the long-term physical changes, caused by the adolescent nicotine exposure, prevent the brain from reaching its full potential, which could result in permanent deficiencies) (Refs. 8 and 9). Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood (Ref. 15). Evidence from animal studies indicate that exposure to substances such as nicotine can disrupt brain development and have long-term consequences for executive cognitive function (such as task-switching and planning) and for the risk of developing a substance abuse disorder and various mental health problems (particularly affective disorders such as anxiety and depression) as an adult (Ref. 16). This exposure to nicotine can also have long-term effects, including decreased attention performance and increased impulsivity, which could promote the maintenance of nicotine use behavior (id.). Further, the 2010 Surgeon General's Report noted that symptoms of dependence could result from even a limited exposure to nicotine during adolescence (Ref. 17).

For all these reasons, FDA is considering limiting the addictiveness of cigarettes by setting a product standard establishing a maximum nicotine level of cigarettes, to help prevent experimenters (who are mainly youth) from becoming addicted to tobacco and, thus, prevent them from initiating regular use and from increasing their risk of tobacco-related death and disease.

FDA is also considering this action because age restrictions on the sale of tobacco products, by themselves, are not entirely effective in preventing youth from obtaining cigarettes or other combusted tobacco products. Youth smokers get their cigarettes from a variety of sources, including directly purchasing them from retailers, giving others money to buy them, obtaining them from other youth or adults (with

[1] The discussion of scientific data discussed in this ANPRM is not intended to cover all available information on this subject matter. Rather, it is intended to provide only a sampling of some of the current research that could be relevant to consideration of a potential nicotine tobacco product standard.

[2] The Family Smoking Prevention and Tobacco Control Act specifically prohibits the Agency from ''requiring the reduction of nicotine yields of a tobacco product to zero'' but generally authorizes FDA to issue a tobacco product standard setting a maximum nicotine level. Section 907(C)(3)(B) of the FD&C Act.

[3] The definitions of ''youth,'' ''young adults,'' and ''adults'' can vary in scientific studies. The term ''youth'' generally refers to middle school and/or high school age students. ''Young adults'' generally refers to individuals 18 to 24 years of age. In some studies, ''adults'' may encompass individuals age 18 to 24 but generally refers to those individual 24 to 65 years of age.

[4] Congress' estimate of approximately $75 billion in savings, if adjusted for inflation, would amount to $83.63 billion in 2017.

or without their knowledge), or using illegal means (*i.e.,* shoplifting or stealing) (Ref. 18). The 2015 National Youth Risk Behavior Surveillance Survey (YRBS) of high school students in grades 9 through 12 found that 12.6 percent of current cigarette smokers under age 18 had purchased their cigarettes directly from stores or gas stations despite the Federal minimum age requirements for cigarettes (Ref. 19). While continued vigorous enforcement of youth access restrictions is critical to protecting public health, FDA is considering taking this additional step to ensure that even if youth do obtain access to cigarettes, they will be less likely to: (1) Become addicted to these products; (2) initiate regular use; and (3) increase their risk of the many diseases caused by, and debilitating effects of, combusted tobacco product use (Ref. 20).

Similarly, limiting the nicotine in cigarettes could have significant benefits for adult tobacco product users, a large majority of whom want to quit but are unsuccessful because of the highly addictive nature of these products (see, *e.g.,* Ref. 21). Data from the 2015 National Health Interview Survey show that 68 percent of current adult cigarette smokers in the United States wanted to quit and 55.4 percent of adult cigarette smokers made a past-year quit attempt of at least 1 day (Ref. 22). In high-income countries, about 7 of 10 adult smokers say they regret initiating smoking and would like to stop (Ref. 23 at p. 2). Decreasing the nicotine 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) could help users quit if they want to—as the large majority of users say they do (*e.g.,* Ref. 21).

Although many factors contribute to an individual's initial experimentation with tobacco products, the addictive nature of tobacco is the major reason people progress to regular use, and it is the presence of nicotine that causes youth, young adults, and adult users to become addicted to, and to sustain, tobacco use (see, *e.g.,* Refs. 24 and 25). While nicotine is the primary addictive chemical in tobacco, sensorimotor stimuli that are repeatedly paired with nicotine through the process of smoking also develop into conditioned reinforcers that contribute to the persistent nature of nicotine dependence (Ref. 26). In cigarette users, the sensory aspects of smoking, such as taste and sensations of smoking (*e.g.,* throat hit), are often reinforcing as they have been paired repeatedly with nicotine exposure and have been found to be reinforcing without concomitant nicotine exposure in experienced users (Ref. 27). Once tobacco users become addicted to nicotine, they require nicotine to avoid certain withdrawal symptoms. In the process of obtaining nicotine, users of combusted tobacco products are exposed to an array of toxicants in tobacco and tobacco smoke that lead to a substantially increased risk of morbidity and mortality (see, *e.g.,* Ref. 10). Although most current U.S. smokers report that they want to quit smoking, have attempted to quit, and regret starting (see, *e.g.,* Refs. 28 and 29), many smokers find it difficult to break their addiction and quit. Because of nicotine addiction, many smokers lack the ability to choose whether or not to continue smoking these toxic combusted products despite their stated desire to quit (see, *e.g.,* Ref. 17).

Accordingly, FDA is considering whether to issue a tobacco product standard to: (1) Give addicted users of cigarettes the choice and ability to quit more easily by reducing the nicotine to a minimally addictive or nonaddictive level and (2) reduce the risk of progression to regular use and nicotine dependence for persons who experiment with the tobacco products covered by the standard. 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, could significantly reduce the morbidity and mortality caused by smoking.

B. Legal Authority

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) was enacted on June 22, 2009, amending the FD&C Act and providing FDA with the authority to regulate tobacco products (Pub. L. 111–31). Section 901 of the FD&C Act (21 U.S.C. 387a), as amended by the Tobacco Control Act, granted FDA authority to regulate the manufacture, marketing, and distribution of cigarettes, cigarette tobacco, RYO tobacco, and smokeless tobacco to protect the public health and to reduce tobacco use by minors. The Tobacco Control Act also gave FDA the authority to issue a regulation deeming other products that meet the statutory definition of tobacco product to be subject to FDA's tobacco product authority under chapter IX of the FD&C Act. On May 10, 2016, FDA issued the deeming rule (81 FR 28973), extending FDA's tobacco product authority to all tobacco products, other than the accessories of deemed tobacco products, that meet the statutory definition of tobacco product.

Among the authorities included in chapter IX of the FD&C Act is the authority to establish tobacco product standards. The Act authorizes FDA to adopt a tobacco product standard under section 907 of the FD&C Act if the Secretary of Health and Human Services (HHS) finds that a tobacco product standard is appropriate for the protection of the public health. In making such a finding, the Secretary of HHS must consider scientific evidence concerning: (1) The risks and benefits of the proposed standard to the population as a whole, including users and nonusers of tobacco products; (2) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (3) the increased or decreased likelihood that those who do not use tobacco products will start using such products (section 907(a)(3)(B)(i) of the FD&C Act).

Section 907(a)(4) of the FD&C Act states that tobacco product standards must include provisions that are appropriate for the protection of the public health. Section 907(a)(4)(B)(i) provides that a product standard must include, where appropriate for the protection of the public health, provisions respecting the construction, components, ingredients, additives, constituents, including smoke constituents, and properties of the tobacco product. Further, section 907(a)(4)(A)(i) states that provisions in tobacco product standards must include, where appropriate, provisions for nicotine yields. Section 907(a)(4)(B)(ii) also provides that a product standard must, where appropriate for the protection of public health, include ''provisions for the testing (on a sample basis or, if necessary, on an individual basis) of the tobacco product.'' In addition, section 907(a)(4)(B)(iv) provides that, where appropriate for the protection of public health, a product standard must include provisions requiring that the results of the tests of the tobacco product required under section 907(a)(4)(B)(ii) show that the product is in conformity with the portions of the standard for which the test(s) were required. Finally, section 907(d)(3)(B) of the FD&C Act prohibits the Agency from issuing a regulation that would require the reduction of nicotine yields of a tobacco product to zero.

The FD&C Act also provides FDA with authority to issue regulations establishing restrictions on the sale and distribution of a tobacco product (section 906(d)(1) of the FD&C Act (21 U.S.C. 387f(d)(1))). These restrictions

may include restrictions on the access to, and the advertising and promotion of, the tobacco product, if the Secretary of HHS determines such regulation would be appropriate for the protection of the public health.

FDA intends to use the information submitted in response to this ANPRM, its independent scientific knowledge, and other appropriate information, to further inform its thinking about options, including the scope, for a potential product standard that would set a maximum nicotine level for cigarettes, and restrictions prohibiting the sale and distribution of any product that violates such a standard.

III. Health Consequences of Combusted Tobacco Products

A. Nicotine in Combusted Tobacco Products and Its Impact on Users

Tobacco products are addictive, primarily due to the presence of nicotine, and the magnitude of public health harm caused by tobacco products is inextricably linked to their addictive nature (Ref. 13 at p. xi). Cigarettes are the most widely used tobacco products among adults and are responsible for at least 480,000 premature deaths in the United States each year (Ref. 7). Other combusted tobacco products that are possible targets of product migration (*i.e.,* switch candidates for smokers to maintain their nicotine addiction) or dual use have similar adverse health effects and can cause nicotine dependence (Refs. 30 and 31). For example, researchers have found that current exclusive cigar smokers and current exclusive pipe smokers have an increased risk for lung cancer and tobacco-related cancers overall, as compared to those who reported never using any type of combusted tobacco product (Ref. 32). We note that there is a dose-response relationship between the number of cigars and pipes smoked and the risk of disease (*i.e.,* the larger the number of cigars or pipes smoked, the higher the risk of disease) (Ref. 31 at 110), but cigar and pipe users are still subject to the addictive effects of nicotine through nicotine absorption (and to the health impacts of long-term use that may follow from regular use due to addiction) even if they report that they do not inhale (Refs. 33–35).

The Surgeon General has reported that ''most people begin to smoke in adolescence and develop characteristic patterns of nicotine dependence before adulthood'' (Ref. 36 at p. 29). Adolescents develop physical dependence and experience withdrawal symptoms when they try to quit smoking (id.). The 2014 Surgeon General's Report states that 5.6 million youth currently 0 to 17 years of age are projected to die prematurely from smoking-related illnesses (Ref. 7 at pp. 666–667). Accordingly, using the best available science to determine a level that is appropriate for the protection of the public health, making cigarettes minimally addictive or nonaddictive would limit the number of youth and young adults who progress from experimentation to regular use and who, thereby, increase their risk for dangerous smoking-related diseases.

Researchers have determined that almost one-third of adolescents aged 11 to 18 (31 percent) are ''early experimenters,'' meaning that they have tried smoking at least one puff of a cigarette (but smoked no more than 25 cigarettes in their lifetime) (Ref. 37). The Centers for Disease Control and Prevention (CDC) and other researchers have estimated that 30 percent or more of experimenters become established smokers (Ref. 37, citing Refs. 38 and 39). Given these past trends, if one applies the 30 percent estimate to the adolescents who were early experimenters in 2000, then 2.9 million of these early experimenters have now or will become established smokers (Ref. 37). Based on the number of persons aged 0 to 17 in 2012, the Surgeon General estimated that 17,371,000 of that group will become future smokers and 5,557,000 will die from a smoking-related disease (Ref. 7 at T. 12.2.1). These high numbers speak to the extreme vulnerability of today's children and adolescents to the health harms of tobacco use resulting from addiction.

Nicotine addiction is a critical factor in the transition of smokers from experimentation to sustained smoking and in the continuation of smoking for those who want to quit (Ref. 7 at p. 113; Ref. 17). Intermittent smokers, even very infrequent smokers, can become addicted to tobacco products (Ref. 40). Longitudinal research has shown that smoking typically begins with experimental cigarette use and the transition to regular smoking can occur relatively quickly by smoking as few as 100 cigarettes (Ref. 8). Other research found that among the 3.9 million middle and high school students who reported current use of tobacco products (including cigarettes and cigars) in 2012, 2 million of those students reported at least one symptom of dependence (Ref. 15).

Although the majority of adolescent daily smokers meet the criteria for nicotine dependence, one study found that the most susceptible youth lose autonomy (*i.e.,* independence in their actions) regarding tobacco within 1 or 2 days of first inhaling from a cigarette (Refs. 41 and 42). Another study found that 19.4 percent of adolescents who smoked weekly also were considered to be nicotine dependent (Ref. 43). In a study regarding nicotine dependence among recent onset adolescent smokers, individuals who smoked cigarettes at the lowest levels (*i.e.,* smoking on only 1 to 3 days of the past 30 days) experienced nicotine dependence symptoms such as loss of control over smoking (42 percent) and irritability after not smoking for a while (23 percent) (Ref. 44). Researchers in a 4-year study of sixth grade students also found that ''[e]ach of the nicotine withdrawal symptoms appeared in some subjects *prior* to daily smoking'' (Ref. 42) (emphasis added). Ten percent of the subjects showed signs of addiction to tobacco use within 1 or 2 days of first inhaling from a cigarette, and half had done so by the time they were smoking seven cigarettes per month (Ref. 42).

It is clear that many adult cigarette smokers want to quit. Data from the 2015 National Health Interview Survey show that 68 percent of current adult smokers in the United States wanted to quit and 55.4 percent of adult smokers made a past-year quit attempt of at least 1 day (Ref. 22). According to an analysis of this survey, only 7.4 percent of former adult cigarette smokers had recently quit (id.).

For adult smokers who report quit attempts, many of these attempts are unsuccessful. For example, among the 19 million adults who reported attempting to quit in 2005, epidemiologic data suggest that only 4 to 7 percent were successful (Ref. 28 at p. 15). Similarly, the Institute of Medicine (IOM), considering data from 2004, found that although approximately 40.5 percent of adult smokers reported attempting to quit in that year, only between 3 and 5 percent were successful (Ref. 13 at p. 82). Adult smokers may make as many as thirty or more quit attempts before succeeding (Ref. 45). FDA also notes that adults with education levels at or below the equivalent of a high school diploma have the highest smoking prevalence levels but the lowest quit ratios (*i.e.,* the ratio of persons who have smoked at least 100 cigarettes during their lifetime but do not currently smoke to persons who report smoking at least 100 cigarettes during their lifetime) (Ref. 46). Nicotine addiction and associated withdrawal symptoms make it difficult for smokers to quit without using cessation counseling and/or cessation medications.

Adolescents also experience low success rates when attempting to quit. As we have noted, most Americans who use tobacco products begin using when they are under the age of 18 and become addicted before reaching the age of 18 (Refs. 36 and 47). Although many adolescents believe ''they can quit [smoking] at any time and therefore avoid addiction,'' nicotine dependence can be rapidly established (Ref. 13 at p. 89; see also Ref. 28 at p. 158). Research has shown that some adolescents report symptoms of withdrawal and craving within days or weeks of beginning to smoke (Ref. 48). As a result, many adolescents are nicotine dependent despite their relatively short smoking histories (Ref. 11). An analysis of data from the 2015 YRBS found that, of those currently smoking cigarettes, 45.4 percent had tried to quit smoking cigarettes during the previous year (Ref. 19). Likewise, an analysis of the 2012 National Youth Tobacco Survey (NYTS) revealed that 51.5 percent of middle and high school student smokers had sought to quit all tobacco use in the previous year (Ref. 49).

Relapse is the principal limiting factor in the transition of smoking to nonsmoking status (Ref. 17). Relapse refers to the point after an attempt to stop smoking when tobacco use becomes ongoing and persistent (Ref. 17, citing Ref. 50). Most smokers who ultimately relapse do so soon after their quit attempt (Ref. 17). One study found that 80 to 90 percent of those individuals who were smoking at 6 months following a quit attempt had resumed smoking within 2 weeks following their quit attempt (Ref. 51). Long-term studies of individuals trying to quit smoking reveal that 30 to 40 percent of those who quit smoking for 1 year eventually relapsed (id.). In fact, one study following 840 participants for more than 8 years found that approximately one-half of smokers who stopped smoking for 1 year relapsed to regular smoking within the subsequent 7 years (Ref. 52). Researchers have found that a higher frequency of smoking predicts more severe withdrawal symptoms and earlier relapse after an attempt to quit smoking and is associated with early lapses after cessation (Ref. 17 at p. 119). FDA specifically requests comment as to whether higher frequency smokers would experience more severe withdrawal symptoms from the use of VLNC cigarettes.

FDA expects that, if cigarettes were minimally addictive or nonaddictive, the nicotine level in cigarettes would be self-limiting (*i.e.,* smokers would be unable to obtain their nicotine dose from cigarettes no matter how they smoked them and eventually would stop trying to do so) (*e.g.,* Refs. 4, 5, and 53), making it potentially easier for smokers to make more successful quit attempts and likely leading to a potentially substantial reduction in the rate of relapse compared to current levels.[5] 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 extent that those products result in less harm, significantly reduce their risk of tobacco-related death and disease. Accordingly, rendering cigarettes minimally addictive or nonaddictive (however that were achieved) would be expected to address the principal reason that smokers are unable to quit smoking.

B. Negative Health Effects of Combusted Tobacco Product Use

Nicotine is a powerfully addictive chemical. The effects of nicotine on the central nervous system occur rapidly after absorption (Ref. 25 at p. 12). Users of combusted tobacco products absorb nicotine readily from tobacco smoke through the lungs (id. at p. iii). Nicotine introduced through the lungs is rapidly distributed to the brain (id. at p. 12). With regular use, nicotine levels accumulate in the body during the day from the tobacco product use and then decrease overnight as the body clears the nicotine (id. at p. iii). Mild nicotine intoxication even occurs in first-time smokers (Ref. 25 at pp. 15–16). Tolerance to the effects of nicotine develops rapidly.

The addiction potential of a nicotine delivery system varies as a function of its total nicotine dosing capability, the speed at which it can deliver nicotine, the palatability and sensory characteristics of the system, how easy it is for the user to extract nicotine, and the cost of the delivery system (Ref. 54). A cigarette is an inexpensive and extremely effective nicotine delivery device, which maximizes the cigarette's addicting and toxic effects (id.). The amount of nicotine delivered and the means through which it is delivered can either reduce or enhance a product's potential for abuse and physiological effects (Ref. 17 at p. 113). Quicker delivery, higher rate of absorption, and higher resulting concentration of nicotine increase the potential for addiction (id. at p. 113). The ultimate levels of nicotine absorbed into the blood for different tobacco products (*e.g.,* cigarettes and cigars) can be similar in magnitude even though individuals may smoke them differently and the rate of absorption may be different (Ref. 25).

The significant negative health effects from cigarettes are a consequence of long-term use. Children and adults continue using cigarettes primarily as a result of their addiction to nicotine (*e.g.,* Ref. 7). Almost all adult smokers started smoking cigarettes as children or young adults, and half of adult smokers became addicted before turning 18 (id.).

Cigarettes are responsible for hundreds of thousands of premature deaths every year from many diseases, put a substantial burden on the U.S. health care system, and cause massive economic losses to society (Ref. 7 at pp. 659–666; another perspective on this issue is provided by Sloan et al. (Ref. 55)). Cigarette smoking causes more deaths each year than AIDS, alcohol, illegal drug use, homicide, suicide, and motor vehicle crashes combined (Ref. 47). Every year, cigarette smoking is the primary causal factor for 163,700 deaths from cancer, 160,600 deaths from cardiovascular and metabolic diseases, and 131,100 deaths from pulmonary diseases (Ref. 7 at p. 659). In the United States, about 87 percent of all lung cancer deaths, 32 percent of coronary heart disease deaths, and 79 percent of all cases of chronic obstructive pulmonary disease (COPD) are attributable to cigarette smoking (id.). The 2014 Surgeon General's Report states that 5.6 million youth currently 0 to 17 years of age are projected to die prematurely from smoking-related illnesses (id. at pp. 666–667).

Data from the CDC's Smoking-Attributable Mortality, Morbidity, and Economic Costs system for 2005–2009 (the most recent years for which analyses are available) indicate that cigarette smoking and exposure to cigarette smoke are responsible for at least 480,000 premature deaths each year (id. at p. 659). However, this estimate does not include deaths caused by other combusted forms of tobacco, such as cigars and pipes (id. at 665).[6]

[5] As stated throughout the document, FDA expects that, to maintain their nicotine dose, some number of addicted cigarette smokers could migrate to other similar, combusted products (or engage in dual use with such products) after the standard went into effect, reducing the benefits of the product standard. Since the scope would impact the potential public health benefits of such a nicotine tobacco product standard, FDA is seeking comment on whether the standard should cover any or all of the following products: Combusted cigarettes (which FDA has previously interpreted to include kreteks and bidis), cigarette tobacco, roll-your-own tobacco, some or all cigars, waterpipe tobacco, and pipe tobacco.

[6] As discussed in Ref. 56, regular cigar smoking was responsible for approximately 9,000 premature deaths and more than 140,000 years of potential life

The three leading causes of smoking-attributable death for current and former smokers were lung cancer, heart disease, and COPD (id. at p. 660). For every person who dies from a smoking-related disease, approximately 30 more people will suffer from at least one smoking-related disease (Ref. 58).

Cigarettes also have deadly effects on nonsmokers. From 2005 to 2009, an estimated 7,330 lung cancer and 33,950 heart disease deaths were attributable to exposure to secondhand smoke (Ref. 7 at p. 660). It is also well established that secondhand tobacco smoke causes premature death and disease in children and in adults who do not smoke (see, *e.g.,* Ref. 59 at p. 11). According to the Surgeon General's Report, ''50 Years of Progress: A Report of the Surgeon General, 2014,'' which summarizes thousands of peer-reviewed scientific studies and is itself peer-reviewed, smoking remains the leading preventable cause of disease and death in the United States, and cigarettes have been shown to cause an ever-expanding number of diseases and health conditions (Ref. 7 at pp. 107–621). As stated in the 2014 Report, ''cigarette smoking has been causally linked to disease of nearly all organs of the body, to diminished health status, and to harm to the fetus . . . [and] the burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products'' (Ref. 7 at p. 7).

Other combusted tobacco products, particularly those that could be cigarette alternatives if users were unable to continue smoking cigarettes, cause similar negative health effects. For example, there is a long-standing body of research, including reports from the Surgeon General and National Cancer Institute (NCI), demonstrating that cigar use can cause serious adverse health effects (Ref. 31 at 119–155; Refs. 60, 61, and 33). NCI's Smoking and Tobacco Control Monograph No. 9 (''Cigars: Health Effects and Trends''), which provides a comprehensive, peer-reviewed analysis of the trends in cigar smoking and potential public health consequences, as well as other research, demonstrates that cigar smoking leads to an increased risk of oral, laryngeal, esophageal, pharyngeal, and lung cancers, as well as coronary heart disease and aortic aneurysm, with the magnitude in risk a function of the amount smoked and depth of inhalation (Ref. 31 at 119–155). Research indicates that most cigar smokers do inhale some amount of smoke, even when they do not intend to inhale, and are not aware of doing so (Refs. 33 and 34). Even when cigar smokers do not breathe smoke into their lungs, they are still subject to the addictive effects of nicotine through nicotine absorption (Refs. 33 and 35). This is because cigar smoke dissolves in saliva, allowing the smoker to absorb sufficient nicotine to create dependence, even if the smoke is not inhaled (Refs. 35 and 62).

Regular cigar smoking (which, in this study, constituted use on at least 15 of the past 30 days) was responsible for approximately 9,000 premature deaths and more than 140,000 years of potential life lost among adults aged 35 years or older in 2010 (Ref. 56). Researchers also have found that the risk of dying from tobacco-related cancers is higher from current exclusive pipe smokers and current exclusive cigar smokers than for those who reported never using combusted tobacco products (Ref. 32).

IV. Requests for Comments and Information

To aid in its consideration regarding development of a nicotine tobacco product standard, FDA is seeking comments, data, research results, and other information related to questions under the following topics: Scope of products to be covered, maximum nicotine level for a nicotine tobacco product standard, implementation, analytical testing, technical achievability, possible countervailing effects (including the potential for an illicit market), and other considerations. We ask that commenters clearly identify the section and question associated with their responsive comments and information.

A. Scope

A tobacco product standard limiting the nicotine level in cigarettes could address one of our nation's greatest public health challenges: The death and disease caused by cigarette use. Approximately 480,000 people die every year from smoking cigarettes (Ref. 7). 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. FDA hypothesizes that a tobacco product standard limiting the nicotine level in cigarettes could significantly increase the number of successful quit attempts by the majority of smokers seeking to quit smoking every year and potentially prevent experimenters from becoming regular smokers. However, if a standard were to apply to cigarettes only, it could be substantially less effective. Specifically, FDA expects that, to maintain their nicotine dose, some number of addicted cigarette smokers could migrate to other similar, combusted products (or begin to engage in dual use with such other products) after the standard went into effect, reducing the benefits of the product standard. Former smokers that choose to switch completely to a potentially less harmful nicotine delivery product (*e.g.,* ENDS) to maintain their nicotine dose also would, to the extent that those products result in less harm, significantly reduce their risk of tobacco-related death and disease. Since the scope would impact the potential public health benefits of such a nicotine tobacco product standard, FDA is seeking comment on whether the standard should cover any or all of the following products: Combusted cigarettes (which FDA has previously interpreted to include kreteks and bidis), cigarette tobacco, RYO tobacco, some or all cigars, pipe tobacco, and waterpipe tobacco. FDA intends that any nicotine tobacco product standard would cover all brands in a product category and, therefore, those products currently on the market and any new tobacco products would be expected to adhere to the standard.

FDA is continuing to weigh several factors as it considers the scope of products that should be subject to any potential nicotine tobacco product standard—including the strength and breadth of the available data derived from studies of VLNC cigarettes on the likely effects of reducing nicotine[7] (as discussed in section IV.B); current prevalence and initiation rates for different classes of tobacco products; the available data on the toxicity, addictiveness, and appeal of the products; the use topography of the products (including quantity, frequency, and duration of use); and the potential for migration to, and dual use of, different products. Current VLNC cigarette literature indicates that reduction of nicotine in cigarettes would make it more likely for smokers (even those not currently expressing a desire to quit) to cease cigarette use (*e.g.,* Refs. 4, 5, 63, and 64). In light of these data, FDA also believes that reduction of nicotine could help prevent

lost among adults aged 35 years or older in 2010. The 2014 Surgeon General Report states that the methodology for estimating the current population burden for use of combusted tobacco products other than cigarettes remains under discussion, but the number of added deaths is expected to be in the thousands per year (Ref. 7 at 665, 14 SG; citing Ref. 57).

[7] VLNC cigarettes do not contain uniform amounts of nicotine.

experimenters from becoming addicted to tobacco, resulting in regular tobacco use.

Based on these considerations, FDA is seeking comment on whether any nicotine tobacco product standard should cover any or all of the following products:

- Combusted cigarettes (which FDA has previously interpreted to include kreteks and bidis),
- Cigarette tobacco,
- RYO tobacco,
- Cigars (some or all categories; *i.e.,* small cigars, large cigars, cigarillos, and/or so-called premium cigars),
- Pipe tobacco, and
- Waterpipe tobacco.

Please explain your responses and provide any evidence or other information supporting your responses to the following questions:

1. If FDA were to propose a product standard setting a maximum nicotine level, should such a standard cover other combusted tobacco products in addition to cigarettes? If so, which other products? If FDA were to propose to include additional categories of combusted tobacco products in a nicotine tobacco product standard, should the standard be tailored to reflect differences in these products? What criteria should be used to determine whether, and which, products should be covered?

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

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

B. Maximum Nicotine Level

As discussed throughout this document, nicotine is addictive and is the primary reason why many smokers who want to quit are unable to do so. Accordingly, FDA is considering developing a proposed product standard to make cigarettes minimally addictive or nonaddictive by setting a maximum nicotine level, using the best available science to determine a level that is appropriate for the protection of the public health. FDA has considered several peer-reviewed studies regarding very low nicotine content (VLNC) cigarettes [8] and the likely effects of reducing nicotine in combusted tobacco. A 2013 survey paper noted that researchers initially estimated that reducing the total nicotine content of cigarettes to 0.5 mg per rod would minimize addictiveness and that a ''more recent analysis suggests that the maximum allowable nicotine content per cigarette that minimizes the risk of central nervous system effects contributing to addiction may be lower'' (Ref. 2). The study authors concluded that ''[p]reventing children from becom[ing] addicted smokers and giving people greater freedom to stop smoking when they decide to quit by reducing the addictiveness of cigarettes is a policy that increasingly appears to be feasible and warranted'' (id.). We specifically request comment regarding this paper's conclusions and the possible impact of higher or lower maximum nicotine levels in a potential nicotine tobacco product standard.

Early ''light'' cigarettes achieved a reduction in machine-measured nicotine yield through a variety of means, including through the use of ventilation holes (although the actual nicotine content was not low). This increase in ventilation led to lower yields of nicotine in smoke as measured by smoking machines, and these products were marketed as low nicotine delivery or ''light'' cigarettes. However, cigarette users could modify their use behaviors to compensate for this increase in ventilation. For example, the vent holes could be easily blocked by users' fingers or mouths, and larger or more frequent puffs could be taken by consumers (Ref. 65). As a result, these products were designed to make them ''appear'' light to the user but could deliver as much nicotine to the user as high nicotine delivery cigarettes. The compensatory behaviors of the cigarette user were able to overcome the changes in ventilation in these higher ventilated products.

VLNC cigarettes, in contrast, have relied on reducing nicotine content in the tobacco filler rather than engineering changes to the cigarette. Patents reveal that more than 96 percent of nicotine can be successfully extracted while achieving a product that ''was subjectively rated as average in smoking characteristics'' (Ref. 66) and that up to a 75 percent reduction in the nicotine contained in a tobacco leaf can be achieved with an ''effective and economical system for producing tobacco products . . . while maintaining other desirable ingredients for good taste and flavor'' (Ref. 67).

In conventional cigarettes manufactured in the United States, nicotine accounts for approximately 1.5 percent of the cigarette weight, or 10–14 mg of nicotine per cigarette (Refs. 68–71) and generally have nicotine yields in the 1.1 mg to 1.7 mg (Ref. 31 at p. 67). Certain VLNC cigarettes have much lower nicotine yields than conventional cigarettes—in the 0.02–0.07 mg nicotine/cigarette range—due to product changes that the user cannot overcome (Ref. 72). Reducing the nicotine in the finished tobacco product places an absolute maximum limit on the amount of nicotine that can be extracted by the user in a given cigarette, unlike modifications such as ventilation holes, which affect nicotine yield in smoke but can be overcome through user behavior. See section IV.C of this document for a discussion of possible compensatory smoking under a single target approach or a stepped down approach to nicotine reduction.

1. VLNC Cigarettes

The first VLNC cigarettes studied by researchers were produced by Philip Morris and marketed under the brand name ''Next,'' which was reported to contain 0.4 mg nicotine/g of tobacco filler (Ref. 73). Later, the National Institute for Drug Abuse (NIDA) contracted with the Ultratech/Lifetech

[8] Scientific studies regarding VLNC cigarettes use both ''yield'' and ''content'' to describe the amount of nicotine in research cigarettes. ''Yield'' is the International Organization for Standardization (ISO) machine-generated nicotine smoke yield, and ''content'' refers to the nicotine in the tobacco filler of the entire finished product. ''Yield'' and ''content'' are not interchangeable terms. If neither ''yield'' nor ''content'' is used, the nicotine levels in these studies refer to content.

Corporation [9] to produce VLNC cigarettes for research purposes (Ref. 74; Ref. 75). The two types of cigarettes produced were: (1) 1.1 mg/cigarette (cig) ISO smoke nicotine (7.2 mg nicotine/cig in filler) and (2) 0.07 mg/cig ISO smoke nicotine (filler levels were reported as 0, but FDA has estimated these levels to be between 0.4 and 0.5 mg/cig) (Ref. 74).

Researchers also have used Quest cigarettes, produced by Vector Tobacco, to study the impact of reduced nicotine (Ref. 76). To provide consumers with reduced risk tobacco products, companies like 22nd Century are using genetic engineering and plant breeding to produce very low nicotine tobacco for incorporation into cigarettes. In 2014, the company was granted patents for its process to virtually eliminate the nicotine in tobacco plants (Ref. 77). Further, low-nicotine cigarettes are produced and distributed for research purposes by Research Triangle Institute (RTI), under a contract for the NIDA's Drug Supply Program (Ref. 78). 22nd Century is acting as a vendor for RTI for this contract manufacturing Spectrum cigarettes that contain 0.4 mg nicotine/gram (g) of tobacco filler (id). Finally, Philip Morris manufactured cigarettes with varying nicotine levels for research only (Ref. 79). FDA requests data and information regarding the risks to smokers from inhalation of VLNC cigarette smoke.

Table 1 includes a list of VLNC cigarettes used in research studies and their reported nicotine levels.

TABLE 1—FILLER NICOTINE AND ISO NICOTINE DELIVERY FOR LOW AND VERY LOW (*) NICOTINE CIGARETTES MADE AVAILABLE EITHER COMMERCIALLY OR FOR RESEARCH

Type of cigarette	Filler nicotine level (mg/g or mg/cig)	ISO Nicotine delivery (mg/cig)
Quest 1	12.5 mg/g; 8.9 mg/cig	0.6
Quest 2	6.4 mg/g; 5.1 mg/cig	0.3
Quest 3	1.0 mg/g; 0.4 mg/cig	*0.5
Ultratech/Lifetech	10.3 mg/g [1]; 7.2 mg/cig	1.1
Ultratech/Lifetech [2]	0.6–0.7 mg/g [1]; 0.4–0.5 mg/cig	*<0.06
Next	0.4 mg/g	*0.08
Spectrum high nicotine	11.4–12.8 mg/g	0.6–1.0
Spectrum intermediate nicotine	5.7–5.8 mg/g	0.3
Spectrum low nicotine	0.4 mg/g	*<0.04
Philip Morris 12 mg (for research only)	14.4 mg/g [1]; 10.1 mg/cig	0.9
Philip Morris 8 mg (for research only)	10.6 mg/g [1]; 7.4 mg/cig	0.6
Philip Morris 4 mg (for research only)	5 mg/g [1]; 3.5 mg/cig	0.3
Philip Morris 2 mg (for research only)	2.1 mg/g [1]; 1.5 mg/cig	0.2
Philip Morris 1 mg (for research only)	0.9 mg/g [1]; 0.6 mg/cig	0.1

[1] mg/g or mg/cigarette (cig) was calculated based on an estimate of 0.7 g of tobacco per cigarette (Ref. 80).
[2] Filler nicotine level was reported as 0 mg/cig, but FDA estimates the cigarette contained 0.4–0.5 mg/cig.

2. Estimate of Addiction Threshold Levels

In 1994, certain scientists proposed the idea of federal regulation of nicotine content, which could result in lower intake of nicotine and a lower level of nicotine dependence (Ref. 81). However, FDA acknowledges that there is individual variability in dose sensitivity to all addictive substances, making it difficult to determine a single addiction threshold which would apply across the population. A proposal to lower the nicotine in conventional cigarettes, or any tobacco product, could merit consideration only if there were a threshold nicotine exposure level below which the nicotine did not produce significant reinforcing effects or sustain addiction in a majority of the population. FDA continues to assess VLNC cigarette studies analyzing addiction threshold levels, as discussed in this section.

Four primary study types speak to the level of nicotine in tobacco that could significantly reduce product addictiveness. The first type uses indirect estimates based on information in humans regarding nicotine intake in smokers who appear not to be addicted to nicotine to estimate a likely threshold level. A second type includes studies of VLNC use by study participants that have reported increased quit attempts and cessation even in smokers not interested in quitting. A third type includes studies that have revealed reduced positive subjective effects and increased negative effects in VLNC smokers. The fourth type includes studies measuring nicotine receptor binding, which indicate that use of VLNC cigarettes yields significantly lower nicotinic acetylcholine receptor (nAChR) occupancy and cerebral response.

a. *Indirect estimates of an addiction threshold.* In 1994, researchers conducted a review to explore indirect estimates of an addiction threshold by focusing on the smoking habits of a small population of smokers who demonstrate reduced nicotine dependence, as compared to other smokers (a group sometimes referred to as tobacco ''chippers'') (Ref. 81, citing Ref. 82,). In the 1994 review, researchers suggested that a threshold level of nicotine per cigarette should be low enough to prevent or limit the development of nicotine addiction in most young people, while providing enough nicotine for taste and sensory sensation (*e.g.,* Ref. 81). These researchers found that based on existing studies at the time, ''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. At the same time, it may provide enough nicotine for taste and sensory stimulation'' (id.), which FDA interprets to mean that there would be enough nicotine for an experienced user to tell that there is nicotine in the tobacco product.

In another study seeking to estimate a reinforcement threshold, scientists reviewed several studies, including one in which abstinent smokers received intravenous nicotine injections by pulling a lever in a fixed ratio task (Ref.

[9] Both Ultratech and Lifetech have been reported as being the company through which NIDA manufactured research cigarettes.

83). The authors found that studies using intravenous nicotine administration suggest that the nicotine reinforcement threshold (*i.e.,* the minimum amount of nicotine intake required to initiate or maintain self-administration) is between 1.5 to 6.0 micrograms/kg in humans and 3 to 10 micrograms/kg in rats (Ref. 84). Although the study's authors noted potential limitations (*i.e.,* intravenous delivery does not mimic inhalation, administration of nicotine alone omits other psychoactive constituents in tobacco smoke, and other factors such as age, sex, and genetic variations may influence nicotine's reinforcing properties) (Ref. 84), the lowest dose in the study overlaps with the upper limit of an addiction threshold estimated by the 1994 study (Ref. 81). Despite the study limitations of both these estimates, they help provide a range on which to potentially base a nicotine level threshold.

b. *Findings of increased cessation for VLNC cigarettes.* Several studies indicate that people using significantly reduced nicotine content cigarettes (as low as 0.4 mg nicotine/g of tobacco filler) are more likely to consider cessation (*i.e.,* consider reducing cigarette intake as a step towards cessation or consider fully ceasing cigarette intake), even if they had not previously considered quitting (see, *e.g.,* Refs. 4, 5, 63, and 64). These studies were not investigating VLNC cigarettes as cessation aids.

Some studies showed that switching to VLNC cigarettes results in a reduced number of cigarettes smoked per day (Ref. 4; Ref. 76), reduced nicotine dependence (Refs. 4, 84, and 85), and minimal evidence of withdrawal distress and increased depression (Ref. 64, Ben 12; Refs. 85–87). On the other hand, other researchers have reported the use of VLNC cigarettes did not change the number of cigarettes smoked per day (Refs. 86 and 88), but they did observe reductions in cotinine and carbon monoxide levels. For example, in the Benowitz et al. 2015 study (Ref. 86), where researchers progressively lowered nicotine content over 7 months, the authors found that, after the 7 months of VLNC cigarette use, nicotine intake remained below baseline (*i.e.,* plasma cotinine at 149 ng/ml vs. 250 ng/ml). The Mercincavage et al. study (Ref. 88), a randomized study of smokers progressively decreasing nicotine content over three ten day periods, also yielded mixed results regarding harm exposure. The researchers found that certain biomarkers of exposure to toxic tobacco-related constituents (*i.e.,* cotinine and NNAL) decreased with decreases in nicotine content, but there was no effect on the biomarker 1-hydroxpyrene (1–HOP) (Ref. 88). One limitation of these studies is that they were conducted in an unregulated environment in which smokers continued to have access to the normal nicotine content (NNC) cigarettes.

One of the more recent studies (Ref. 85) on this issue was a double-blind, parallel, randomized clinical trial conducted between June 2013 and July 2014 that evaluated 840 participants (780 completed the 6-week study) who were not interested in quitting smoking. 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 (16.5, 16.3, and 14.9 cigarettes per day, respectively) than for those assigned to their usual cigarette brand or those cigarettes containing 5.2 or 15.8 mg per gram (22.2 and 21.3 cigarettes per day, respectively) (Ref. 85). 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 (id.). The authors concluded that this study provides ''preliminary-short term data . . . [that] suggest that if nicotine content is adequately reduced, smokers may benefit by smoking fewer cigarettes and experiencing less nicotine dependence, with few negative consequences'' (id.).

While these results, 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. As noted by the investigators of the 2015 double-blind, parallel, randomized clinical trial, ''no large-scale clinical trials of reduced nicotine cigarettes have been conducted. Furthermore, little is known about the dose-related effects of reduced nicotine. Data derived from trials assessing a range of reduced-nicotine cigarettes are critical for providing an empirical basis for regulatory decisions pertaining to nicotine product standards'' (Ref. 85). As a result, FDA requests submission of additional data that may be used to explore further the hypotheses presented in this ANPRM (*e.g.,* extended duration studies) and supports the development of additional studies to further analyze these conclusions.

c. *Subjective effects and relief of withdrawal symptoms associated with VLNC cigarettes.* Individuals who smoke VLNC cigarettes experience some of the same subjective effects as those individuals who smoke traditional, NNC cigarettes. For example, VLNC users report experiencing reductions in certain physiological withdrawal symptoms (*e.g.,* craving, anxiety, irritability, depression) but do not experience other symptoms associated with full nicotine content cigarettes (*e.g.,* relief of physical withdrawal symptoms, increased stimulation and alertness, reduction in restlessness) (Refs. 44, 72, 74, 75, 89–93). Exposure over multiple days generally leads to a reduction in cigarettes smoked per day (Ref. 87). Furthermore, physiological responses after VLNC cigarettes, such as the increase in heart rate that is typically observed following nicotine administration, are less than those seen with higher nicotine cigarettes and are absent in some cases (Ref. 74, 94, and 95). Thus, it appears that transitioning to VLNC cigarettes (from NNC cigarettes) may result in some behavioral and physiological responses commonly experienced when using standard NNC cigarettes (*e.g.,* reduced appetite, increased alertness). These responses, where present, are lower than those seen with standard nicotine cigarettes and get progressively lower over time.

d. *Lower nAChR occupancy and cerebral response from the use of VLNC cigarettes.* VLNC cigarettes contain some nicotine, albeit at very low levels. Although there is enough nicotine in VLNC cigarettes to bind to acetylcholine receptors in the brain, there is not enough to consistently produce the full range of subjective responses (*i.e.,* those responses based on or influenced by individual, internal perceptions or experiences) observed following use of NNC cigarettes (Refs. 74, 92, 96, and 97). Therefore, VLNC cigarettes may not produce the full range of subjective effects as NNC cigarettes. This supports the hypothesis that many subjective and physiological effects observed following exposure to smoke from VLNC cigarettes could be due to repeated pairing of nicotine with sensory and conditioned cues or to other psychoactive chemicals. Given that these subjective and physiological effects have been directly linked to nicotine, it is likely that they are learned responses through repeated pairing with nicotine and not due to other chemicals in the smoke.

Please explain your responses and provide any evidence or other information supporting your responses to the following questions:

1. The Tobacco Control Act prohibits FDA from reducing nicotine yields in any combusted tobacco product to zero

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

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

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

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

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

If FDA were to issue a product standard establishing a maximum nicotine level for cigarettes, such a standard would need to either propose a single target (where the nicotine is reduced all at once) or a stepped-down approach (where the nicotine is gradually reduced over time through a sequence of incremental levels and implementation dates) to reach the desired maximum nicotine level. Some have suggested that any maximum nicotine level should be established as a single target (rather than a stepped-down approach) to limit exposure to harmful tobacco while providing similar cessation rates to those that could occur with a stepped-down approach. Some level of compensatory smoking behavior (*i.e.,* smokers seeking to obtain the amount of nicotine they need to sustain their addiction by smoking more cigarettes per day, taking more and deeper puffs, and/or puffing with a faster draw rate) theoretically could occur under either a single target or stepped-down approach and could impact the public health benefits of a possible nicotine tobacco product standard. According to studies involving VLNC cigarettes and other reduced nicotine cigarettes, researchers expect there could be very little or no compensatory smoking with a single target approach and that it would be self-limiting (*i.e.,* smokers would be unable to obtain their nicotine dose from cigarettes no matter how they smoke them and eventually would stop trying to do so), which could maximize the benefits of such a tobacco product standard (Refs. 3–5). If individuals were to engage in compensatory smoking with a single target approach, researchers find that any compensatory smoking at the maximum nicotine levels that FDA is considering here could only be minimal and transient (*e.g.,* Refs. 103, 104, 92, and 93).

In contrast, during a stepped-down approach, tobacco users may attempt to compensate for the loss of nicotine during the early stages of a stepped-down approach by smoking additional tobacco products or by smoking more intensely, since the intermediate-stage products could allow for extraction of nicotine through such efforts in a way that VLNC cigarettes would not (*e.g.,* Refs. 64, 76, and 105).[10]

FDA is aware of several studies that have demonstrated the impact of an immediate (*e.g.,* Refs. 53, 106–108) or a stepped-down approach (Ref. 64) to nicotine reduction on smoking cessation outcomes. Researchers have found that the single target approach may be associated with better cessation outcomes. Data from the International Tobacco Control Policy Evaluation 4-Country Survey, a telephone survey of more than 8,000 adult smokers in the United States, the United Kingdom, Canada, and Australia, illustrates the cessation benefits from abrupt abstinence from cigarettes (''cold turkey'') when compared to a gradual reduction of smoking prior to complete abstinence (''cut down'') (Ref. 109). While this differs from the approaches considered in this ANPRM, it provides helpful insight into the effects of a gradual vs. single change in nicotine intake. Researchers concluded that immediate nicotine cessation was ''clearly associated with more successful outcomes'' (Ref. 109). Scientists also found higher abstinence rates for those using the single target approach in studies comparing two levels of commercial low-yield nicotine cigarettes and nicotine lozenges (Ref. 4).

Nevertheless, some studies have found that both reduction strategies increase a smoker's probability of cessation. For example, in a study of smokers with no strong preference for a quitting method who were randomly assigned to study arms requiring either that they quit immediately or gradually reduce their cigarette consumption over 2 weeks, both the immediate and gradual cessation methods produced similar results (Ref. 110). Likewise, in a meta-analysis of 10 studies to determine the impact of stepped reduction of nicotine versus a single nicotine target in participants interested in quitting smoking, scientists determined that a stepped reduction in nicotine ''provides similar quit rates to abrupt quitting with no evidence that one method is significantly superior to the other in adults trying to quit smoking'' (Ref. 111 at p. 13) and concluded that there were no additional cessation benefits for the stepped-down approach (Ref. 111 at p. 2).

FDA understands the argument that a stepped-down approach to limiting the nicotine levels in tobacco products

[10] However, the IOM has cited one study showing that when nicotine content is stepped down, smokers do not engage in compensatory smoking when nicotine is extracted from tobacco and, therefore, do not increase their toxic exposures (Ref. 13 at p. 349).

could undermine the public health goals of such a standard by allowing for prolonged exposure to tobacco-related toxicants during the step-down period. Although both approaches likely would result in comparable quit rates eventually, some studies have indicated a greater likelihood of cessation success with the use of a single target. In addition, preliminary studies show that a single target approach could limit further exposure to harmful tobacco (when compared with the stepped-down approach to limiting nicotine levels). FDA continues to weigh these factors, and will consider the information submitted in response to this ANPRM, as it decides the appropriate approach for a potential nicotine tobacco product standard.

Please explain your responses and provide any evidence or other information supporting your responses to the following questions:

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

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

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

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

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

D. Analytical Testing Method

As part of its consideration regarding a potential nicotine tobacco product standard, FDA is also considering whether such a product standard should specify a method for manufacturers to use to detect the level of nicotine in their tobacco products. FDA believes that the results of any test method to measure the nicotine in combusted tobacco products should be comparable across different accredited testing facilities and products. It is critical that the results from the test method demonstrate a high level of specificity, accuracy, and precision in measuring a range of nicotine levels across a wide variety of tobacco blends and products.

A variety of methods have been in development that allows nicotine in tobacco or tobacco product filler to be quantified for various products. For example, two Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) methods have undergone round-robin method validation studies in accordance with ISO 5725–1 through ISO 5725–2: (1) Continuous flow analysis (CFA) and (2) gas chromatography-flame ionization detector (GC–FID). The CFA method measured a nicotine range of 0.69–3.30 percent (or 6.9–33 mg/g) in burley and flue-cured tobaccos and exhibited a repeatability range of 0.03–0.17 and a reproducibility range of 0.12–0.67, dependent on the mean (Ref. 112). A GC–FID method for determining nicotine in fermented extractions from tobacco leaves was validated in accordance with FDA and International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use specifications, including specificity, linearity, precision, accuracy, and robustness (Ref. 113). Gas chromatography-mass spectrometry (GC–MS) was used as the confirmation technique in this study, in which a recovery of 117.8 percent was achieved; recovery was within FDA guidelines (<120 percent) (Ref. 113). Nicotine content of 0.43 percent (4.3 mg/g) in the extract was reliably measured and stability testing on this same extract was conducted for 360 days (id.). In addition, the WHO's Tobacco Laboratory Network (TobLabNet) has developed a standard operating procedure for determination of nicotine in cigarette tobacco filler using gas chromatography (Ref. 114). The WHO's TobLabNet determined that this method is suitable for the quantitative determination of nicotine in cigarette tobacco filler by gas chromatography (GC) (id.).

We also note that ISO 10315 and CORESTA Method No. 62 have been used in substantial equivalence reports submitted to the Agency. ISO 10315 is a method for analyzing nicotine in smoke. With this method, conditioned cigarettes are smoked under ISO 4387 conditions and smoke is captured on a Cambridge filter pad and extracted in propan-2-ol containing internal standard such as n-heptadecane or quinaldine (carvone or n-octadecane are other alternatives to internal standards) and analyzed immediately using GC coupled with flame ionization detection (Ref. 115).

CORESTA Method No. 62 is a standard method used to analyze nicotine in tobacco filler and smokeless tobacco products (Ref. 116). This method describes extraction of nicotine in solid tobacco in basified extraction solution (using sodium hydroxide to deprotonate the nicotine in solution) of either hexane containing n-heptadecane or quinaldine internal standards or basified extraction solution (using sodium hydroxide) of methyl-t-butyl ether solution containing quinoline internal standard (id.).

FDA is also aware of other methods that have been used to analyze nicotine levels. Such methods include GC combined with various detectors, GC–MS with solid-phase microextraction as a preconcentration step for low detection, other formats of GC–FID, capillary electrophoresis combined with either ultraviolet (UV) or electrochemical detection, and alternative chromatography techniques including supercritical fluid chromatography-ion mobility detection (Ref. 117), reversed phase ion-pair liquid chromatographic extraction (Ref. 118), and high-pressure liquid chromatography with UV detection (Ref. 119).

Please explain your responses and provide any evidence or other information supporting your responses to the following questions:

1. If FDA were to issue a product standard, should the Agency require a standard method of product testing to analyze the nicotine levels in products subject to the standard? If so, what method or methods should FDA use?

2. Should the Agency require manufacturers to sample their products in a specific manner to ensure that products do not contain excess levels of nicotine? Should manufacturers be required to test each manufactured batch to ensure compliance with a product standard limiting nicotine levels? What criteria should be used to determine if a batch passes or fails testing?

E. Technical Achievability

FDA continues to analyze the technical achievability of a maximum nicotine level for cigarettes as part of its overall assessment of how best to implement this authority and is seeking comments from interested parties regarding this issue, including with respect to the technical achievability of such a standard for small cigarette and/or small combusted tobacco product manufacturers.

The industry and consumer product companies have developed versions of denicotinized cigarettes and a range of brands with differing nicotine levels. By blending tobaccos based on nicotine levels, tobacco companies have manufactured their products to specifications that ensure the final product will have precise levels of nicotine and have ensured that nicotine levels vary only minimally within cigarette packs and from pack to pack (60 FR 41453 at 41505, 41509, August 11, 1995). In fact, the tobacco industry has had programs in place since the 1960s to obtain ''any level of nicotine desired'' (Ref. 120, citing Ref. 121). The industry also has recognized that the techniques it has used to increase nicotine levels can be used to reduce nicotine levels as well (60 FR 41453 at 41722).

As previously described, VLNC cigarettes have been produced since the 1970s. During this time, NCI contracted for production of a line of cigarettes with widely varying nicotine concentrations (Ref. 122, 81 SG). In the late 1980s, a major cigarette manufacturer had plans to develop VLNC cigarettes with a reduction in mainstream nicotine yields of greater than 95 percent (Ref. 123). More recently, 22nd Century, acting as vendor for RTI's contract with NIDA, has developed cigarettes, not currently commercially available, that are similar in many sensory characteristics to conventional cigarettes but with extremely low nicotine levels (Refs. 54, 124, and 125).

Significant reductions of nicotine in combusted tobacco products can be achieved principally through tobacco blending and cross-breeding plants, genetic engineering, and chemical extraction. Agricultural practices (*e.g.,* controlled growing conditions, fertilization, harvest) as well as more recent, novel techniques also can help to reduce nicotine levels. One or a combination of these processes could be used to achieve the nicotine levels that FDA is considering for a nicotine tobacco product standard.

1. Tobacco Blending/Cross Breeding

Most of the cigarettes sold in the United States are blended cigarettes (Ref. 126). A tobacco industry executive previously testified that the main component of a cigarette that contributes to nicotine delivery is the tobacco blend and that year-to-year crop variation does not determine the nicotine content in a cigarette (Ref. 127). The term ''leaf blending'' describes the selection of tobaccos to be used in a product by tobacco type (*e.g.,* flue-cured, burley, oriental), geographical origin, year, and grade of the tobacco (Ref. 128). Blend differences can produce significant variations in nicotine concentration in the tobacco rod, leading to differences in smoke composition and yield (Ref. 120 at p. 469). Grading, which is used to evaluate and identify differences within tobacco types and is a function of both plant position (*i.e.,* higher or lower on the stalk) and of quality (*i.e.,* ripeness), and segregation of grades by nicotine content, already has become common practice (Ref. 128 at p. 2–3).

Many tobacco lines are available, including approximately 1,000 different tobacco varieties (Ref. 126). The tobacco industry has used breeding and cultivation practices to develop high nicotine tobacco plants to give manufacturers greater flexibility in blending and in controlling the amount of nicotine to be delivered (60 FR 41453 at 41694). These practices could be used to develop low nicotine plants as well. In fact, tobacco industry documents show that in the 1960s, tobacco companies recognized the increasing demand for low nicotine tobacco and began instituting projects that found that low nicotine cigarettes can be made by selecting grades of tobacco with low nicotine content (Ref. 128; citing Ref. 129; Ref. 130).

Because the nicotine content of tobacco plants varies, manufacturers could replace more commonly used nicotine-rich varieties like *Nicotiana rustica* with lower nicotine varieties (Ref. 131). Oriental Turkish-type cigarettes also deliver substantially less nicotine than cigarettes that contain air-cured Burley tobacco (Ref. 120; citing Ref. 132). In addition, manufacturers could select specific tobacco seedlings that are low in nicotine and plant only those low nicotine seedlings (Ref. 133). Even without this selective breeding, manufacturers could use careful tobacco leaf purchasing plans to control the nicotine content in their products (60 FR 41453 at 41694). By maintaining awareness of the differences and monitoring the levels in purchased tobacco, companies could produce cigarettes with nicotine deliveries consistent to one-tenth of one percent (despite variations of up to 25 percent in the nicotine content of the raw material grown in the same area, from year to year) (60 FR 41453 at 41694).

The position of leaves on the plant stalk also affects nicotine levels; tobacco leaves located near the top of the plant can contain higher concentrations of nicotine and lower stalk leaves generally contain lower nicotine levels (Ref. 114; Ref. 120). For example, flue-cured tobacco leaves harvested from the lowest stalk position may contain from 0.08 to 0.65 percent nicotine, whereas leaves from the highest positions may contain between 0.13 and 4.18 percent nicotine (Ref. 126, citing Ref. 134). Therefore, substituting leaves found lower on the plants could reduce the nicotine content of tobacco products (Ref. 131).

A number of internal tobacco industry documents describe the use of leaf blending and tobacco selection to control the nicotine content of cigarettes (Ref. 128 at p. 3). For example, one company project determined that low nicotine cigarettes can be made by selecting grades of tobacco with low nicotine content (Ref. 128 at p. 3, citing Ref. 135). Another observed that the demand for low nicotine tobacco has increased worldwide and necessitated a shift in purchasing standards (Ref. 128 at p. 3, citing Ref. 136).

2. Chemical Extraction

Nicotine also can be removed from tobacco via chemical extraction technology. By the 1970s, tobacco manufacturers regularly practiced nicotine extraction as a method to control nicotine delivery (Ref. 128, citing Ref. 137; Refs. 138 and 139). Extraction methods include water extraction (coupled with steam or oven drying), solvent extraction, and extractions of nicotine without usable leaf (Ref. 128). Supercritical fluid extraction also yielded success in the 1990s, allowing for optimum extraction times and the elimination of more time-consuming steps (Refs. 140 and 141). FDA notes that there are existing patents for chemical extraction of nicotine in tobacco, which reveal that more than 96 percent of nicotine can be successfully extracted while achieving a product that ''was subjectively rated as average in nicotine characteristics'' (Refs. 142 and 66).

In addition, a major tobacco manufacturer has used a high-pressure carbon dioxide process similar to the process used to decaffeinate coffee. In this process, tobacco leaf is treated with ammonium salt, then treated with carbon dioxide/water vapor, which has achieved a 95 to 98 percent reduction in nicotine (Ref. 133, citing Ref. 143) Although some manufacturers believe that previous water extraction practices may have rendered the tobacco ''unsuitable for use,'' other water extraction projects yielded suitable smoking material with sizeable nicotine reductions (80 to 85 percent reduction in leaf nicotine) (Ref. 128, citing Ref. 144; Refs. 145 and 146).

3. Genetic Engineering

Tobacco industry scientists have long recognized the potential for genetic engineering to control nicotine content (Ref. 147). The first practical application of biotechnology by a major tobacco manufacturer was the development of low nicotine tobacco in the 1980s, which led to the receipt of a patent for biotechnology for altering nicotine in tobacco plants (Refs. 133 and 148). Other tobacco researchers and major manufacturers also recognized the value of biotechnology for developing low nicotine tobacco for cigarettes, including for use as part of a smoking cessation program (Ref. 149).

Several American and international tobacco companies genetically engineered low nicotine varietals in the 1960s and 1970s, including a strain with nicotine levels as low as 0.15 percent (Ref. 128; citing Refs. 150–155). During that time period, the Kentucky Tobacco Research Board worked on genetic strains of low nicotine tobacco (with a nicotine content of 0.2 percent) to be used for experimental studies on the role of nicotine in smoking behavior (Ref. 128, citing Refs. 156–159). In addition, Canadian researchers examined low nicotine strains of tobacco, particularly in association with efforts to develop a strain of flue-cured or air-cured tobacco that would be suitable as the base material for reconstituted tobacco (Ref. 128, citing Refs. 151 and 160). In 2003, Vector Tobacco began marketing the Quest cigarette, which was produced from genetically modified tobacco and contained only trace amounts of nicotine (Ref. 133) (this product is no longer on the market). Genetic engineering has resulted in reductions of nicotine levels in the range of 80 to 98 percent (id.). In 2014, the U.S. Patent and Trademark Office granted two patents for two genes that may be suppressed to achieve a substantial decrease in nicotine in tobacco plants (Ref. 161).

4. Other Practices

Industry studies have shown that changes to growing and harvesting practices affect the development of tobacco chemistry, including nicotine content (Ref. 128). Some manufacturers have revised their agricultural practices specifically to meet new product development goals, such as the production of low nicotine tobacco (id.). For example, one manufacturer evaluated various experimental agricultural practices that could affect the tobacco's chemistry, including bulk-curing, once-over harvesting, and high plant density (id., citing Ref. 162). In other cases, chemical agents were observed to reduce nicotine content (Ref. 128 citing Refs. 163–165).

After growers harvest tobacco, it is cured and aged before use in tobacco products. The aging process naturally changes the chemistry of the tobacco, including some reduction in nicotine content (Ref. 128). At least one manufacturer has explored efforts to speed up the process of aging tobacco, in part to alter or limit the changes in chemistry that naturally occur (id., citing Ref. 166). Other approaches to curing and fermenting tobacco were explored as a method for altering nicotine content (Ref. 128). For example, in one manufacturer's report, researchers observed that the properties of tobacco, including nicotine content, could be altered without the need for nontobacco additives by modifying curing practices (id., citing Ref. 167). In addition, manufacturers have explored approaches to identify microbial bacteria that actively degraded nicotine while leaving other components of the leaf intact (Ref. 128, citing Refs. 168 and 169). Consumer product testing showed that the ''product acceptability'' of that tobacco was equal to that of untreated tobacco (Ref. 128, citing Ref. 170).

Researchers have developed novel approaches to reducing the nicotine in tobacco products in recent years. For example, a salivary excretion produced by a caterpillar (containing the enzyme glucose oxidase) is applied to tobacco plant leaves and can reduce the nicotine in tobacco leaf by up to 75 percent and provide an ''effective and economical system for producing tobacco products which contain about 0.01 mg nicotine per cigarette or less . . . while maintaining the other desirable ingredients for good taste and flavor'' (Ref. 67).

Please explain your responses and provide any evidence or other information supporting your responses to the following questions:

1. What methods are tobacco product manufacturers currently using to maintain consistency of the nicotine in their products, given the variability of nicotine levels over growing seasons and crop type? How could these methods be adapted to ensure that certain combusted tobacco products meet a potential nicotine tobacco product standard?

2. What is the feasibility of using the techniques discussed in this section, or other nicotine reduction techniques, to reduce the nicotine in cigarettes?

3. What is the feasibility of using the techniques discussed in this section, or other nicotine reduction techniques, for non-cigarette combusted tobacco products (*e.g.,* cigarette tobacco, RYO tobacco, little cigars, large cigars, cigarillos, pipe tobacco, and waterpipe tobacco) that FDA is considering covering under a nicotine tobacco product standard?

4. If FDA were to propose a tobacco product standard setting a maximum nicotine level, how, if at all, would such a product standard impact tobacco farmers' growing and/or curing practices? If FDA were to finalize a nicotine tobacco product standard, what would be the costs and benefits for tobacco farmers and tobacco processors, particularly regarding how any such rulemaking might affect them in light of new technologies and business opportunities that are foreseeable, but not now in place? In addition, if FDA were to finalize a nicotine tobacco product standard, what would be the costs for farmers in light of such a standard?

5. Section 907(d)(2) of the FD&C Act provides that a tobacco product standard must set forth the effective date of the standard, which may not be less than 1 year after publication of a final rule unless FDA determines that an earlier effective date is necessary for the protection of the public health (and that such effective date be established ''to minimize, consistent with the public health, economic loss to, and disruption or dislocation of, domestic and international trade''). This section also provides that the effective date be a minimum of 2 years after publication of a final rule if the tobacco standard can be met only by requiring ''substantial changes to the methods of farming the domestically grown tobacco used by the manufacturer.'' Therefore, if FDA were to propose a product standard setting a maximum nicotine level, when should this standard become effective? What implementation timeframe would allow adequate time for industry to comply? Should the same timeframe be required for all tobacco product manufacturers, regardless of their number of employees and/or annual revenues? [11] Given the currently available processes to reduce the nicotine in tobacco products (*e.g.,* chemical processes, genetic engineering), what do manufacturers

[11] The Tobacco Control Act defines ''small tobacco product manufacturer'' to be a tobacco product manufacturer that employs fewer than 350 employees (21 U.S.C. 387(16)). In the preamble to the deeming rule, FDA defined ''small-scale tobacco product manufacturers'' to be a manufacturer of any regulated tobacco product with 150 employees or fewer and annual total revenues of $5 million or less (81 FR 28973 at 28980). If you are providing comments or information relevant to these definitions or a different definition, please note that definition in your comments.

and others with relevant expertise consider an appropriate timeframe to implement a product standard to reduce nicotine? Would a 2-year, 4-year, or 6-year timeframe be appropriate?

6. Should the standard include provisions that would allow manufacturers, distributors, or retailers to sell off existing nonconforming inventory of manufactured combusted tobacco products? If so, what would be a reasonable sell-off period?

7. What are the potential outcomes of implementing methods to reduce nicotine content in cigarettes in terms of impact on characteristics of cigarettes (flavor, taste, aroma, etc.) and user experience?

F. Possible Countervailing Effects

Section IV. B discusses some of the potential benefits that FDA expects could occur as a result of one possible nicotine tobacco product standard. There may be possible countervailing effects that could diminish the population health benefits expected as a result of a nicotine tobacco product standard. As part of any subsequent rulemaking FDA would need to assess these effects in comparison to the expected benefits, including among population subgroups.

One possible countervailing effect is continued combusted tobacco product use. Current smokers of tobacco products covered by a nicotine tobacco product standard could turn to other tobacco products to maintain their nicotine dependence, both in combination with cigarettes (*i.e.,* dual use) or in place of cigarettes (*i.e.,* switching). For those users seeking to switch to a potentially less hazardous tobacco product (*e.g.,* electronic nicotine delivery systems), FDA expects that the increase in consumer demand for such other products likely would be met by the tobacco industry, which has a history of being responsive to market shifts (see FDA's Draft Concept Paper published elsewhere in this issue of the **Federal Register**). For example, traditional cigarette manufacturers began to expand into the smokeless market when restrictions on where smokers were allowed to smoke were in enacted in the 1980s, 1990s, and early 2000s (id., citing Ref. 171). FDA also wishes to better understand whether users would switch to premium cigars if these products were excluded from the scope of a nicotine tobacco product standard. FDA has requested data and information on whether large and/or so-called premium cigars would be migration or dual use candidates, or whether and how there is a way to define ''premium cigar'' to minimize such consequences.

While FDA believes that some consumers would be satisfied with VLNC cigarettes, the Agency expects that there would be a subset of consumers uninterested in switching to VLNC cigarettes or quitting tobacco products altogether. This subset of consumers may seek to obtain illicit tobacco products after a standard becomes effective (see FDA's Draft Concept Paper). As a result, FDA is considering whether an increase in illicit trade might occur as a result of a nicotine tobacco product standard and how that could impact the marketplace and public health. The analysis of possible illicit trade includes considerations regarding the sources of tobacco, how illicit tobacco products might be manufactured, possible workarounds (such as adding nicotine in liquid or other form to a product with minimally addictive or nonaddictive nicotine levels), the ability to distribute illicit products, the development of consumer awareness, and how illicit trade sales might take place (id.). The capacity to produce illicit tobacco products would depend upon a variety of factors, including the ease of acquiring the raw materials (particularly tobacco), the sophistication required to construct the desired product, and the purpose (whether it is for an individual's personal use, or for wider distribution and sale). Large, commercial, tobacco product manufacturers have the resources, sophistication, and ability to manufacture illicit tobacco products (id.). Illicit tobacco products also may be smuggled and sold through the internet. It is unclear, however, to what extent such companies would be willing to risk their businesses (and resulting profits) to manufacture illicit tobacco products (id.). Tribal manufacturers are an additional source of tobacco products, having relatively high sophistication and machinery in some instances, but they are also subject to the same disincentives as large manufacturers and generally lack widespread distribution and sales capabilities (id.).

The IOM has explored the issue of possible illicit trade if FDA were to issue a tobacco product standard limiting the levels of nicotine in cigarettes. The IOM found that although there is insufficient evidence to draw firm conclusions regarding how the U.S. illicit tobacco market would respond to regulations requiring a reduction in the nicotine content of cigarettes, limited evidence suggests that the demand for illicit conventional cigarettes would be ''modest'' (Ref. 172). The IOM suggests that demand would be limited, because some smokers may quit and other will use modified products or seek legal alternatives (id.). Although some smokers may seek to purchase illicit products if available and accessible, the IOM finds that this ''would require established distribution networks and new sources of product (which would either have to be smuggled from other countries or produced illegally) to create a supply of cigarettes with prohibited features'' (id.). Given that individuals have utilized distribution networks to smuggle cigarettes and avoid higher taxes, FDA is considering whether there might be additional incentive to create or obtain the prohibited cigarettes that are not available elsewhere in the United States. In addition, the report explains that comprehensive interventions by several countries show that it is possible to reduce the size of the illicit tobacco market through enforcement mechanisms and collaborations across jurisdictions (id.).

If a nicotine tobacco product standard were to prompt the development of an illicit market, FDA would have the authority to take enforcement actions regarding the sale and distribution of illicit tobacco products. The FD&C Act provides FDA with several tools that it may use against noncompliant parties. For example, FDA could issue a Warning Letter, an advisory action in which FDA notifies a regulated entity that FDA has found evidence that the party violated the law. A Warning Letter is used to achieve prompt voluntary compliance. In a Warning Letter, FDA informs the regulated entity that failure to comply with the requirements of the FD&C Act and its implementing regulations may result in FDA enforcement action. These actions may include initiating administrative actions or referring cases to the Department of Justice for initiation of judicial action. FDA may seek to initiate an administrative legal action against a regulated entity that can result in the imposition of a fine or civil money penalty. Possible judicial actions may include seizures, injunctions, and criminal prosecution.

Another possible countervailing effect is the potential for increased harm due to continued VLNC smoking with altered smoking behaviors. Some studies of VLNC cigarettes with nicotine levels similar to what FDA is considering have not found compensatory smoking behavior and have found reductions in the number of cigarettes smoked per day and, consequently, decreased exposure to harmful constituents (as discussed in

section IV.B of this document). If FDA decides to pursue a proposed nicotine product standard, FDA will continue to consider this potential countervailing effect.

Another possible countervailing effect of setting a maximum nicotine level for cigarettes could be that users would seek to add nicotine in liquid or other form to their combusted tobacco products. Therefore, FDA is considering whether any action it might take to reduce nicotine in combusted tobacco products should be paired with a provision that would prohibit the sale or distribution of any tobacco product designed for the purposes of supplementing the nicotine content of a combusted tobacco product (or any product where the reasonably foreseeable use is for the purposes of supplementing this nicotine content). FDA is also considering what other regulatory options may be available to address this concern and requests comments on such options.

Please explain your responses and provide any evidence or other information supporting your responses to the following questions:

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

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

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

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

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

6. If an illicit market developed, what percentage of current smokers would switch to illicit conventional cigarettes rather than quitting or switching to other legal products? How would this change if illicit conventional cigarettes were more expensive and/or harder to obtain? How would this change with the implementation of improved monitoring and enhanced enforcement by FDA and its partners?

7. If a nicotine tobacco product standard prompted growth of an illicit market, how long would it likely last? Would demand likely decrease over time, stay the same, or increase?

8. If a nicotine tobacco product standard prompted growth of an illicit market, what effect, if any, would this have on the market for illegal drugs? Are there data showing a relationship between illicit tobacco use and illegal drug use?

9. What mechanisms may be used to prevent, control, or contain illicit markets in conventional cigarettes that may develop if FDA establishes a product standard? What State and Federal entities may be responsible for these mechanisms, and how much would they cost?

G. Other Considerations

To aid in its consideration regarding development of a nicotine tobacco product standard, FDA is seeking data, research results, and other information regarding the following:

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

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

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

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

5. In what ways might a change in nicotine levels in cigarettes spur innovation in the market for both combusted and noncombusted tobacco products?

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

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

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

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

V. Potential Public Health Benefits of Preventing Initiation to Regular Use and Increasing Cessation

If FDA were to issue a proposed tobacco product standard setting a maximum nicotine level, FDA would provide an analysis explaining how the proposed rule would be appropriate for the protection of the public health (section 907(a)(3)(A) of the FD&C Act). For the purposes of this ANPRM, this section briefly describes the potential public health benefits FDA believes could result from the increased cessation and decreased initiation to regular use that FDA expects could occur if cigarettes and possibly some other combusted tobacco products were minimally addictive or nonaddictive. It also references findings from a

population-based simulation model that quantified the potential public health impact of enacting a regulation lowering nicotine levels in cigarettes and some other combusted tobacco products to minimally addictive levels, utilizing inputs derived from empirical evidence and expert opinion. We are seeking public comment regarding the inputs that should be used for modeling the impact of a nicotine tobacco product standard.

A. Smoking Cessation Would Lead to Substantial Public Health Benefits for People of All Ages

Significant declines in the deaths caused by the use of combusted tobacco products can be achieved by reducing the prevalence of smoking cigarettes and other combusted tobacco products. Smoking cessation has major and immediate health benefits for men and women of all ages, regardless of health status (Ref. 173 at p. i). Smoking cessation decreases the risk of the health consequences of smoking, and former smokers live longer than continuing smokers. For example, persons who quit smoking before age 50 have one-half the risk of dying in the next 15 years compared with continuing smokers (id. at p. v).

Smoking cessation reduces the risk of cancers throughout the body (Ref. 173). For example, although the risk of dying from lung cancer is 22 times higher for male smokers than male nonsmokers (and 12 times higher for female smokers than female nonsmokers), the risk of lung cancer after 10 years of abstinence is 30 to 50 percent that of continuing smokers (id.; Refs. 174 and 175).

Smoking cessation also reduces the risk of other life-threatening illnesses that occur in smokers. In addition to reducing the risk of cancers and the mortality rates of smoking-related diseases, smoking cessation substantially reduces the risk of other dangerous diseases that can lead to death or disability and cause a financial strain on health care resources. For example, smoking cessation substantially reduces risk of peripheral artery occlusive disease (which can cause complications that lead to loss of limbs) (Ref. 173). Former smokers also have half the excess risk of experiencing an abdominal aortic aneurysm compared to current smokers (id.). Cigarette smoking also complicates many diseases (*e.g.,* smokers with diabetes have higher risk of complications, including heart and kidney disease, poor blood flow in the legs and feet, retinopathy and peripheral neuropathy), and smoking cessation can alleviate those complications as well (Ref. 17).

Youth and young adults would experience the greatest benefits from a nicotine tobacco product standard, because many of them may not progress beyond experimentation and, therefore, may not experience dangerous and deadly tobacco-related health effects. Fetuses and children also would benefit if their parents quit smoking, given the negative health consequences to the fetus of a smoking mother and the dangers of secondhand smoke. In addition, children of parents who smoke, when compared with children of nonsmoking parents, have an increased frequency of respiratory infections like pneumonia and bronchitis (Ref. 173). Smoking cessation reduces the rates of these respiratory symptoms and of respiratory infections (Ref. 176 at p. 467). Children exposed to tobacco smoke in the home also are more likely to develop acute otitis media (middle ear infections) and persistent middle ear effusions (thick or sticky fluid behind the eardrum) (Ref. 173). If parents were more able to quit because these products become minimally addictive or nonaddictive, youth would experience these health problems much less frequently.

Although the health benefits are greater for people who stop smoking at earlier ages (Refs. 173 and 176), researchers estimate that smokers can gain years of additional life expectancy no matter when they quit (Ref. 177). In addition, scientists using data from the Cancer Prevention Study (CPS–II), but accounting for bias caused by smoking cessation after baseline, found that even smokers who quit at age 65 had an expected life expectancy increase of 2 years for men and 3.7 years for women (Ref. 178).

The benefits continue for those who remain smoke free. At year one, an individual's added risk of coronary heart disease becomes half that of a smoker's (Ref. 175). Between 2 and 5 years after cessation, an individual's stroke risk is reduced to that of a nonsmoker (id.). In addition, a former smoker's risk of cancers of the mouth, throat, esophagus, and bladder is halved within five years (id.). By 10-years post cessation, an individual's risk of cancers of the kidney and pancreas decreases (id). The risk of coronary heart disease becomes that of a nonsmoker after 15 years of abstinence (id.).

B. A Nicotine Tobacco Product Standard Could Lead to Substantial Improvement in Public Health

As stated throughout this document, nicotine at levels currently found in tobacco products is highly addictive, and addiction to nicotine is the ''fundamental reason that individuals persist in using tobacco products'' (Ref. 17 at p. 105). Although nicotine itself is not the direct cause of most tobacco-attributable disease, addiction to the nicotine in tobacco products is the proximate cause of these conditions because it sustains tobacco use (Refs. 54 and 179). Addiction caused by nicotine in tobacco is critical in the transition of smokers from experimentation to sustained smoking and in the maintenance of smoking for those who want to quit (Ref. 7 at p. 113; Ref. 17). As a result, 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. In this section, we summarize the approach used to describe the possible impact of a potential nicotine tobacco product standard to the population as a whole and present the findings of this analysis.

As discussed elsewhere in this document, FDA is considering the scope of a potential product standard, and has asked for public comment. To assess the impact of one potential option that might maximize the potential public health impact, it may be appropriate to consider the Apelberg et al. 2018 publication, which presented simulation modeling of a policy scenario in which the scope of a potential product standard restricted the nicotine level in cigarettes, cigarette tobacco, RYO tobacco, cigars (including little cigars, large cigars, and cigarillos, but not so-called ''premium'' cigars), and pipe tobacco (other than waterpipe/hookah tobacco). As part of a formal expert elicitation process (this process centered around three online conferencing sessions held during January and February 2015, following a written protocol designed to elicit opinions using a structured, standardized approach (see Ref. 181 for more details)), eight subject matter experts were asked to provide their individual estimates of the anticipated impacts of a hypothetical policy (setting a ''maximum limit on the amount of nicotine in cigarette tobacco filler'' for the purpose of reducing nicotine in cigarettes ''to minimally addictive levels'') and to develop subjective probability distributions for parameters of interest.

A more detailed description of the methodology, data sources and inputs, and results from this analysis can be

found in two peer-reviewed publications (Refs. 180 and 181).

1. Approach to Estimating Impacts to the Population as a Whole

As described in this document, FDA expects that making cigarettes minimally addictive or nonaddictive (however that were achieved) would impact currently addicted smokers by increasing their ability to quit smoking and affect nonsmokers by reducing the likelihood that they would become established and addicted smokers. Apelberg et al. 2018 updated a previously published discrete system dynamic population model to compare projected outcomes for a status-quo scenario (in which no maximum nicotine level is implemented) with outcomes for a policy scenario in which a hypothetical regulation lowering nicotine in cigarettes, and selected other combusted tobacco products, to minimally addictive was implemented [12] (Ref. 181).

The model incorporated, based on estimates of subject matter experts, the following tobacco use transitions to estimate the impact of the policy: (1) Cigarette smoking cessation; (2) cigarette smokers switching to noncombusted tobacco products (*e.g.,* smokeless tobacco and/or electronic cigarettes) rather than quitting tobacco use entirely; (3) continuing smokers becoming dual users of cigarettes and noncombusted tobacco products; (4) nonsmokers initiating regular cigarette smoking; and (5) nonsmokers who have been dissuaded from smoking cigarettes and certain other combusted tobacco products, who may instead initiate use of a noncombusted tobacco product. The model, based on input parameters derived from expert estimates, projected the impact of the policy on four main outcomes: (1) Prevalence of cigarette smoking and noncombusted tobacco product use; (2) the number of individuals dissuaded from cigarette smoking; (3) cumulative number of tobacco-attributable deaths avoided; and (4) cumulative life years gained as a result of a regulation setting a maximum nicotine level.

[12] The policy scenario presented in Apelberg et al. 2018 (Ref. 181) did not define a specific level of nicotine as minimally addictive. Rather, the policy scenario simulated implementation of a hypothetical standard in which cigarettes and certain other combusted tobacco products were made minimally addictive, informed by a formal expert elicitation process (Ref. 181), used to estimate the impact of decreasing the addictiveness of cigarettes on certain tobacco use behaviors. Given the lack of specificity in the hypothetical scenario posed in the Apelberg et al. study, caution is warranted in extrapolating its results to the assessment of a particular policy.

The methodology implemented in this analysis has been detailed elsewhere (Refs. 180 and 181). Briefly, the simulation begins with an initial population that reflects the sex, age, and tobacco use distribution (*i.e.,* never, current, and former use of cigarettes and noncombusted products) of the U.S. population in 2015, based on U.S. Census Bureau estimates. The analysis projects population changes for 2016–2100 in 1-year increments, while accounting for births, net migration (which accounts for immigration and emigration) and deaths, the last of which is a function of age, sex, and tobacco use status. Baseline estimates for tobacco use status (combinations of current, former, and never use for cigarettes and noncombusted products) by sex, age, and time since cessation (for cigarettes only) were obtained from the 2015 National Health Interview Survey (NHIS) for adults (Ref. 1) and the 2015 NYTS for youth (Ref. 182). Mortality rates and relative risks by tobacco use status were obtained from U.S. vital statistics data, NHIS data linked for mortality followup (for never smoker mortality rates and cigarette smoking relative risks), and the CPS–II (for smokeless tobacco product relative risks). In the absence of data on the long-term health risks of ENDS, Apelberg et al. assumed that the ENDS products carried the same risks associated with traditional smokeless tobacco (see Ref. 181 for more detail).

Quantitative inputs for rates of post-policy smoking cessation, switching, and dual use in the hypothetical policy scenario were obtained through a formal expert elicitation process. The methodology used to identify experts, develop the protocol, conduct the elicitation, and summarize the findings has been described in detail elsewhere (Ref. 181 at Appendix). Briefly, elicitation candidates with expertise in tobacco science and policy were identified, ranked, and recruited in accordance with a pre-specified protocol, based on publication history and accounting for potential conflicts of interest. Candidates were required to self-certify that they were free of any actual, apparent, or potential conflicts of interests. The elicitation process centered around three online conferencing sessions held during January and February 2015, following a written protocol designed to elicit opinions using a structured, standardized approach (see Ref. 181 for more details). Briefing books with key papers on the topics of interest as well as background data on tobacco use and policy were provided to a panel of eight experts prior to the conference sessions. Experts were asked to identify any other relevant information to share with the panel. Detailed written questionnaires were completed by each expert as independent take-home exercises. To maintain the independence of the experts and encourage open discussion, involvement of FDA staff was limited.

To explore the potential impact of a product standard that would maximally benefit population health, the experts were asked to assume that combusted tobacco products that could be viewed as highly likely to serve as substitutes for traditional cigarettes (*i.e.,* RYO tobacco, pipe tobacco, nonpremium cigars) would be included in the policy, while other tobacco products (*i.e.,* premium cigars, waterpipe/hookah, ENDS, smokeless tobacco) would be excluded.[13] The eight experts were asked to predict and quantify the anticipated impact of the policy on the following model parameters: (1) Cigarette smoking cessation rates; (2) switching from cigarette smoking to other tobacco products excluded from the hypothetical policy scenario; (3) dual use rates; (4) cigarette smoking initiation rates; and (5) initiation rates for other tobacco products excluded from the hypothetical policy scenario. Each of the eight experts was asked to provide his or her best estimate of the parameters' true value, estimates of the minimum and maximum plausible values, and estimates of the 5th, 25th, 75th and 95th percentile values. Experts were asked first about impacts in the first year immediately following the potential product standard's implementation and then about the impacts in the years following the first full year of implementation. Experts had the option of providing separate estimates of impacts for males and females for the initial and subsequent years. For each question, experts were asked to provide the factors they considered pertinent to answering the question, including the studies and research findings most influential to informing their views, and to rate their familiarity with the relevant literature. The elicitation process provided the experts with opportunities to interact and discuss divergent views, from

[13] While the policy scenario presented in Apelberg et al., 2018 (Ref. 181) is based on reduction in nicotine level in cigarettes, cigarette tobacco, RYO tobacco, certain cigars and pipe tobacco, the estimated population impact is based on reductions in cigarette smoking. FDA notes that not accounting for reductions in the use of other combusted tobacco products may underestimate the overall impact of this policy scenario.

which each expert generated his/her initial and final estimates.

The eight experts' judgments about the potential values of these parameters are published in Apelberg et al. 2018 (Ref. 181). While parameter estimates and their probability distributions varied somewhat between participants, most experts had the view that making cigarettes and certain other combusted tobacco products minimally addictive would lead to substantial initial and long-term increases in smoking cessation among cigarette smokers and decreased initiation among nonsmokers. Distributions provided by the eight experts' parameter estimates were substantially broad in range. For example, for both male and female nonsmokers, the median minimum and maximum estimates from the eight experts on the ''percent of reduction in annual smoking initiation rates'' after the first year in response to the policy ranged from 10 percent to 90 percent. For both male and female smokers, the median minimum and maximum estimates from the eight experts on the ''percent of current smokers who quit smoking as a result of the policy'' within the first year after policy implementation ranged from 4 percent to 50 percent.

To account for uncertainty associated with the expected impact of the policy scenario, Apelberg et al. 2018 used the distributions of the experts' estimates in a Monte Carlo simulation. A Latin Hypercube sampling with 1,000 sample values was performed for each of the expert's response distributions. For each simulation, the policy scenario was compared to the baseline scenario to estimate changes in the outcomes described above. A summary of distribution responses are provided in Apelberg et al. 2018.

2. Projected Impacts to Users, Nonusers, and the Population as a Whole

As illustrated in Figure 1 (Ref. 181), using the experts' input estimates for the parameters described previously, and assuming that the policy is implemented in 2020, the simulation model projected that cigarette smoking prevalence declines substantially in the policy scenario within the first year of implementation of the hypothetical policy scenario to a median value of 10.8 percent compared with 12.8 percent in the baseline scenario. In subsequent years, the simulation model projects that the difference in cigarette smoking prevalence between the scenarios continues to grow due to the experts' estimates of sustained increases in cessation and decreases in initiation in the policy scenario. The projected smoking prevalence drops to a median value of 1.4 percent (5th and 95th percentile projections range from 0.2 percent to 5.9 percent) under the policy scenario by 2060 compared to 7.9 percent under the baseline. Smoking prevalence estimates for the year 2100 are comparable to those for 2060.

Concurrent with a projected reduction in cigarette smoking is a projected increase in noncombusted product use. Adult noncombusted tobacco product use is higher in the hypothetical policy scenario compared to the baseline scenario within the first year of implementation of the potential product standard (Ref. 181 at Figure 1), due to estimated increases in switching from cigarette smoking and transitions to dual cigarette and noncombusted product use as a result of the hypothetical policy scenario. The prevalence of noncombusted tobacco product use remains higher in the policy scenario over time due to the experts' predictions that there would be both increased uptake among smokers (through either complete switching or dual use) and increased initiation due to some dissuaded cigarette initiators taking up noncombusted products instead.

Table 2 provides a projection of the number of individuals who would not become cigarette smokers over time as a result of the hypothetical policy scenario. Since it is assumed, based on expert input, that there would be a sustained decrease in cigarette smoking initiation rates, the model projects that the cumulative number of dissuaded smoking initiates continues to increase over time. By 2100, the median estimate from the model, based on the experts' estimates of potential initiation rates as a result of the policy, is that more than 33 million youth and young adults who would have otherwise initiated regular smoking would not start as a result of the hypothetical policy scenario (5th and 95th percentile projections range from 8.0 million to 64.1 million).

Using the eight experts' estimates for the percent of current smokers who would quit smoking after implementation of the policy, approximately 5 million additional smokers are estimated to quit smoking within one year after implementation of the product standard (5th and 95th percentile projections range from 110,000 to 19.7 million), compared to the baseline scenario. The number of additional smokers quitting would increase by approximately 13 million within 5 years after policy implementation (5th and 95th percentile projections range from 430,000 to 30.5 million), compared to the baseline scenario.

TABLE 2—PROJECTED NUMBER OF INDIVIDUALS WHO WOULD NOT INITIATE REGULAR SMOKING AS A RESULT OF A NICOTINE TOBACCO PRODUCT STANDARD IMPLEMENTED IN 2020

Year	Cumulative new smoking initiates avoided (in millions)		
	5th percentile	Median	95th percentile
2040 ..	2.0	8.1	15.6
2060 ..	3.9	16.0	31.0
2080 ..	5.9	24.4	47.2
2100 ..	8.0	33.1	64.1

Table 3 presents the estimated cumulative number of tobacco-attributable deaths potentially avoided and life years gained due to the experts' determinations that smoking rates would decrease as a result of the hypothetical policy scenario. By 2060, it is estimated that a median value of almost 3 million deaths due to tobacco would be avoided (5th and 95th percentile projections range from 0.7 million to 4.3 million), rising to 8.5 million by the end of the century (5th and 95th percentile projections range from 2.2 million to 11.2 million). The reduction in premature deaths attributable to the hypothetical policy scenario would result in approximately 33 million life years gained by 2060 (5th and 95th percentile projections range from 7.8 million to 53.9 million) and over 134 million life years gained by 2100 (5th and 95th percentile projections range from 31.6 million to 183.0 million).

TABLE 3—PROJECTED NUMBER OF TOBACCO-ATTRIBUTABLE DEATHS AVOIDED AND LIFE YEARS GAINED DUE TO REDUCED SMOKING AS A RESULT OF A NICOTINE TOBACCO PRODUCT STANDARD IMPLEMENTED IN 2020

Year	Cumulative tobacco attributable deaths avoided (millions)			Cumulative life years gained (millions)		
	5th percentile	Median	95th percentile	5th percentile	Median	95th percentile
2040	0.3	0.9	1.4	2.5	6.8	11.5
2060	0.7	2.8	4.3	7.8	33.1	53.9
2080	1.3	5.6	7.9	16.5	79.6	118.0
2100	2.2	8.5	11.2	31.6	134.4	183.0

3. Request for Comments

Based on the experts' judgments that reducing nicotine levels in combusted tobacco products would increase smoking cessation and decrease smoking initiation, and calculations from the simulation model describing the potential impact of reducing nicotine to minimally addictive levels in cigarettes and selected other combusted tobacco products, FDA anticipates a significant public health benefit to the United States. This hypothesis is based on the assumption that the reduction in nicotine levels in combusted tobacco products would create substantial reductions in smoking prevalence due to increased smoking cessation and reduced initiation of regular smoking. Given that research studies cannot easily replicate the condition of a nationally enforced restriction on nicotine to minimally addictive levels in cigarettes, FDA sought expert opinion through an established elicitation process to provide the best estimates for the potential values and associated ranges of the likely impact of a hypothetical reduction in cigarettes' nicotine content (to be achieved by a potential product standard) on tobacco use behaviors. FDA requests data, evidence, and other information regarding the potential public health benefits (or risks) if FDA were to move forward in this area. Specifically, FDA is seeking data, evidence, and other information that could inform the following five parameter inputs that would be helpful in determining the public health impact of a nicotine tobacco product standard:

- Percent of current cigarette smokers who would quit cigarette smoking as a result of a standard restricting nicotine to minimally addictive levels.
- Percent of quitters switching to other combusted or noncombusted tobacco products.
- Percent of continuing smokers who become dual product users of cigarettes and noncombusted tobacco products.
- Percent reduction in annual smoking initiation rates.
- Percent of dissuaded smoking initiates who initiate noncombusted tobacco product use instead.

Please include your assumptions about the scope of the standard and data that supports your estimates.

4. Additional Public Health Benefits

While the projections from the simulation model calculating the potential impact from reducing nicotine to minimally addictive levels in cigarettes suggest a significant public health benefit to the United States resulting from substantial reductions in smoking prevalence (based on the model's inputs, which reflect the experts' assessments that the reduction in nicotine levels in combusted tobacco products would create substantial increases in smoking cessation and reductions in initiation of regular smoking), the analysis does not address certain potential added benefits. First, the model does not account for increased quality of life from decreased tobacco-related morbidity, nor does it account for cost savings from medical care averted. Second, the analysis does not account for the impacts of secondhand smoke exposure on public health in the United States. Third, the analysis does not account for reductions in harms caused by smoking-related fires. Fourth, the potential impact described does not account for the potential impact on population health from use of the other combusted products (*e.g.,* cigars, pipes) if the assumed rule were to cover such products. Finally, these projections do not assess whether there could be potential health benefits associated with smokers cutting down on the number of cigarettes smoked as a result of the standard.

VI. References

The following references are on display in the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m. Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

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