DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 1160

[Docket No. FDA–2024–N–5471]

RIN 0910–AI76

Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing a tobacco product standard that would regulate nicotine yield by establishing a maximum nicotine level in cigarettes and certain other combusted tobacco products. FDA is proposing this action to reduce the addictiveness of these products, thus giving people who are addicted and wish to quit the ability to do so more easily. The proposed product standard is anticipated to benefit the population as a whole. For example, it would help to prevent people who experiment with cigarettes and cigars from developing addiction and using combusted tobacco products regularly.

DATES: Either electronic or written comments on the proposed rule must be submitted by September 15, 2025. Submit comments (including recommendations) on the collection of information under the Paperwork Reduction Act of 1995 (PRA) by September 15, 2025.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of September 15, 2025. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received 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–2024–N–5471 for ''Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted 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, 240–402–7500.

- 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.govinfo.gov/content/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, 240–402–7500.

Go to the Federal eRulemaking Portal at *https://www.regulations.gov* for access to the rulemaking docket, including any background documents and the plain-language summary of the proposed rule of not more than 100 words in length required by the Providing Accountability Through Transparency Act of 2023.

Submit comments on the information collection under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at *https://www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently under Review—Open for Public Comments'' or by using the search function. The title of this proposed collection is ''Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products.''

FOR FURTHER INFORMATION CONTACT: *With regard to the proposed rule:* Nate Mease or Dhanya John, Center for Tobacco Products, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002, 877–287–1373, *CTPRegulations@fda.hhs.gov.*

With regard to the information collection: JonnaLynn Capezzuto, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–3794, *PRAStaff@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

Each year, 480,000 people die prematurely from a smoking-attributable disease, making tobacco use the leading cause of preventable disease and death in the United States (Ref. 1). Nearly all these adverse health effects are ultimately the result of addiction to the nicotine in combusted tobacco products, leading to repeated exposure to toxicants from those products. Nicotine, the primary addictive constituent in tobacco products, can be delivered through a variety of products along a continuum of risk. To protect youth and reduce tobacco-related disease and death, the Agency utilizes a comprehensive approach to tobacco and nicotine regulation (*https://www.fda.gov/media/174911/download*). As part of this comprehensive approach, FDA is proposing a tobacco product standard that would regulate nicotine yield by establishing a maximum nicotine level in cigarettes [1] and certain other combusted tobacco products (proposed product standard).

As the U.S. District Court for the District of Columbia recognized in *United States* v. *Philip Morris USA, Inc. et al.,* 449 F.Supp.2d 1 (D.D.C. 2006), *aff'd in relevant part,* 566 F.3d 1095 (D.C. Cir. 2009), the tobacco industry has long known that nicotine creates and sustains addiction, and the industry is dependent on maintaining this addiction. *Id.* at 307. The court noted how cigarette companies have engaged in extensive research to understand how nicotine operates within the human body and then designed their cigarettes to precisely control nicotine delivery and provide nicotine doses to create and sustain addiction. *Id.* at 307–309. Moreover, the court confirmed that industry documents supported the conclusion that these companies ''knew early on in their research that if a cigarette did not deliver a certain amount of nicotine, new smokers would not become addicted, and 'confirmed' smokers would be able to quit.'' *Id.* at 219. In fact, the tobacco industry has had programs in place since the 1960s to obtain ''any level of nicotine desired'' (Ref. 2). These companies sought to identify the ''optimum'' dose needed to ''satisfy'' people who smoke cigarettes and, thereby, assure their continued smoking. *Philip Morris,* 449 F.Supp.2d at 309–10. This proposed product standard would seek to set a maximum nicotine level such that cigarettes and certain other combusted tobacco products could no longer create and sustain this addiction among people who smoke cigarettes and certain other combusted tobacco products.

The proposed product standard would limit the addictiveness of the most toxic and widely used tobacco products, which would have significant public health benefits for all age groups. The proposal would have cessation benefits for adults who use cigarettes and certain other combusted tobacco products, most of whom want to quit but are repeatedly unsuccessful because of the highly addictive nature of these products (see section IV.A of this document). Because these products would not create and sustain addiction, users would be able to quit when they would like, something many who use these products currently do not have the ability to do. Additionally, combusted tobacco products at minimally addictive or nonaddictive levels of nicotine would remain on the market for those who currently smoke and would like to continue to do so.

It would also help prevent people who experiment with cigarettes or certain other combusted tobacco

[1] Throughout this document, FDA generally uses the term ''cigarettes'' to refer to combusted cigarettes, unless specifically stated or context indicates that noncombusted cigarettes are referenced. In general, the term is not meant to include any noncombusted tobacco products that meet the definition of cigarette in section 900(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 387(3)).

products (mainly youth) from moving beyond experimentation, developing an addiction to nicotine, and progressing to regular use of combusted tobacco products as a result of that addiction (see section VIII.B of this document). Reducing the number of people who experiment with cigarettes or certain other combusted tobacco products who then transition to regular use of these products would prevent severe adverse health consequences of long-term smoking at the individual level and result in public health benefits at the population level. Based on FDA's population health model, by the year 2100, in the United States, approximately 48 million youth and young adults who would have otherwise initiated habitual cigarette smoking would not as a result of the proposed product standard. The model also projects that more than 12.9 million additional people who smoke cigarettes would quit smoking cigarettes [2] 1 year after implementation of the proposed product standard; this estimate increases to 19.5 million additional people within 5 years of implementation (this includes people who exclusively smoke cigarettes quitting all tobacco products or completely switching to noncombusted tobacco product use, as well as people who engage in dual use of cigarettes and noncombusted tobacco products quitting cigarette use). In addition, the model estimates that, by the year 2060, in the United States, this proposed product standard would result in 1.8 million tobacco-related deaths averted, rising to 4.3 million deaths averted by the end of the century. The reduction in premature deaths attributable to the proposed product standard would result in 19.6 million life years gained by 2060 and 76.4 million life years gained by 2100. For the reasons discussed in the preamble, FDA finds that the proposed product standard would be appropriate for the protection of the public health.

As explained in section VIII.A., the population health model uses inputs derived from available empirical evidence and expert opinion to estimate the impact of this proposed rule. To obtain expert opinion for the model inputs, FDA conducted a formal expert elicitation process in 2015 and repeated it in 2018. FDA is conducting another expert elicitation process and intends to publish the results of this update for public review and additional comment on this proposed standard in light of that update.

B. Summary of the Major Provisions of the Proposed Rule

There are currently no tobacco product standards regulating nicotine in tobacco products. The proposed rule would establish a maximum level of nicotine in cigarettes and certain other combusted tobacco products. FDA issued an Advance Notice of Proposed Rulemaking regarding a potential nicotine tobacco product standard (Nicotine ANPRM), and the Agency reviewed and analyzed the comments to that ANPRM (83 FR 11818 (March 16, 2018)). FDA also conducted an extensive and robust review of the relevant scientific literature, as discussed throughout this document. FDA is proposing the following provisions based on the comments received and the Agency's analysis of relevant scientific literature.

Proposed scope—Given that approximately 28 million adults and 380,000 youth in the United States currently smoke cigarettes and the toxicity and addictiveness of these products, cigarettes are the tobacco product category that causes the largest amount of harm to public health in the United States (Refs. 3 and 4). However, if a product standard were to cover only cigarettes, it is likely that a significant number of addicted people who smoke cigarettes would migrate to other similar combusted tobacco products after the standard went into effect to maintain their nicotine exposure, thereby undermining the public health benefits of the standard (Ref. 5) (see also section VI.B of this document). Therefore, to increase the public health benefits, we are proposing to cover the following products under this proposed product standard: Cigarettes (other than noncombusted cigarettes, such as heated tobacco products (HTPs [3]) that meet the definition of a cigarette), cigarette tobacco, roll-your-own (RYO) tobacco, cigars (including little cigars, cigarillos, and large cigars but excluding premium cigars [4]), and pipe tobacco (other than waterpipe tobacco [5]). FDA requests comments, data, and research regarding this proposed scope.

FDA is proposing to exclude noncombusted cigarettes, such as HTPs that meet the definition of a cigarette in section 900(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 387(3)) from the scope of this proposed product standard (proposed § 1160.3 includes a definition of cigarette). Therefore, ''cigarettes'' in this proposed rule refers to combusted cigarettes, not HTPs. Based on FDA's experience with application review, certain noncombusted cigarettes produce fewer or lower levels of some toxicants than combusted cigarettes. FDA recognizes that tobacco products exist on a continuum of risk, with combusted cigarettes being the deadliest, and that certain non-combusted cigarettes pose less risk to individuals who use cigarettes or certain other combusted tobacco products or to population health than other products meeting the definition of a cigarette. Accordingly, FDA requests comments, data, and research regarding the proposal to exclude noncombusted cigarettes from the scope of this proposed rule, including any data that could justify otherwise.

FDA also proposes to exclude waterpipe tobacco from the proposed product standard because, unlike cigarette tobacco, pipe tobacco, RYO tobacco, and cigars (other than premium cigars), FDA believes there is little risk of switching under the proposed product standard. Waterpipes as currently marketed and used generally require substantial time for preparation and use (*i.e.,* an approximately 1-hour session with waterpipes compared to 5–7 minutes with cigarettes). In addition, they are generally large and unwieldy and thus ill-suited for mobile usage, such as while driving or walking. FDA requests comments, data, and research regarding the proposal to exclude waterpipe tobacco from the scope of this proposed rule, including any data that could justify otherwise.

FDA is also not including noncombusted non-cigarette tobacco products, such as electronic nicotine delivery systems (ENDS) (which include e-cigarettes) and smokeless tobacco products, in the scope of this proposed product standard. As discussed throughout this document, nicotine is the primary addictive constituent in

[2] For the purposes of this proposed rule, where describing expected transition behaviors, we also use the shorter phrase ''quit smoking'' to refer to stopping use of combusted cigarettes.

[3] *Tobacco products that meet the statutory or regulatory definition of a cigarette but are not combusted (do not exceed 350 °C) are categorized as ''heated tobacco products'' (HTPs) for purposes of FDA's premarket review. HTPs that meet the definition of a cigarette must be in compliance with the applicable statutory and regulatory requirements for cigarettes, unless otherwise noted in a marketing authorization order (Ref. 6).*

[4] See section III.B.3 of this document.

[5] Waterpipe tobacco (also known as hookah tobacco) is a type of tobacco product that produces smoke that people inhale when a hookah device is heated. Hookah tobacco (also known as waterpipe tobacco, maassel, shisha, narghile, or argileh) typically contains a mixture of tobacco, sweeteners, and flavoring. The hookah device (or waterpipe) used to smoke the hookah tobacco works by passing charcoal or electric heated air through the tobacco mixture and ultimately through a water-filled chamber (Ref. 7).

tobacco products, and it is the nicotine in such products that both creates and sustains addiction and ultimately leads to the significant adverse health effects caused by these products. While these effects raise concerns in the context of any tobacco product—none of which is without risk—at this time, FDA is focusing this proposed rule on nicotine levels in cigarettes and certain other combusted tobacco products because combusted tobacco products are responsible for the majority of death and disease due to tobacco use. FDA expects that, if this proposed rule is finalized as proposed, many people who smoke cigarettes will quit smoking, either by quitting all tobacco use or by completely switching to a noncombusted tobacco product. Those who switch completely to use of a noncombusted tobacco product may sustain their nicotine dependence but may significantly reduce their risk of tobacco-related death and disease because switching completely to a noncombusted tobacco product would reduce exposure to the chemical constituents created through combustion, which are currently the primary contributors of tobacco-related harm (Ref. 8). Importantly, this action would also help to prevent people who experiment with cigarettes and cigars (mainly youth) from moving beyond experimentation, developing an addiction to nicotine, and progressing to regular use of combusted tobacco products as a result of that addiction. We request comments, data, and research regarding the proposed scope of this rule.

For further discussion regarding considerations and request for comments on the proposed scope of this rule, see section IX.C of this document.

Proposed product standard for nicotine—FDA is proposing to make cigarettes and certain other combusted tobacco products minimally addictive or nonaddictive [6] by limiting the nicotine yield of these products. We propose to limit nicotine yield by setting a maximum nicotine content level of 0.70 milligrams (mg) of nicotine per gram of total tobacco in these tobacco products. For comparison, the average nicotine content in the top 100 cigarette brands for 2017 is 17.2 mg/g of total tobacco (Ref. 9). Nicotine yield is the amount of nicotine in smoke, in other words, the amount of nicotine to which a smoker potentially is exposed. While nicotine yield can be measured through machine-generated smoking methods (*e.g.,* International Organization for Standardization (ISO) machine smoking method, Canadian Intense (CI) smoking method, Federal Trade Commission (FTC) smoking method), it can vary due to a user's compensatory behaviors—*e.g.,* inhaling more deeply, taking larger puffs, and blocking cigarette features designed to reduce nicotine yield—such that users can increase the amount of nicotine yield compared to the machine-generated yield. In contrast, nicotine ''content,'' which refers to the amount of nicotine present in tobacco filler, is not affected by smoking behavior or cigarette design features. Reducing the nicotine content to the proposed 0.70 mg of nicotine per gram of total tobacco limit in the finished tobacco products subject to this proposed product standard places an absolute maximum limit on the amount of nicotine present in tobacco smoke available for intake by users of these products. There are many different tobacco product characteristics that can be manipulated to affect nicotine yield, one of which is nicotine content. Setting a limit on nicotine content and measuring that content is more effective in reducing yield (*i.e.,* the amount of nicotine the user is exposed to) than setting a limit based on a direct measurement of yield under standardized smoking-machine protocols because nicotine content cannot be affected by the compensatory behavior described above. Therefore, limiting nicotine yield through a maximum nicotine content level would better achieve the public health benefits that come from reducing the amount of the nicotine to which a user is exposed than would setting a limit based on a measurement of the maximum machine-measured yield of tobacco products. For further discussion, see section VII.A.

The proposed limit of 0.70 mg of nicotine per gram of total tobacco is based on FDA's analysis of studies regarding the likely effects of reducing nicotine, which shows that extended exposure to very low nicotine content (VLNC) combusted cigarettes is associated with reduced addiction potential, dependence levels, number of cigarettes smoked per day and increased quit attempts among people who currently smoke cigarettes, without increasing toxicant exposure, craving, withdrawal, or compensatory smoking. Throughout this preamble, ''VLNC cigarettes'' refers to combusted cigarettes that have been reported to contain ≤ 1.0 mg nicotine per gram of total tobacco, ''low nicotine content (LNC) cigarettes'' refers to cigarettes with > 1.0 mg and < 11.4 mg nicotine per gram of total tobacco, and ''normal nicotine content (NNC) cigarettes'' refers to cigarettes with ≥ 11.4 mg nicotine per gram of total tobacco.[7] FDA uses these acronyms in places where we have confirmed that the nicotine content of the cigarettes referenced meets these definitions. In documents that reference nicotine content in tobacco, but do not specify the levels of nicotine and therefore cannot be confirmed to meet these definitions, we have maintained the full description that best reflects what was used in the original document (*e.g.,* low nicotine content tobacco).

FDA is not seeking to require the reduction of nicotine yields in any tobacco product to zero, which would violate section 907(d)(3) of the FD&C Act (21 U.S.C. 387g(d)(3)). FDA requests comments, data, and research regarding this proposed maximum nicotine level.

Immediate nicotine reduction approach—FDA is proposing an immediate nicotine reduction (*i.e.,* single target) approach to reach the proposed maximum nicotine level (rather than a gradual reduction, or stepped-down, approach) to limit additional toxicant exposure. Based on studies involving VLNC cigarettes and other reduced nicotine content (RNC) cigarettes, we expect that there would be very little or no compensatory smoking (and, consequently, additional limited toxicant exposure) with an immediate reduction approach, as opposed to a gradual reduction approach which showed evidence of increased compensatory smoking. As such, an immediate reduction approach would increase the benefits of the proposed product standard. FDA also notes that this immediate nicotine reduction approach would reduce manufacturing costs for those products covered by the proposed standard because manufacturers would not have reason to formulate multiple products and then prepare and submit premarket review applications at each phase of a gradual reduction approach. We request comments, data, and information regarding the selection of an immediate reduction approach.

Analytical test method—To assist FDA in determining compliance with this rule, the proposed product standard would require manufacturers to analyze

[6] FDA is using the term ''nonaddictive'' throughout this preamble specifically in the context of the available data on very low nicotine content cigarettes. We acknowledge the highly addictive potential of nicotine itself depending upon the route of delivery. As discussed elsewhere in this preamble, questions remain with respect to the precise level of nicotine in cigarettes that might render them either minimally addictive or nonaddictive for specific individual members or segments of the population.

[7] The term VLNC should not be confused with the cigarette brand name ''VLN;'' ''VLN'' refers to cigarette products authorized for marketing by FDA in 2019. See *https://www.fda.gov/media/133633/download?attachment* and *https://www.fda.gov/media/133635/download?attachment.*

the nicotine levels of cigarettes and certain other combusted tobacco products covered by the rule using an analytical test method that has been validated in an analytical test laboratory. In addition, FDA is proposing to require product testing prior to commercial distribution in the United States to prevent nonconforming tobacco products from entering the stream of commerce and reaching consumers.

Sampling plan—The proposed product standard would require tobacco product manufacturers to design and implement a sampling plan that covers each batch of finished tobacco product [8] that they manufacture. This sampling plan would be based on a valid scientific rationale (such as representative sampling) to ensure that each product complies with the proposed product standard. This sampling plan would provide procedures for the manufacturer to select samples to demonstrate conformance to the proposed product standard requirement. The required procedures would help ensure that products that do not conform to the product standard are not sold or distributed to consumers.

Nonconforming tobacco product—The proposed product standard would require tobacco product manufacturers to establish procedures for the control and disposition of tobacco products that do not conform to the requirements of this rule. These procedures are necessary to help prevent the distribution of nonconforming tobacco products by ensuring that all potential nonconforming products are identified, investigated, and segregated and that appropriate disposition and followup are taken for products determined to be nonconforming. This proposed requirement would ensure that any reports of nonconforming products, whether as a result of manufacturer testing or otherwise, are examined and investigated and that appropriate measures are taken to ensure that nonconforming products are not distributed to consumers and to prevent future nonconformity.

Manufacturing code—Currently, there is no requirement for the use of a manufacturing code for tobacco products. However, the proposed regulation Requirements for Tobacco Product Manufacturing Practice (TPMP) (see *https://www.federalregister.gov/documents/2023/03/10/2023-04591/requirements-for-tobacco-product-manufacturing-practice*) includes a requirement for a manufacturing code, and this rulemaking's provision is modeled on the proposed TPMP provision. The proposed product standard would require the use of a manufacturing code to serve as a common identifier for production and distribution records. The purpose of the manufacturing code is to allow manufacturers and FDA to identify the production batch of a particular finished product that has been released for distribution. This information is intended to help determine the product's history (*e.g.,* batch production records) and assist manufacturers and FDA in the event of a nonconforming tobacco product investigation and any corrective actions to be taken by a manufacturer as a result of the investigation.

Recordkeeping requirements—To assist FDA in determining compliance with the rule and aid in nonconforming product investigations, the proposed product standard would require that manufacturers establish and maintain records regarding the results of testing conducted on each batch to determine conformance with the proposed standard. In addition, this proposed product standard would require that manufacturers maintain records of sampling plans and sampling procedures, records related to manufacturing controls, and all records related to its analytical test method validation. FDA also is proposing to require that it be possible to identify the production batch of a particular finished product that has been released for distribution.

Proposed effective date—FDA proposes that any final rule that may issue based on this proposed rule become effective 2 years after the date of publication of the final rule. Therefore, after the effective date no person could distribute, sell, or offer for sale or distribution within the United States finished tobacco products that are not in compliance with part 1160 (21 CFR part 1160). Prior to the effective date of any final rule that may issue based on this proposed rule, wholesalers, retailers, and related entities would be able to sell available stock of finished tobacco products were not in compliance with part 1160 while transitioning inventory in anticipation of the effective date of the final rule; however, they would not be permitted to sell off such stock after the effective date. FDA believes this approach would allow adequate time for developing any necessary changes in technology or inputs to comply with a finalized product standard. It also would provide sufficient time for tobacco product manufacturers to submit, and FDA to review, applications for new tobacco products that comply with the finalized product standard. Additionally, FDA believes that this approach would allow adequate time for making any changes to tobacco purchasing choices and curing methods, and for preparation or changes needed in facilities and processes. FDA requests comments and data on this proposed effective date. For further discussion regarding considerations and request for comments on the proposed effective date of this rule, see section XI of this document.

Given that any new tobacco products that comply with this product standard would be required to undergo premarket review, FDA is considering options for addressing any influx of applications.

C. Legal Authority

Section 907 of the FD&C Act authorizes FDA to adopt tobacco product standards, including product standards that include provisions for nicotine yields; for the reduction or elimination of other constituents (including smoke constituents) or harmful components; respecting the construction, components, ingredients, additives, constituents (including smoke constituents), and properties of tobacco products; for the testing of tobacco products; and for restricting the sale of tobacco products to the extent consistent with section 906 (21 U.S.C. 387f) (section 907(a)(3), (a)(4)(A)(i) to (iii), and (a)(4)(B)(i) to (ii) and (iv) to (v)). The FD&C Act also establishes FDA's authority to require tobacco product manufacturers to establish and maintain records in section 909 (21 U.S.C. 387i); authority related to adulterated and misbranded tobacco products in sections 902 and 903 (21 U.S.C. 387b and 387c); authority regarding premarket review of new tobacco products in section 910 (21 U.S.C. 387j); authority related to prohibited acts in section 301 (21 U.S.C. 331); and FDA's rulemaking and inspection authorities in sections 701 and 704 (21 U.S.C. 371 and 374).

D. Costs and Benefits

The main quantified benefits come from averted mortality and morbidity as a result of reduced prevalence for people who currently use combusted

[8] For the purpose of this document, the term ''finished tobacco product'' refers to those products subject to this proposed rule. FDA proposes to define a ''finished tobacco product'' to mean a tobacco product, including all components and parts, sealed in final packaging (*e.g.,* filters or filter tubes sold to consumers separately or as part of kits) or in the final form in which it is intended to be sold to consumers. For a discussion of products FDA proposes to include within the scope of this product standard, see sections IX.C and X.A.1 of this document.

tobacco products, and reduced mortality from reduced exposure to secondhand smoke among people. Unquantified benefits include medical cost savings, productivity loss savings, reduced exposure to thirdhand smoke, and environmental impacts. We expect this proposed rule, if finalized, to impose costs on industry to follow the product standard, on the broader economy to repurpose land, labor, and capital, on consumers impacted by the product standard, and on FDA to enforce this product standard. In addition to benefits and costs, this rule would cause transfers from the Federal Government and State governments in the form of tax revenue, from firms in the form of reduced revenue, and transfers between or within firms to cover shifts in user fee obligations.

The annualized monetized benefits over a 40-year time horizon far exceed the annualized monetized costs over the same time. We estimate that the annualized benefits over a 40-year time horizon would be $1.1 trillion at a 2 percent discount rate, with a low estimate of $0.27 trillion and a high estimate of $1.2 trillion. Over a 40-year time horizon, we estimate that the annualized costs would be $2.07 billion at a 2 percent discount rate, with a low estimate of $0.7 billion and a high estimate of $2.73 billion.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/ acronym	What it means
3–HPMA	3-hydroxypropyl mercapturic acid.
AI/AN	American Indians/Alaska Native.
ANPRM	Advance Notice of Proposed Rulemaking.
BAP	Benzo[a]pyrene.
CDC	Centers for Disease Control and Prevention.
CFR	Code of Federal Regulations.
CISNET	Cancer Intervention and Surveillance Modeling Network.
CO	Carbon monoxide.
COHb	Carboxyhemoglobin.
COPD	Chronic obstructive pulmonary disease.
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco.
CPD	Cigarettes per day.
CPS–I	Cancer Prevention Study I.
CPS–II	Cancer Prevention Study II.
CRM	CORESTA Recommended Method.
DSM	Diagnostic and Statistical Manual of Mental Disorders.
ENDS	Electronic nicotine delivery systems.
E.O.	Executive Order.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FDA	Food and Drug Administration.
FR	**Federal Register**.
FTCD	Fagerström Test for Cigarette Dependence.
FTND	Fagerström Test for Nicotine Dependence.
GC–MS	Gas chromatography-mass spectrometry.
HHS	U.S. Department of Health and Human Services.
HPHCs	Harmful and potentially harmful constituents.
HTP	Heated tobacco product.
IOM	Institute of Medicine.
LGBTQI+	Lesbian, gay, bisexual, transgender, queer, and intersex.
LNC	Low nicotine content.
mg	milligram.
MNWS	Minnesota Nicotine Withdrawal Scale.
MRI	Magnetic resonance imaging.
nAChR	Nicotinic acetylcholine receptor.
NATS	National Adult Tobacco Survey.
NCI	National Cancer Institute.
NDSS	Nicotine Dependence Syndrome Scale.
NHANES	National Health and Nutrition Examination Survey.
NHIS	National Health Interview Survey.
NHIS–LMF	National Health Interview Survey-Linked Mortality Files.
NIDA	National Institute on Drug Abuse.
NIH	National Institutes of Health.
NJATS	New Jersey Adult Tobacco Survey.
NLMS	National Longitudinal Mortality Study.
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.
NNC	Normal nicotine content.
NNN	N-Nitrosonornicotine.
NPRM	Notice of proposed rulemaking.
NRC	National Research Council.
NRT	Nicotine replacement therapy.
NSDUH	National Survey on Drug Use and Health.
NYTS	National Youth Tobacco Survey.
OOS	Out-of-specification.
PAH	Polycyclic aromatic hydrocarbon.
PATH	Population Assessment of Tobacco and Health.
PET	Position emission tomography.
PD	Product static ID number.
QALYs	Quality-adjusted life years.

Abbreviation/ acronym	What it means
QSU	Questionnaire of Smoking Urges.
RCT	Randomized clinical trial.
RNC	Reduced nicotine content.
RR	Relative risk.
RYO	Roll-your-own.
S–PMA	S-phenylmercapturic acid.
SE	Substantial Equivalence.
SES	Socioeconomic status.
STN	Submission tracking number.
TNE	Total nicotine equivalents.
TPSAC	Tobacco Products Scientific Advisory Committee.
TUS–CPS	Tobacco Use Supplement to the Current Population Survey.
U.S.	United States.
VLNC	Very low nicotine content.
WISDM	Wisconsin Inventory of Smoking Dependence Motives.
YRBS	Youth Risk Behavior Survey.

III. Background

A. Need for the Regulation

Cigarettes are responsible for the majority of tobacco-related death and disease in the United States. Each year, 480,000 people die prematurely from a smoking-attributable disease, putting a substantial burden on the U.S. healthcare system and causing massive economic losses to society (Ref. 1). In terms of a monetary measure of the impact of cigarette smoking on the public health, in 2018, cigarette smoking cost the United States more than $600 billion, including more than $240 billion in healthcare spending (Ref. 10), nearly $185 billion in lost productivity from smoking-related illnesses and health conditions (Ref. 10), nearly $180 billion in lost productivity from smoking-related premature death (Refs. 1 and 10), and $7 billion in lost productivity from premature death from secondhand smoke exposure (Refs. 1 and 11). The mortality rate among people who currently smoke cigarettes is 2 to 3 times as high as that among individuals who never smoked (Ref. 12). Nicotine, the primary addictive constituent in tobacco products, can be delivered through a variety of products along a continuum of risk, with combusted tobacco products at the most harmful end of this continuum. To protect youth and reduce tobacco-related disease and death, FDA utilizes a comprehensive approach to tobacco and nicotine regulation. Shortly after FDA announced its comprehensive approach in 2017 (*https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death*), the Agency began a public dialogue about lowering nicotine levels in combusted cigarettes to minimally addictive or nonaddictive levels through achievable product standards. On March 16, 2018, FDA issued a Nicotine ANPRM to seek input on the potential public health benefits and any possible adverse effects of regulating nicotine yield by lowering nicotine levels in cigarettes and invited comments on many issues associated with the development of a product standard to establish a maximum nicotine level (83 FR 11818). The Nicotine ANPRM also acknowledged that if FDA were to establish a nicotine tobacco product standard that covered only cigarettes, some number of people who smoke cigarettes could migrate to other similar combusted tobacco products to maintain their nicotine dependence (or engage in dual use with other combusted tobacco products), potentially reducing the positive public health impact of such a rule. FDA sought comments on whether the standard therefore should cover other combusted tobacco products. Based on FDA's scientific knowledge, extensive research regarding VLNC cigarettes, and comments submitted in response to this Nicotine ANPRM, FDA is proposing a tobacco product standard that would regulate nicotine yield by establishing a maximum nicotine level in cigarettes and certain other combusted tobacco products.

As the U.S. District Court for the District of Columbia recognized in *United States* v. *Philip Morris USA, Inc. et al.,* 449 F.Supp.2d 1 (D.D.C. 2006), *aff'd in relevant part,* 566 F.3d 1095 (D.C. Cir. 2009), the tobacco industry has long known that nicotine creates and sustains addiction, and the industry is dependent on maintaining this addiction. *Id.* at 307. The court noted how cigarette companies have engaged in extensive research to understand how nicotine operates within the human body and then designed their cigarettes to precisely control nicotine delivery and provide nicotine doses to create and sustain addiction. *Id.* at 307–309. Moreover, the court confirmed that industry documents supported the conclusion that these companies ''knew early on in their research that if a cigarette did not deliver a certain amount of nicotine, new smokers would not become addicted, and 'confirmed' smokers would be able to quit.'' *Id.* at 219. In fact, the tobacco industry has had programs in place since the 1960s to obtain ''any level of nicotine desired'' (Ref. 2). These companies sought to identify the ''optimum'' dose needed to ''satisfy'' people who smoke cigarettes and, thereby, assure their continued smoking. *Philip Morris* 449 F.Supp.2d at 309–11. This proposed product standard would seek to set a maximum nicotine level requirement such that cigarettes and certain other combusted tobacco products would no longer be able to create and sustain this addiction among people who smoke cigarettes.

The proposed product standard would limit the addictiveness of the most toxic and widely used products, which would have significant benefits for all age groups. Adults who use tobacco products, most of whom want to quit, are often unsuccessful because of the highly addictive nature of these products (Ref. 13). Researchers estimate that each year, only between 5.4 and 5.6 percent of adults who use cigarettes successfully quit for good (Ref. 14). Similar analysis of 2022 NHIS data indicates that only 8.8 percent of adults who formerly smoked cigarettes had quit smoking cigarettes in the past year (Ref. 4). Lowering nicotine to minimally addictive or nonaddictive levels would improve their ability to successfully quit using the products within the proposed scope of this rule. It also would prevent people who experiment with cigarettes and non-premium cigars, including youth, from moving beyond experimentation, developing an

addiction to nicotine, and progressing to regular use as a result of that addiction. Furthermore, it is well-established that secondhand tobacco smoke causes premature death and disease in children and in adults who do not smoke (Ref. 15 at p.11). It is estimated that exposure to secondhand smoke caused 41,280 deaths per year in the United States from 2005 to 2009 (Ref. 1 at Table 12.4). This increased cessation and reduced initiation, in turn, would result in a significant decrease in harms from the products to people who currently or would otherwise use cigarettes and certain other combusted tobacco products, as well as harms to people who do not use the products, including harms caused by secondhand smoke to both adults and children, harmful perinatal effects due to parental tobacco use, and fires.

Preventing people who do not smoke cigarettes, particularly youth, from regularly smoking cigarettes due to nicotine addiction would allow them to avoid the severe adverse health consequences of smoking and would result in significant public health benefits. Without changes like those proposed here, an estimated 3.66 million youth under the age of 18 who were alive in 2018—and 2.54 million youth who are alive in 2024, accounting for the projected continued decline in smoking prevalence—will die prematurely later in life from a smoking-related disease (Ref. 16). As a result of the proposed product standard, many youth and young adults would not be subjected to the impacts of nicotine addiction from cigarette smoking and certain other combusted tobacco products (which have a significantly stronger effect on youth due, in part, to their developing brains, as described in sections IV.B and IV.C of this document), nor would they suffer from the adverse health effects and mortality that these products cause.

Nicotine is powerfully addictive, and youth and young adults [9] are particularly susceptible to developing a nicotine addiction. Multiple Surgeon General's Reports on smoking and health have noted that almost 90 percent of adults who regularly smoke cigarettes initiated smoking by age 18, and 98 percent initiated smoking by age 26, which is notable given that 25 is the approximate age at which the brain has completed development (Refs. 1, 17 to 19). The developing brain is more vulnerable to nicotine dependence than the adult brain is, and the earlier an individual begins smoking the less likely they are to quit (Ref. 20). 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 (Ref. 21). It is clear that many youth who smoke cigarettes want to quit but have difficulty doing so. An analysis of data from the 2015 Youth Risk Behavior Survey (YRBS) looking at youth cigarette quit attempts found that 45.4 percent of high school students currently smoking cigarettes had sought to quit in the previous year (Ref. 22); 2020 National Youth Tobacco Survey (NYTS) data were congruent, indicating that 68.1 percent of middle and high school students who smoke cigarettes had sought to quit in the previous year (Ref. 23).

More than half (52.2 percent) of U.S. middle and high school students who use cigarettes, cigars, smokeless tobacco—including those with low levels of use—report experiencing at least one symptom of nicotine dependence (Ref. 24). Notably, 12.7 percent of youth using tobacco products 1 to 2 days per month and 21.2 percent of youth using tobacco products 3 to 5 days per month reported sometimes/often/always feeling irritable or restless when not using tobacco products for a while, and 15.6 percent of youth using tobacco products 1 to 2 days per month and 32.0 percent of youth using tobacco products 3 to 5 days per month reported having strong cravings for a tobacco product during the past 30 days (Ref. 24). Additionally, other researchers analyzing data from the 2021 NYTS found that a sizeable proportion of high school students using tobacco products in the past 30 days report symptoms of nicotine dependence, including 27.2 percent reporting a strong craving for tobacco use and 19.5 percent reporting wanting to first use tobacco products within 30 minutes of waking (Refs. 25 and 26). While prevalence rates of youth use of noncombusted tobacco products (*e.g.,* ENDS) in recent years have exceeded those of cigarettes and other combusted tobacco products (Refs. 25 and 26), FDA expects that this proposed product standard would have significant benefits for youth by reducing the risk that youth who experiment with cigarettes and certain other combusted tobacco products, or who may consider using these products as an alternative to noncombusted tobacco products, would progress to regular use of these products as a result of nicotine dependence.

The adolescent and young adult brain is more vulnerable to developing nicotine dependence than the adult brain is; data indicate that nicotine has stronger rewarding effects in adolescents than in adults (Ref. 17). Adolescents who use tobacco and initiated 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. 24). Additionally, the earlier that individuals begin smoking—and therefore the greater amount of time that individuals experience nicotine dependence—the less likely they are to successfully quit (Ref. 27). Evidence indicates that exposure to substances such as nicotine can disrupt brain development and have long-term consequences for executive cognitive functioning (such as decreased attention and working memory and increased impulsivity) and for the risk of developing a substance use disorder and various mental health problems (particularly affective disorders such as anxiety and depression) as an adult (Ref. 27). Furthermore, the 2010 Surgeon General's report noted that adolescents report symptoms of dependence even at low levels of cigarette smoking, and thus may be particularly vulnerable to addiction (Ref. 28). FDA expects that this proposed product standard, therefore, would have significant benefits for youth and young adults by reducing the risk that those who experiment with cigarettes and certain other combusted tobacco products would progress to regular use as a result of nicotine dependence.

Research studies involving VLNC cigarettes—defined previously in this document as cigarettes containing up to 1.0 mg of nicotine per gram of total tobacco—demonstrate that setting the maximum nicotine level we are proposing here, would lead to a reduction in nicotine dependence, which would help people who smoke cigarettes quit smoking. In studies that immediately reduced the nicotine content of cigarettes by switching participants from usual brand cigarettes to LNC or VLNC cigarettes, dependence decreased in people who smoked cigarettes who were not interested in quitting compared to those who smoked normal nicotine content (NNC) or usual brand cigarettes for 6 weeks (Ref. 29), 10 weeks (Ref. 30), or 12 weeks (Ref. 31). In smoking cessation studies in which participants endorsed wanting to quit, VLNC cigarettes were also associated

[9] Though age ranges for youth and young adults vary across studies, in general, ''youth'' or ''adolescent'' encompasses those ages 11–17, while those who are ages 18–25 are considered ''young adults'' (even though, developmentally, the period between 18–20 years of age is often labeled late adolescence); those ages 26 and or older are considered ''adults'' (Ref. 17).

with reductions in nicotine dependence over time (Refs. 32 to 35).

FDA is issuing this proposal because the tobacco products subject to this proposed product standard remain addictive due to the nicotine yield they offer users and because combusted tobacco products are responsible for the majority of tobacco-related death and disease (see section IV.D of this document for a discussion regarding the serious negative health effects of smoking cigarettes and other combusted tobacco products). Cigarettes have been precisely designed to create and maintain addiction among people who smoke. *United States* v. *Philip Morris USA, Inc. et al.,* 449 F.Supp.2d 1, 307 (D.D.C. 2006). To protect the public health, particularly youth, FDA is proposing this standard, in part, to ensure that people who smoke these products would be less likely to: (1) initiate regular use; (2) become addicted to these products; and (3) suffer from the many diseases and debilitating effects, including death, caused by combusted tobacco product use.

Similarly, FDA expects that the proposed product standard would have significant benefits for adults who use combusted tobacco products, most of whom want to quit but are often unsuccessful because of the highly addictive nature of these products (Ref. 13). Data from the 2022 National Health Interview Survey (NHIS) and 2018–2019 Tobacco Use Supplement to the Current Population Survey (TUS–CPS) indicate that 67.7 and 76.6 percent, respectively, of adults who smoke cigarettes wanted to quit (Ref. 36), while 2022 NHIS data (Ref. 4) and 2018–2019 TUS–CPS data (Ref. 36) show that 53.3 and 51.3 percent, respectively, of adults who smoke cigarettes in the United States actually made a quit attempt within the past year. However, analyses of NHIS and TUS–CPS data for these years indicate that only 8.8 and 7.5 percent of adults had successfully quit smoking cigarettes, respectively (Refs. 4 and 36). Adults who smoke cigarettes may make 30 or more quit attempts before succeeding (Ref. 37). FDA expects that decreasing the nicotine yield of cigarettes and certain other combusted tobacco products covered by this rule, by reducing nicotine content, so that they are minimally addictive or nonaddictive would likely help people who smoke reduce their dependence on combusted tobacco products, thereby making it easier for them to quit smoking. As discussed throughout this document, FDA also expects that decreasing the nicotine content in these products, and thus the nicotine yield offered to users, would prevent people who experiment with cigarettes and cigars (mainly youth) from moving beyond experimentation, developing an addiction to nicotine, and progressing to regular use as a result of that addiction.

Although many factors contribute to an individual's initial experimentation with tobacco products, the addictive nature of tobacco is the key reason people progress to regular use, and scientists agree that it is the presence of nicotine that causes addiction and sustains a person's tobacco use (Refs. 1 HHS at p. 113 and 28). While nicotine is the primary addictive chemical in tobacco, sensorimotor stimuli (*e.g.,* smell/taste of smoke; airway sensations; holding the cigarette) repeatedly occur during smoking (Ref. 38). These stimuli often act as secondary or conditioned reinforcers that contribute to the cycle of nicotine dependence by motivating and maintaining smoking behavior (Ref. 38). Once people who use tobacco become addicted to nicotine, they require nicotine to avoid withdrawal symptoms. In the process of obtaining their nicotine, people who use 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 (Ref. 28). Because of their nicotine addiction, many people who smoke cigarettes struggle to stop using these toxic tobacco products despite their stated desire to quit (Ref. 28).

An advisory report from the World Health Organization notes that the ultimate health benefits of a nicotine reduction strategy, like the one FDA is proposing here, would require that the standard cover other combusted tobacco products—not just cigarettes (Ref. 39). In alignment with this recommendation from the World Health Organization, this proposed rule would cover combusted cigarettes and certain other combusted tobacco products (*i.e.,* cigarette tobacco, RYO tobacco, cigars other than premium cigars, pipe tobacco). The World Health Organization report also noted that such a strategy should be accompanied by the provision of cessation treatments to help people quit, including behavioral support and nicotine replacement therapy (NRT) or other medications (Ref. 39). FDA remains committed to facilitating the development and use of therapeutic nicotine products for tobacco product cessation and increased availability of services alongside enhanced outreach efforts to support tobacco use cessation. For example, FDA's Nicotine Steering Committee, which helps to develop and implement nicotine policy and regulation for the Agency, held a 21 CFR part 15 hearing in early 2018 on the Agency's approach to evaluating the safety and efficacy of NRT products, including how they should be used and labeled (82 FR 56759 (November 30, 2017)). Also, in May 2023, FDA's Center for Drug Evaluation and Research announced the availability of a final guidance for industry entitled ''Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products,'' which provides guidance to assist sponsors in the clinical development of NRT drug products, including but not limited to those intended for smoking cessation and related chronic conditions (88 FR 26559, May 1, 2023; see *https://www.fda.gov/media/167599/download*). Additionally, as described further below, the Agency is contributing to a comprehensive effort coordinated by the U.S. Department of Health and Human Services (HHS or the Department) to support tobacco use cessation.

Rendering cigarettes and certain other combusted tobacco products minimally addictive or nonaddictive through a nicotine product standard would address the principal reason that people who smoke cigarettes have difficulty quitting smoking. If this proposed product standard is finalized, people who use cigarettes and other combusted tobacco products covered by this rule would be unable to obtain enough nicotine from those products to sustain addiction no matter how they smoked the products (*e.g.,* more frequent smoking, intensive puffing) (Refs. 32, 40, and 41), facilitating people who currently smoke cigarettes to make more successful quit attempts.[10] At the same time, combusted tobacco products at minimally addictive or nonaddictive levels of nicotine would remain on the market for those who currently smoke and would like to continue to do so.

FDA expects that, if this proposed rule is finalized and a nicotine product standard for cigarettes and certain other combusted tobacco products is in place, many people who smoke cigarettes will either quit all tobacco-product use or switch to a noncombusted tobacco product. Those who switch completely to use of a noncombusted tobacco product may sustain their nicotine dependence but may significantly

[10] As stated throughout this preamble, in the event that a nicotine product standard addresses only cigarettes, FDA expects that, to maintain their nicotine dependence, some number of people who are addicted to cigarettes would likely migrate to other similar combusted tobacco products (or engage in dual use with such products) after the product standard goes into effect, reducing the benefits of the standard.

reduce their risk of tobacco-related death and disease because switching completely to a noncombusted tobacco product would reduce exposure to the chemical constituents created through combustion, which are the primary contributors of tobacco-related harm (Ref. 8).

The benefits of this rule have been determined without taking into consideration the impact of any smoking cessation services that may be coordinated by HHS, and are expected to be significant. Also, FDA expects that unassisted cessation attempts, *i.e.,* those made by people who smoke without help, may be more successful in an environment in which the product being quit is no longer addictive as compared to historic quitting success rates where it has been easy to relapse to the same highly addictive product. Nevertheless, FDA recognizes that increasing and improving cessation resources, particularly in communities where access to cessation resources have been historically lacking, may provide an opportunity to further increase the expected benefits of this proposed product standard and to enhance the degree to which such benefits are experienced by people in populations that are disproportionately impacted by combusted tobacco use. Accordingly, FDA is contributing to a comprehensive effort being coordinated by HHS to support and accelerate cessation of combusted tobacco products.[11] With input from subject matter experts from across HHS Operating Divisions, the Department has finalized the ''HHS Framework To Support and Accelerate Smoking Cessation'' (Framework). The Framework aims to accelerate smoking cessation and reduce smoking-related disparities by building on current activities and collaborations across the Department. The Framework vision is to ensure that every person in America has access to comprehensive, evidence-based cessation treatment and can benefit from HHS cessation supports, programs, and policies. Specific Framework goals are to: (1) reduce smoking and cessation-related disparities; (2) increase awareness and knowledge related to smoking and cessation; (3) strengthen, expand, and sustain cessation services and supports; (4) increase access to and coverage of comprehensive, evidence-based cessation treatment; (5) advance, expand, and sustain surveillance and strengthen performance measurement and evaluation; and (6) promote ongoing and innovative research to support and accelerate smoking cessation (*https://www.hhs.gov/about/news/2024/03/08/hhs-announces-new-smoking-cessation-framework-support-quitting.html*). With increased availability and accessibility of services, more people who smoke may be motivated to take advantage of cessation resources, whether they smoke cigarettes or other combusted tobacco products. Additionally, FDA has numerous processes and tools at its disposal to communicate directly with consumers, including communities that are underserved by cessation services and/or are disproportionately impacted by tobacco use, and will continue to evaluate the need for additional public outreach, including targeted education initiatives, in support of this proposed rule. However, the Agency does not have evidence to suggest that such an effort is necessary at this time in order to experience the public health benefits of this proposed product standard.

For the reasons stated here and throughout this document, FDA is proposing this tobacco product standard to: (1) reduce the risk of progression to regular use and nicotine dependence for those who experiment with such tobacco products, especially youth and (2) make it easier for people who are addicted to cigarettes and certain other combusted tobacco products and who are interested in quitting to quit by reducing the nicotine in these products to minimally addictive or nonaddictive levels. FDA expects that this proposed product standard would significantly reduce the morbidity and mortality caused by smoking. Based on FDA's population health model, by the year 2100, in the United States, approximately 48 million youth and young adults who would have otherwise initiated smoking would not start as a result of the proposed product standard. The model also projects that more than 12.9 million additional people who smoke cigarettes would quit smoking (including those who switch to noncombusted tobacco products) 1 year after implementation of the proposed product standard, increasing to 19.5 million additional people who formerly smoked cigarettes within 5 years of implementation. Section XII discusses that the main quantified benefits come from averted mortality and morbidity, as a result of tobacco use transitions, including switching. In terms of mortality benefits, the model considers a higher risk for people who switch to noncombusted products compared to those who quit tobacco product use entirely. Specifically, the model assumes that the risk for people who switch to noncombusted product use is 8 percent higher than the risk for those who quit tobacco use entirely. Details of this approach can be found in the FDA's modeling document (Ref. 42). In addition, the model estimates that, by the year 2060, in the United States, this proposed product standard would result in 1.8 million tobacco-related deaths averted, rising to 4.3 million deaths averted by the end of the century (Ref. 42). The reduction in premature deaths attributable to the proposed product standard would result in 19.6 million life years gained by 2060 and 76.4 million life years gained by 2100 (see section VIII.A of this document for further discussion of the model) (Ref. 42).

B. Relevant Regulatory History

In its implementation of the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Pub. L. 111–31) since its passage in 2009, FDA has engaged in close study and careful consideration of the scientific evidence and complex policy issues related to nicotine in cigarettes and other combusted tobacco products. FDA issued an ANPRM to solicit data and information for consideration in developing a tobacco product standard to regulate nicotine yield by setting the maximum nicotine level for cigarettes, conducted a robust scientific assessment related to a nicotine product standard for combusted tobacco products, developed a population health model to assess the potential public health impacts of such a product standard, and sponsored research on a variety of nicotine-related topics through contracts and interagency agreements with Federal partners, including the National Institutes of Health (NIH).[12] FDA has considered the comments and information received in response to the ANPRM, scientific assessment, and population health model in developing this proposed rule. Please see the remainder of this section for further discussion.

1. ANPRM

In July 2017, FDA announced a comprehensive approach to tobacco and nicotine regulation to protect youth and reduce tobacco-related disease and death (Ref. 43). As part of the public dialogue on the comprehensive approach, in March 2018, FDA issued three ANPRMs related to the regulation

[11] See, for *e.g., https://www.fda.gov/tobacco-products/ctp-newsroom/fda-and-nih-joint-public-meeting-advancing-smoking-cessation-priorities-registration-open?utm_campaign=ctp-research&utm_content=landingpage&utm_medium=email&utm_source=govdelivery&utm_term=stratcomms.*

[12] Information on specific projects supported by FDA is available at *https://www.fda.gov/tobacco-products/tobacco-science-research/research.*

of nicotine in combusted cigarettes (83 FR 11818), flavors (including menthol) in tobacco products (83 FR 12294, March 21, 2018) (Flavors ANPRM), and premium cigars (83 FR 12901, March 26, 2018). In addition, FDA announced the availability of a draft concept paper entitled ''Illicit Trade in Tobacco Products After Implementation of a Food and Drug Administration Product Standard,'' and sought public comment (83 FR 11754, March 16, 2018). This paper analyzes the potential for illicit trade markets to develop in response to a tobacco product standard (Ref. 44).

The Nicotine ANPRM requested data and information for consideration in developing a tobacco product standard to set a maximum nicotine level for cigarettes to make them minimally addictive or nonaddictive. Specifically, FDA sought comments, evidence, and other information regarding whether a potential tobacco product standard should cover tobacco products other than cigarettes (*e.g.,* cigarette tobacco, RYO tobacco, some or all cigars, pipe tobacco, waterpipe tobacco); what maximum level of nicotine would be appropriate for the protection of the public health, in light of scientific evidence about the addictive properties of nicotine in cigarettes; whether such a standard should propose either a single target (*i.e.,* an immediate reduction, where the nicotine is reduced all at once) or a stepped-down approach (*i.e.,* a gradual reduction, where the nicotine is reduced gradually over time) to reach the desired maximum nicotine level; whether such a product standard should specify a method for manufacturers to use to detect the level of nicotine in their products; the technical feasibility of current as well as more recent, novel nicotine reduction techniques; and the proper timeframe for implementation of a possible nicotine tobacco product standard to allow adequate time for industry to comply. The Nicotine ANPRM also requested comment on possible negative effects that could diminish the population health benefits expected as a result of a nicotine product standard, such as continued combusted tobacco product use, where people who currently use 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); the potential for increased harm due to continued VLNC cigarette smoking with altered smoking behaviors (*e.g.,* increase in number of cigarettes smoked, increased depth of inhalation); people seeking to add nicotine in liquid or other form to their combusted tobacco product; and whether illicit trade could occur as a result of a nicotine product standard and how that could impact public health. Finally, FDA also sought comments, data, research results, and other information regarding economic impacts of a potential nicotine tobacco product standard.

FDA received over 7,700 comments on the Nicotine ANPRM, with approximately 6,700 of those comments submitted as part of 20 different organized campaigns. The key ANPRM areas of comments are covered in the relevant sections in this document and include the possible scope of products covered by the rule (section IX.C), technical achievability (section VII.E), illicit trade (section IX.D), and implementation/effective date (section XI). Some of the issues raised in the comments to the ANPRM are highlighted below.

Comments generally in support of setting a maximum nicotine level in cigarettes stated that a nicotine product standard would be appropriate for the protection of the public health. In particular, many comments argued that reducing the nicotine content in cigarettes to minimally addictive or nonaddictive levels would be appropriate for the following reasons: (1) reduced nicotine content in cigarettes will contribute to smoking cessation, as well as decreased initiation and addiction by people newly using cigarettes and certain other combusted tobacco products and youth and (2) such increased cessation and decreased initiation will reduce the instances of preventable deaths and other negative health effects caused by smoking. Some comments also urged FDA to issue a nicotine product standard as part of a comprehensive package of tobacco regulatory measures, including increasing consumer access to reduced risk products, regulating flavors in tobacco products, taking action as soon as possible, fully reviewing premarket applications for new tobacco products, and making effective smoking cessation treatments and ongoing cessation support accessible and affordable to people who smoke cigarettes.

FDA received many comments expressing concern about the effect of nicotine on the adolescent brain and its role in addicting those who experiment with tobacco products, particularly youth and young adults, leading them to progress to regular use. Some comments recommended extending the scope of a nicotine product standard to noncombusted tobacco products (*e.g.,* smokeless, ENDS) to prevent migration to such products, particularly among youth; a significant number of comments urged FDA to extend the scope of a nicotine product standard to combusted tobacco products other than cigarettes. Citing national survey data trends and various recent studies, numerous comments—including those from public health associations, government agencies, and advocacy groups—asserted that including all combusted tobacco products, not only cigarettes, would prevent potential youth initiation of, migration to, and dual use with other combusted products with higher nicotine content that may be harmful to health, thus aligning with the public health goals of a nicotine product standard. Additionally, citing studies relating to tobacco use patterns by young people, a joint submission from several nicotine and tobacco researchers stated that adolescents who use tobacco are particularly prone to dual and multiple tobacco product use; therefore, the potential for adolescents to shift to other nicotine-containing tobacco products underscores the need for a nicotine reduction policy to cover all combusted tobacco products. The joint submission comment further stated that if the scope of a nicotine product standard only covered combusted cigarettes, there is evidence from adult studies that cigars—and in particular little cigars—would be an attractive substitute for full nicotine content combusted cigarettes. These researchers noted, if the scope of a proposed nicotine product standard included combusted cigarettes and other combusted products, it would increase the likelihood that people who use combusted cigarettes, including youth and young adults, who migrate to other nicotine-containing products (rather than quit), would transition to noncombusted products, thereby increasing the health benefits of the policy.

FDA also received comments from individuals, advocacy groups, and members of the tobacco industry generally opposing efforts to reduce nicotine levels in cigarettes to minimally addictive or nonaddictive levels. These comments generally stated that such a regulation would stifle free enterprise or would negatively limit consumer freedom of choice and that the regulation would result in a de facto ban on cigarettes that would have a devastating impact on tobacco farming, as well as the manufacturing, distribution, and retail sectors. Some comments discussed the technical feasibility of achieving lower nicotine

levels. Some comments opposed to a nicotine product standard stated that there is not enough scientific research to support reducing nicotine in cigarettes. Other comments argued that FDA should instead focus on giving adults who smoke cigarettes access to a wider choice of less harmful tobacco products and truthful information about the benefits of switching to those products, as well as focus resources on a plan to reduce harm through proven strategies to prevent initiation and encourage cessation.

FDA has reviewed and closely considered the comments to the Nicotine ANPRM, as well as additional evidence and information not available at the time of the Nicotine ANPRM, in developing this proposed rule.

2. Scientific Review

As the body of evidence has continued to grow, FDA undertook a robust systematic review of the scientific evidence regarding the likely effects of reducing nicotine in combusted tobacco products. This review, entitled ''The Science of a Nicotine Standard for Combusted Tobacco Products'' (Ref. 45), covers peer-reviewed, publicly available literature and focuses on the likely effects of reducing nicotine in combusted tobacco products. This scientific assessment has been peer reviewed by independent external experts. Taking into consideration comments from this peer review (Ref. 46), FDA revised the scientific assessment, and the final peer-reviewed document is available in the docket for this proposed rule (Ref. 45). Additionally, this final peer-reviewed document and other related documents such as FDA's response to the peer review comments can be found at *https://www.fda.gov/science-research/peer-review-scientific-information-and-assessments/completed-peer-reviews.*

FDA's peer reviewed scientific assessment examined the effects of reducing the level of nicotine in combusted tobacco products on use behavior, dependence, and toxicant exposure, as well as the knowledge, beliefs, and perceptions around nicotine and VLNC cigarettes. This scientific review found that the totality of the evidence supports that extended exposure to combusted cigarettes containing VLNC tobacco filler is associated with reduced addiction potential, dependence levels, and number of cigarettes smoked per day, and increased quit attempts among people who currently smoke cigarettes, without evidence of increased toxicant exposure, craving, withdrawal, or compensatory smoking. The review also determined that if FDA were to establish a nicotine product standard that covered only cigarettes, a portion of people who are currently addicted to cigarettes would likely migrate to other, similar combusted tobacco products to maintain their nicotine dependence (or engage in dual use without substantially reducing their combusted tobacco product use), thereby reducing the positive public health impact of such a rule. Based on FDA's review of the literature on combusted tobacco products, including cigarettes, cigarette tobacco, RYO tobacco, cigars, and pipe tobacco, the final scientific assessment concluded that use of any of these combusted products is sufficient to create or sustain nicotine dependence and would therefore continue to expose people who use these products to toxicants. Further, FDA's scientific assessment concluded that the establishment of a maximum nicotine level in combusted tobacco products that would render them minimally addictive or nonaddictive could increase the likelihood of successful quit attempts and help prevent people who experiment with cigarettes and cigars (mainly youth) from progressing to regular use, thereby significantly reducing the morbidity and mortality caused by smoking. FDA has considered the scientific assessment conclusions in the development of this proposed product standard.

In addition, to assess the potential public health impacts of a nicotine product standard, FDA developed a population health model using inputs derived from available empirical evidence and expert opinion to estimate the impact of changes in tobacco product initiation, cessation, switching, and dual use on tobacco use prevalence, morbidity, and mortality in the United States. Details of this modeling approach have been previously published in two peer-reviewed publications (Refs. 47 and 48), which describe the overall model in terms of the inputs, transition behaviors, and outputs that it contains, along with results from simulation studies. In preparation for this proposed product standard, FDA updated a previously-published model (Ref. 47), which describes the impact of a potential product standard that limits the level of nicotine in cigarettes, RYO tobacco, non-premium cigars, and pipe tobacco so that they are minimally addictive or nonaddictive. In this updated modeling document, entitled ''Methodological Approach to Modeling the Potential Impact of a Nicotine Product Standard on Tobacco Use, Morbidity, and Mortality in the U.S.'' (Ref. 42), we estimated the potential impacts of a nicotine product standard by modeling a baseline scenario of use of cigarettes and noncombusted tobacco products including smokeless tobacco, e-cigarettes, and HTPs. These product classes (cigarettes and noncombusted products) were selected because of the magnitude of population health effects from cigarette smoking and the likelihood of product switching to noncombusted products, especially e-cigarettes. Estimates of changes in mortality from other exposures including non-premium cigar and pipe tobacco use are not produced directly by the model but are derived from model outputs instead. We then compared the baseline scenario to a product standard scenario characterized by the introduction of a potential nicotine product standard that would apply to cigarettes, cigarette tobacco, RYO tobacco, non-premium cigars, and pipe tobacco. FDA's modeling framework and methodological approach and the associated data inputs and assumptions have been peer reviewed by independent external experts. Taking into consideration comments from this peer review (Ref. 49), FDA revised the modeling document, and the final modeling document is available in the docket for this proposed product standard (Ref. 42). FDA's modeling work informed the development of this proposed product standard. Additionally, the modeling document, model code, and inputs are publicly available at *https://www.fda.gov/science-research/peer-review-scientific-information-and-assessments/completed-peer-reviews.* Further discussion of FDA's estimates of the public health impact of this proposed product standard can be found in section VIII of this document.

3. Premium Cigars

On August 9, 2023, the U.S. District Court for the District of Columbia issued an order vacating FDA's rule deeming tobacco products to be subject to FDA's tobacco product authorities ''insofar as it applies to premium cigars.'' [13] *Cigar*

[13] For purposes of its ruling, the court specified that a premium cigar is a cigar that: (1) is wrapped in whole tobacco leaf; (2) contains a 100 percent leaf tobacco binder; (3) contains at least 50 percent (of the filler by weight) long filler tobacco (*i.e.,* whole tobacco leaves that run the length of the cigar); (4) is handmade or hand rolled (*i.e.,* no machinery was used apart from simple tools, such as scissors to cut the tobacco prior to rolling); (5) has no filter, nontobacco tip, or nontobacco mouthpiece; (6) does not have a characterizing flavor other than tobacco; (7) contains only tobacco,

Continued

Ass'n of Am. v. *FDA,* No. 16–cv–01460, 2023 WL 5094869 (D.D.C. Aug. 9, 2023), *appeal docketed,* No. 23–5220 (D.C. Cir. argued Sept. 13, 2024). The government has appealed this decision. When the deemed status of premium cigars is resolved, FDA will consider any impacts with respect to this proposed rule and take additional steps as warranted, including for example, by reopening the comment period and/or issuing a supplemental notice of proposed rulemaking. References to premium cigars in this document serve merely to clarify the current proposed scope of products covered, evaluate the scientific evidence related to non-premium cigars, and describe FDA's approach to modeling the projected public health impacts of this proposed standard.

C. Legal Authority

1. Product Standard Authority

The Tobacco Control Act was enacted on June 22, 2009, amending the FD&C Act and providing FDA with the authority to regulate tobacco products. Section 901 of the FD&C Act (21 U.S.C. 387a) granted FDA the 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 youth. The Tobacco Control Act also gave the Agency authority to conduct rulemaking to ''deem'' any other tobacco products subject to chapter IX of the FD&C Act (21 U.S.C. 387 to 387t). In 2016, FDA issued a final rule deeming products meeting the statutory definition of ''tobacco product'' (including cigars and pipe tobacco), except accessories of the newly deemed products, to be subject to chapter IX of the FD&C Act, as amended by the Tobacco Control Act (81 FR 28974) (deeming final rule).

Among the tobacco product authorities provided to FDA is the authority to adopt tobacco product standards where FDA determines that such standard is appropriate for the protection of the public health (section 907(a)(3)(A) of the FD&C Act). To establish a tobacco product standard, section 907(a)(3)(A) and (B) of the FD&C Act requires that FDA find that the standard is appropriate for the protection of the public health, taking into consideration scientific evidence concerning:

- The risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard;
- The increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- The increased or decreased likelihood that those who do not use tobacco products will start using such products.

2. Authority To Establish a Maximum Nicotine Level and Related Provisions

Section 907 of the FD&C Act authorizes FDA to adopt tobacco product standards that are appropriate for the protection of the public health, including expressly authorizing FDA to adopt product standards with provisions for nicotine yields; for the reduction or elimination of other constituents (including smoke constituents) or harmful components; and respecting the construction, components, ingredients, additives, constituents (including smoke constituents), and properties of tobacco products (section 907(a)(3), (a)(4)(A)(i) to (iii), and (a)(4)(B)(i)). This includes the authority to issue a new product standard to establish a maximum level of nicotine in tobacco products.

FDA is proposing to limit nicotine yield by setting a maximum nicotine content level for finished cigarettes and certain other finished combusted tobacco products not to exceed 0.70 mg of nicotine per gram of total tobacco. FDA is not seeking to require the reduction of nicotine yields in any tobacco product to zero, which is prohibited under section 907(d)(3) of the FD&C Act. To ensure that tobacco products subject to the product standard comply with the proposed maximum nicotine level, FDA also is including provisions that would require manufacturers to test their products using an analytical test method for conformance with the maximum nicotine level pursuant to section 907(a)(4)(B)(ii) and (iv) of the FD&C Act.

3. Sale and Distribution Restrictions

Section 907(a)(4)(B)(v) of the FD&C Act states that product standards shall, where appropriate for the protection of the public health, include provisions requiring that the sale and distribution of tobacco products be restricted but only to the extent that the sale and distribution of a tobacco product may be restricted under section 906(d) of the FD&C Act. Similar to section 907, section 906(d) of the FD&C Act gives FDA authority to require restrictions on the sale and distribution of tobacco products by regulation if the Agency determines that such regulation would be appropriate for the protection of the public health. The finding as to whether a regulation is appropriate for the protection of the public health must be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco products, and must take into account:

- The increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- The increased or decreased likelihood that those who do not use tobacco products will start using such products (see section 906(d)(1) of the FD&C Act).

Under these authorities and section 701 of the FD&C Act, which provides FDA with the authority to promulgate regulations for the efficient enforcement of the FD&C Act, FDA is proposing provisions that would restrict the manufacture, sale, and distribution of cigarettes and certain other combusted tobacco products that are not in compliance with this standard. These provisions are not intended to restrict the manufacture of cigarettes intended for export. Consistent with section 801(e)(1) of the FD&C Act (21 U.S.C. 381(e)(1)), a tobacco product intended for export shall not be deemed to be in violation of section 907 of the FD&C Act or this product standard, if it meets the criteria enumerated in section 801(e)(1) of the FD&C Act, including not being sold or offered for sale in domestic commerce. These provisions are critical to maintain the purpose of the standard by helping to ensure that the tobacco products conform to the proposed maximum nicotine level when used by consumers.

FDA is also proposing, under these authorities and others described herein regarding testing and recordkeeping, a requirement that the labels of tobacco products covered under this proposed product standard contain a manufacturing code to identify, among other things, the date of manufacture of a production batch, so that FDA can determine whether a product on store shelves is in conformance with the proposed product standard. The proposed manufacturing code would allow manufacturers and FDA to identify the production batch of a particular finished product that has been released for distribution. This information is intended to help determine the product's history (*e.g.,* batch production records) and assist manufacturers and FDA in the event of a nonconforming tobacco product investigation and any corrective actions to be taken by a manufacturer as a result

water, and vegetable gum with no other ingredients or additives; and (8) weighs more than 6 pounds per 1,000 units.

of the investigation. The manufacturing code must also contain an ''-NS'' designation. The ''-NS'' designation will enable retailers to readily identify that a finished tobacco product conforms with this standard. Finished tobacco products that do not have this designation do not conform to this standard. The manufacturing code information also would aid FDA in ensuring compliance with this proposed product standard by clearly identifying those products that conform to the standard and linking those products to records that substantiate their conformance.

4. Testing Requirements

This proposal contains provisions regarding testing requirements pursuant to sections 907(a)(4)(A)(iii) and 907(a)(4)(B) of the FD&C Act to help ensure that finished cigarettes and certain other finished combusted tobacco products conform to the requirements of the proposed product standard before they are distributed to consumers.

Section 907(a)(4)(A)(iii) states that product standards shall include provisions that are appropriate for the protection of the public health, including provisions, where appropriate, relating to any requirement under section 907(a)(4)(B) of the FD&C Act. Section 907(a)(4)(B)(ii) of the FD&C Act, in turn, provides that a product standard shall, where appropriate for the protection of the public health, include provisions for testing the tobacco product. In addition, section 907(a)(4)(B)(iv) of the FD&C Act provides that, where appropriate for the protection of the public health, a product standard shall include provisions requiring that the results of test(s) 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. FDA is proposing testing requirements because it finds that such requirements are appropriate for the protection of the public health.

Consistent with these statutory provisions, proposed §§ 1160.12, 1160.14, and 1160.16 would establish product testing and sampling plan requirements. Proposed § 1160.12 would require that a manufacturer conduct testing on each batch of finished cigarettes and certain other finished combusted tobacco products to determine whether the products conform to the proposed maximum nicotine level requirement and would also require the manufacturer to document all testing. Proposed § 1160.14 would require manufacturers to use an analytical test method and to demonstrate that the test method was validated in an analytical test laboratory. Proposed § 1160.16 would require that manufacturers design and implement a sampling plan for finished cigarettes and certain other finished combusted tobacco products to ensure the batch consistently conforms to the proposed maximum nicotine level.

To support these proposed requirements, proposed § 1160.18(b) would require each tobacco product manufacturer to investigate all potential nonconforming tobacco products to determine if the product is nonconforming. For example, if any representative samples from a batch of finished cigarettes or certain other finished combusted tobacco products are determined to be out of conformance or if FDA notifies a tobacco product manufacturer that a finished tobacco product in commercial distribution does not conform to the requirements of this part, the manufacturer must conduct an investigation to determine the extent of the nonconformity and locations to which nonconforming tobacco products have been distributed. This proposed requirement would ensure that any reports of nonconforming products, whether as a result of manufacturer testing or otherwise, are examined and investigated and that appropriate measures are taken to ensure that nonconforming products are not distributed to consumers and to prevent future nonconformity.

5. Recordkeeping

Section 909 of the FD&C Act authorizes FDA to require tobacco product manufacturers to establish and maintain records, make reports, and provide such information as the Agency may by regulation reasonably require to assure that a tobacco product is not adulterated or misbranded and to otherwise protect public health.

FDA is proposing a requirement that manufacturers maintain certain records, including the results of batch testing and analyses conducted to determine conformance with the proposed product standard, records of sampling plans and sampling procedures, records related to manufacturing controls, and all records related to the analytical test method used to assess finished cigarettes and certain other finished combusted tobacco products for conformance with the proposed maximum nicotine level requirement. FDA is also proposing to require that manufacturers use a manufacturing code, from which the Agency must be able to identify the production batch of finished cigarettes and certain other finished combusted tobacco products that have been released for distribution. The maintenance of these records for the time period specified in this proposed product standard is necessary to help ensure that such tobacco products are in conformance with the proposed product standard and are not adulterated or misbranded, consistent with the authority provided in section 909 of the FD&C Act. FDA has authority to inspect manufacturers, including access to these records, under, among other authorities, section 704 of the FD&C Act. In addition, the recordkeeping and record access requirements would help FDA with the efficient enforcement of the Act, consistent with the rulemaking authority provided by section 701(a) of the FD&C Act.

IV. Nicotine in Cigarettes and Other Combusted Tobacco Products: Addiction, Initiation, Dependence, Cessation, Relapse, Health Effects, and Consumer Perceptions

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. 50 at p. xi). Some evidence suggests that nicotine is more addictive than many other addictive substances. For example, one study showed the probability of transitioning from first use to dependence was 68 percent for nicotine, but less than 23 percent for alcohol, cocaine, and cannabis (Ref. 51). While cigarettes are the most widely used tobacco products among adults, other combusted tobacco products that are possible targets of product migration (*i.e.,* alternatives that allow people who smoke cigarettes to maintain their nicotine addiction) or dual use have similar adverse health effects, and also cause nicotine dependence (Refs. 52 and 53). For example, persons who use cigars and pipe tobacco 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. 54 to 56).

A. Nicotine Is Addictive

The scientific evidence is clear that nicotine is the primary chemical in tobacco products that causes addiction through its psychoactive and reinforcing effects (Ref. 57). Since 1988, the U.S. Surgeon General has determined that there is a causal relationship between smoking and addiction to nicotine (Refs. 1 and 57), and the earlier that individuals begin smoking, the less likely they are to successfully quit (Ref.

27). Upon inhaling smoke from a burning cigarette, nicotine is absorbed into the lungs and rapidly travels to the brain. Once in the brain, nicotine produces its initial effects by binding to nicotinic receptors—the primary targets for nicotine in the brain—and inducing release of the chemical dopamine (Refs. 58 and 59). Dopamine plays a major role in the pleasurable and reinforcing effects of smoking that promote continued use (Refs. 58 and 59). Nicotine addiction occurs as the result of repeated exposure to nicotine, which induces changes in the brain (Refs. 58 to 60). Addiction to nicotine can lead to symptoms of nicotine dependence, which may include tolerance to the effects of nicotine, withdrawal symptoms upon cessation of use, and craving cigarettes (Refs. 1 and 58).

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 rate of absorption, its palatability and sensory characteristics, how easy it is for the person using the product to extract nicotine, and its cost (Ref. 61). 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. 28 at p.113). Quicker delivery, higher rate of absorption, and higher resulting concentration of nicotine increase the potential for addiction (Ref. 28 at p.113). A cigarette is an inexpensive and extremely effective nicotine delivery system that maximizes the cigarette's addicting and toxic effects (Ref. 61).

Tobacco use disorder is a psychiatric disorder, defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) as being characterized by tolerance to the effects of tobacco products, withdrawal symptoms that are mitigated by the self-administration of nicotine-containing products, and unsuccessful attempts at reducing or quitting the use of nicotine-containing products (Ref. 62). Researchers consider several behaviors indicative of a substance with addictive properties. These behaviors include reinforcement, tolerance, withdrawal, and craving—all of which support the fact that nicotine is the primary addictive constituent in tobacco products. The scientific evidence is clear that nicotine is the primary chemical in tobacco products that causes and maintains addiction.

1. Reinforcement

The reinforcement threshold for nicotine can be defined as the lowest nicotine level that would maintain or increase nicotine self-administration behavior. Currently, most marketed cigarettes are above that threshold; people who smoke cigarettes develop and maintain their addiction through continued smoking (Refs. 17 and 63). Evidence supports that VLNC cigarettes (see table 1 of this document) are below that threshold, as studies show a reduction in the level of addiction based on dependence scales (Ref. 32) and cigarettes per day (CPD) (Refs. 32, 64, and 65). The maximum nicotine level included in this proposed product standard is based on FDA's analysis of studies regarding the likely effects of reducing nicotine, which demonstrates that extended exposure to VLNC cigarettes, which result in very low nicotine yield that cannot be overcome by use behaviors, is associated with reduced addiction potential, dependence levels, number of cigarettes smoked per day, and increased quit attempts among people who currently smoke cigarettes, without evidence of increased toxicant exposure, craving, withdrawal, or compensatory smoking (Ref. 45).

2. Tolerance

Tolerance is defined as a state in which, after repeated exposure, a substance produces less of an effect than previously (Ref. 66) and increasing amounts are required to achieve the effect observed with the first exposure. Both clinical and preclinical research has shown that nicotine has euphoric effects, produces a ''pleasurable buzz,'' and directly enhances positive affect or indirectly increases the reward value of pleasurable situations (Refs. 67 to 70). With repeated exposure to nicotine, neuroadaptation occurs to some of these positive effects, and symptoms of craving and withdrawal begin during periods of abstinence (Ref. 58). Nicotine addiction results from a combination of positive reinforcement from smoking and avoidance of these withdrawal symptoms (Ref. 58). Evidence of tolerance in people who smoke cigarettes is demonstrated as they tend to progressively increase the number of cigarettes they smoke over a period of several years before plateauing to a relatively constant level of use (Ref. 71).

3. Withdrawal and Craving

Nicotine produces a characteristic withdrawal syndrome manifested by irritability/anger/frustration, anxiety, depressed mood, difficulty concentrating, increased appetite, insomnia, and restlessness (Ref. 72). Symptoms typically emerge within the first 1–2 days following abstinence, peak within the first week, and last 2–4 weeks (Ref. 73). The symptoms and time course are consistent with most prototypical addictive substances (*e.g.,* alcohol, benzodiazepines, opioids, amphetamines, cocaine, caffeine) (Ref. 74). While some have asserted that people smoke cigarettes as a ''tool'' or ''resource'' that provides them with needed ''psychological benefits,'' such as increased mental alertness and anxiety reduction (Ref. 75), this view is not borne out by the scientific evidence. In fact, the claimed ''psychological benefits'' (*i.e.,* increased mental alertness, anxiety reduction, coping with stress) that have been ascribed to a smoking ''habit'' are actually symptoms of withdrawal suppression (Ref. 76). Craving or urge is described as a motivation for substance use, which is seen in people who use nicotine (Refs. 77 to 79). Although craving is often characterized as a symptom of nicotine and tobacco withdrawal, it is also a prominent symptom of nicotine dependence (Ref. 72), and it can occur in the absence of other withdrawal symptoms.

4. Nicotine Use Is an Addiction, Not a Habit

A few individual reports have challenged the conclusion that nicotine is the constituent in tobacco products that causes addiction, stating that nicotine only causes habitual behavior (Refs. 67 and 75), and that the craving associated with nicotine is determined by nonpharmacological factors that are disassociated from smoking withdrawal (Ref. 80). However, nicotine has been extensively studied and the evidence overwhelmingly demonstrates that nicotine is an addictive drug and the fundamental reason that individuals continue using tobacco products (Refs. 57 and 28). Since 1988, the U.S. Surgeon General has concluded that nicotine is the substance in tobacco products that causes addiction through its psychoactive effects, reinforcing effects, tolerance, and physical dependence/withdrawal, and that nicotine use is not habitual (Ref. 57). The tobacco industry also has acknowledged that nicotine is addictive (Refs. 81 and 82).

For these reasons, FDA concludes that the addictiveness of nicotine in tobacco products leads to regular use (even when people wish to quit), which is at the root of tobacco-related disease and death from cigarettes and certain other combusted tobacco products.

B. The Developing Brain's Vulnerability to the Effects of Nicotine Leads to Progression to Regular Cigarette Use Among Youth and Young Adults Who Experiment

Youth and young adults are particularly susceptible to developing an addiction to nicotine. Due to the brain's ongoing development during adolescence and young adulthood—until about age 25—it is more vulnerable to nicotine's effects than the adult brain is (Refs. 83 to 85). The 1994, 2012, 2014, and 2020 Surgeon General's Reports on smoking and health note that almost 90 percent of adults who currently and regularly smoke initiated smoking by age 18, and 98 percent initiated smoking by age 26, which is notable given that 25 is the approximate age at which the brain has completed development (Refs. 1, 17 to 19). The developing brain is more vulnerable to developing nicotine dependence than the adult brain is, and the earlier an individual begins smoking the less likely they are to quit (Ref. 20). The maximum nicotine level requirement included in this proposed product standard to regulate nicotine yield would make cigarettes and certain other combusted tobacco products minimally addictive or nonaddictive, limiting the number of youth and young adults who progress from experimentation to regular use and reducing their risk for smoking-related diseases.

There are three primary stages that occur as an individual transitions from never smoking to smoking cigarettes regularly: initiation, experimentation, and regular use. An individual initiates smoking once he or she first tries a cigarette, even one or two puffs (Ref. 17). The vast majority of smoking initiation occurs during adolescence (Ref. 17). Initiation can progress to experimentation, where individuals continue to occasionally try cigarettes, but do not smoke every day, and then to smoking regularly (*i.e.,* smoking daily or on most days) (Ref. 17).

Adolescence is a period of development when individuals who experiment with tobacco products are more susceptible to transitioning to regular use and developing addiction to nicotine. Data from the 2024 NYTS found that 10.1 percent of high school students and 5.4 percent of middle school students reported current use of any tobacco product (Ref. 3). Each day, approximately 1,200 youth (ages 18 and below) try their first cigarette (Ref. 86 at Table A.13A). The transition to regular cigarette use (*i.e.,* smoking on ≥20 of the past 30 days) can occur relatively quickly and can be achieved by smoking as few as 100 cigarettes (Ref. 17). Longitudinal and nationally representative cross-sectional data indicate that an established pattern of cigarette use—including those who ''rapidly escalate'' to regular use—typically occurs by early adulthood (ages 20–22) (Refs. 87 and 88). The Centers for Disease Control and Prevention (CDC) and other researchers have estimated that 30 percent or more of people who experiment with cigarettes transition to regular cigarette use (Refs. 89 to 92). Researchers applied the 30 percent estimate to the number of adolescents who were at the early experimentation stage in 2000, translating to approximately 2.9 million of these adolescents who have or will become people who regularly smoke cigarettes (Ref. 91). Based on the number of persons under the age of 18 in 2012 in the United States, the U.S. Surgeon General estimated that 17,371,000 of that group would begin smoking cigarettes regularly and 5,557,000 will die from a smoking-related disease (Ref. 1 at Table 12.2.1). These concerningly high numbers speak to the extreme vulnerability of youth and young adults to the health harms of tobacco use resulting from addiction to nicotine.

Nicotine addiction is a critical factor in the transition of people who smoke cigarettes from experimentation to regular smoking and in the continuation of smoking for those who want to quit (Ref. 28 at p.113, Ref. 1). Although the majority of adolescents who smoke daily 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. 93 and 94). Another study found that 19.4 percent of adolescents (initially ages 12–13 and followed over 6 years) who smoked weekly were dependent on nicotine (Ref. 95). In a study regarding nicotine dependence among adolescents who recently initiated smoking (9th and 10th grade students), adolescents 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. 96). Researchers in a 4-year study of 6th grade students also found that ''[e]ach of the nicotine withdrawal symptoms appeared in some subjects *prior* to daily smoking'' (Ref. 93) (emphasis added). Ten percent of the study participants showed signs of tobacco dependence 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. 93).

Similarly, researchers have 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—including those who used intermittently (*e.g.,* smoking cigarettes on a monthly basis)—reported at least one symptom of dependence (Ref. 24). Other researchers analyzing data from the 2021 NYTS found that a sizeable proportion of high school students using tobacco products in the past 30 days report symptoms of nicotine dependence, including 27.2 percent reporting a strong craving for tobacco use and 19.5 percent reporting wanting to first use tobacco products within 30 minutes of waking (Ref. 25). Overall, these findings demonstrate that youth and young adults who experiment with cigarettes (and other tobacco products) are particularly vulnerable to the effects of nicotine on progression to regular use and dependence, leading to maintained tobacco product use into adulthood.

C. Youth and Adult Cigarette Smoking Cessation and Relapse

Like adults, many youths who smoke cigarettes want to quit but have difficulty doing so. An analysis of data from the 2015 YRBS looking at youth cigarette quit attempts found that 45.4 percent of high school students currently smoking cigarettes had sought to quit in the previous year (Ref. 22); 2012 NYTS data were congruent, indicating that 51.5 percent of middle and high school students who smoke cigarettes had sought to quit all tobacco use in the previous year (Ref. 22).

For adults who smoke who report quit attempts, few are successful. As of 2019, researchers estimate that only between 5.4 and 5.6 percent of people who smoked cigarettes successfully quit for good, according to data from the NHIS and National Survey on Drug Use and Health (NSDUH), respectively (Ref. 14). According to recent data regarding adult quit attempts, analyses of 2022 NHIS and 2018–2019 TUS–CPS data indicate that 67.7 and 76.6 percent of adults, respectively, who smoke cigarettes were interested in quitting (Refs. 4 and 36), while the 2022 NHIS data and 2018–2019 TUS–CPS data show that only 53.3 and 51.3 percent, respectively, of U.S. adults who smoke actually made a quit attempt within the past year (Refs. 4 and 36). Analyses of 2022 NHIS and 2018–2019 TUS–CPS data indicates that only 8.8 and 7.5 percent of adults who

formerly smoked cigarettes had successfully quit smoking cigarettes, respectively (Ref. 4 and 36). Adults who smoke may make 30 or more quit attempts before succeeding (Ref. 37). Some population groups are less successful than others: for example, 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. 97). Nicotine addiction and associated withdrawal symptoms make it difficult for people who smoke cigarettes to quit, and quit rates rarely exceed 25 percent (Ref. 98).

Relapse is the principal limiting factor in the transition from smoking to nonsmoking status (Ref. 28). Relapse refers to the point after an attempt to stop smoking when a person's tobacco use again becomes ongoing and persistent (Ref. 28 citing Brandon et al., 1986). Most people who relapse do so soon after their quit attempt (Ref. 28). One study found that 80 to 90 percent of individuals who were smoking at 6 months following a quit attempt had resumed smoking within 2 weeks following their quit attempt (Ref. 99). However, even those who quit smoking for longer periods of time frequently relapse. 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 (Ref. 99). In addition, one study following 840 participants for more than 8 years found that approximately one-half of people who smoke who stopped smoking for 1 year relapsed to regular smoking within the subsequent 7 years (Ref. 100). Researchers have found that a higher frequency of smoking is associated with earlier lapses after cessation (*e.g.,* smoking on the first day of cessation or within the first 2 weeks), which in turn is strongly associated with an increased risk of relapse, and is also associated with more severe withdrawal symptoms and earlier relapse after an attempt to quit smoking (Ref. 28 at p.119). These findings confirm the powerful addictive properties of nicotine in tobacco products, a principal factor limiting the ability to quit for a person who uses combusted tobacco products, and further underscore the public health importance of decreasing the addictiveness of these products by decreasing nicotine yield, particularly for youth and young adults who experiment with smoking and for people currently smoking and who hope to quit.

D. Smoking Cigarettes and Other Combusted Tobacco Products Causes Serious Negative Health Effects

Nicotine is a powerfully addictive chemical. The effects of nicotine on the central nervous system occur rapidly after absorption (Ref. 57 at p.12). People who use cigarettes and other combusted tobacco products absorb nicotine readily from tobacco smoke through the lungs (Ref. 57 at p. iii), and, from the lungs, nicotine is then rapidly transmitted to the brain (Ref. 57 at p.13). In the case of cigars, nicotine is also absorbed through the mouth. With regular use, nicotine levels accumulate in the body during the day from tobacco product use and the nicotine persists overnight, allowing for continuous exposure throughout the entire 24-hour period (Ref. 57 at p.38). While mild nicotine intoxication can occur among people who are smoking for the first time (Ref. 57 at p. 15–16), tolerance to the effects of nicotine develops rapidly.

Cigarette smoking is responsible for 480,000 premature deaths every year from many diseases, puts a substantial burden on the U.S. healthcare system, and causes massive economic losses to society (Ref. 1 at p. 659–666). In terms of a monetary measure of the impact of cigarette smoking on the public health, in 2018 smoking cost the United States more than $600 billion, including more than $240 billion in healthcare spending (Ref. 10), nearly $185 billion in lost productivity from smoking-related illnesses and health conditions (Ref. 10), nearly $180 billion in lost productivity from smoking-related premature death (Refs. 1 and 10), and $7 billion in lost productivity from premature death from secondhand smoke exposure (Refs. 1 and 11). Current evidence shows that, while nicotine itself is not the direct cause of most smoking-related diseases, addiction to the nicotine in tobacco products is the proximate driver of tobacco-related death and disease because it sustains tobacco use even when people who smoke want to quit (which most people who smoke report wanting to do) (Refs. 1, 13, 28, 58, and 61). Inhalation of smoke from cigarettes and other combusted tobacco products exposes people who use the products to over 7,000 chemicals, many known to be hazardous to health and lead to disease (Ref. 28). According to the 2014 Surgeon General's Report, 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. 1). 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. 1 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 (Ref. 1). Smoking during pregnancy can result in negative outcomes for a newborn baby, such as low birth weight, lungs that fail to develop properly, birth defects such as cleft lip and/or cleft palate, and Sudden Infant Death Syndrome (Ref. 101). As stated in the 2014 Surgeon General's Report, ''[c]igarette smoking has been causally linked to diseases 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. 1 at p.7).

Tobacco and cigarette smoking-related morbidity and mortality also have been experienced differentially across different sociodemographic characteristics, such as race, ethnicity, socioeconomic status, educational attainment, mental health status, and homelessness. Black [14] adults, and in particular Black men, experience the highest rates of incidence and mortality from many tobacco-related cancers, such as lung and bronchus cancer and head and neck cancer, compared to those from other racial and ethnic groups (Refs. 102 to 104). Deaths from other tobacco-related conditions such as heart disease, stroke, and hypertension are higher among Black individuals compared to other racial and ethnic groups regardless of tobacco use status (Refs. 105 to 110). Compared to persons identifying as non-Hispanic White, Hispanic and Black persons smoke fewer cigarettes (Refs. 111 to 113) and are more likely to be people who do not smoke daily (Refs. 111 and 114), yet

[14] Throughout this document, FDA uses both the terms ''Black'' and ''African American.'' The term ''African American'' is used to describe or refer to a person of African ancestral origins or who identifies as African American. ''Black'' is used to broadly describe or refer to a person who identifies with that term. Though these terms may overlap, they are distinct concepts (*e.g.,* a Black person may not identify as African American). As a result, FDA relies on the specific term used by researchers when citing to specific studies. FDA uses the term ''Black'' when not citing to a specific study.

have greater risk of lung cancer morbidity and mortality (Refs. 1, 115 to 118). Additionally, American Indian/Alaska Native (AI/AN) populations have the highest cigarette use prevalence (Refs. 119 to 121) and are more likely to suffer disproportionate rates of tobacco-related death (Ref. 119). An analysis of 2001–2009 mortality data for people living in the Indian Health Service Contract Health Service Delivery Area counties in the United States indicated that age-adjusted death rates, smoking-attributable fractions, and smoking-attributable mortality for all-cause mortality were statistically significantly higher among AI/AN populations than among White populations for adult men and women aged 35 years and older (Ref. 122). Cigarette smoking caused 21 percent of ischemic heart disease, 15 percent of other heart disease, and 17 percent of stroke deaths in AI/AN men, compared with 15 percent, 10 percent, and 9 percent, respectively, for White men (Ref. 122). Among AI/AN women, smoking caused 18 percent of ischemic heart disease deaths, 13 percent of other heart disease deaths, and 20 percent of stroke deaths, compared with 9 percent, 7 percent, and 10 percent, respectively, among White women (Ref. 122). Some Asian populations, Native Hawaiians, and other Pacific Islander populations also suffer from disproportionate rates of tobacco-related mortality as compared to non-Hispanic White persons (Refs. 115, 117, 123, and 124).

Disparities in tobacco-related morbidity and mortality have also been observed for additional population groups that have higher levels of tobacco use. Those with low household income and/or educational attainment bear a disproportionate burden of myocardial infarction prevalence and coronary heart disease-related mortality (Ref. 125). National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2010 indicate that prevalence of co-occurring obesity and smoking was linearly associated with educational attainment as women with the lowest levels of education had greater likelihood of being obese and smoking than women with the highest levels of education (Ref. 126). Some research also indicates that race/ethnicity status interacts with the effects of higher educational attainment on the likelihood of current smoking. The protective effect of higher education against current smoking was shown to be a stronger effect for White as compared to Black respondents (Ref. 127). Research has also demonstrated that individuals with behavioral health conditions and other medical comorbidities have higher prevalence of combusted tobacco use compared to those without these conditions (Refs. 128 and 129) and have increased risk of tobacco-related morbidity and mortality (Refs. 120, 130, and 131). Inpatient hospital admission data from 1990 to 2005 from California indicate that approximately half of the deaths in those who had been hospitalized for schizophrenia, bipolar disorder, or major depressive disorder were due to diseases causally linked to tobacco use (Ref. 130) and that the majority of deaths for those hospitalized for opioid-related conditions were related to tobacco and alcohol, not to opioids (Ref. 132). Tobacco-related cancers are a leading cause of death among adults experiencing homelessness (Ref. 133). While cigarette smoking and exposure to cigarette smoke are responsible for significant mortality—480,000 premature deaths annually, as previously stated—this estimate does not include deaths caused by other tobacco products, such as cigars and pipes (Ref. 1 at p. 665).[15] Additionally, for every person who dies from a smoking-related disease in the United States, approximately 30 more people will suffer from at least one smoking-related disease (Ref. 1).

Inhalation of the chemicals produced by combustion results in numerous adverse health outcomes through mechanisms that include DNA damage, inflammation, and oxidative stress (Ref. 28). The three leading causes of smoking-attributable death for people who currently and formerly smoke cigarettes are lung cancer, heart disease, and COPD (Ref. 1 at p. 660). Cigarette smoking results in a chronic inflammatory state in the cardiovascular system that is known to be a powerful predictor of cardiovascular events including heart disease (Ref. 28). For COPD, although studies have shown that the disease can be almost completely prevented with the elimination of smoking (Ref. 63), for those who have already developed the disease, evidence indicates that the related morbidity persists long after cessation of smoking (Ref. 28). In addition, it has been established that more than 85 percent of lung cancers are due to smoking, and lung cancer is the country's leading cause of cancer death (Refs. 1, 28, 63, and 136).

Cigarettes and other combusted tobacco products also have deadly effects on people who do not smoke because they produce secondhand smoke. It is well-established that secondhand tobacco smoke causes premature death and disease in children and in adults who do not smoke (Ref. 15 at p.11). Secondhand smoke exposure is currently estimated to be responsible for over 41,000 deaths annually in the United States (Ref. 1). For example, an estimated 7,300 lung cancer deaths and nearly 34,000 coronary heart disease deaths annually can be attributed to secondhand smoke (Ref. 1). Additionally, productivity losses due to secondhand smoke-attributable deaths are estimated to cost the United States $5.6 billion each year (Ref. 1).

Secondhand smoke is particularly harmful to children. For instance, the 2014 Surgeon General's Report estimated that each year, secondhand smoke is associated with 150,000 to 300,000 lower respiratory tract infections in infants and children under 18 months of age, 790,000 doctor's office visits related to ear infections, and 202,000 asthma cases (Refs. 1 and 137). In addition, thirdhand smoke—the chemical residue from combusted tobacco smoke that can become embedded in the environment (*e.g.,* carpet, dust)—results in exposure to harmful constituents such as tobacco specific nitrosamines (Ref. 138). Exposure to thirdhand smoke is especially concerning for young children given their size and behaviors, like crawling on the ground and frequently putting their hands in their mouths.

Additionally, the burden of secondhand smoke exposure is experienced disproportionately among members of some racial and ethnic groups and people with lower household income and educational attainment. Among people who do not smoke, ages 3 and older, findings from 2011 to 2018 NHANES data indicate that non-Hispanic Black respondents and those living below the poverty level had the highest levels of secondhand smoke exposure compared to people of other races and those living above the poverty level, respectively; these disparities persisted across all years of the study analysis from 2011 to 2018 (Ref. 139). From 1999 to 2012, the percentage of persons who do not smoke (ages 3 and older) with detectable serum

[15] Regular cigar smoking 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. 134). The 2014 Surgeon General's 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 (Refs. 1 and 135).

cotinine [16] levels (defined in the study as levels ≥0.05 nanogram per milliliter to indicate secondhand smoke exposure) declined across all racial and ethnic groups (Ref. 141). However, a higher proportion of non-Hispanic Black individuals who do not smoke continued to have detectable serum cotinine levels, compared to Hispanic and non-Hispanic White individuals who do not smoke. For example, in 2017–2018, nearly 50 percent of non-Hispanic Black people who do not smoke had detectable serum cotinine levels, compared with 22 percent of non-Hispanic White and 17 percent of Mexican American people who do not smoke (Ref. 141). Moreover, disparities in trends in detectable serum cotinine levels among people who do not use cigarettes over time have been observed on the basis of race/ethnicity. One analysis of NHANES data and found that from 1999 to 2012 among children ages 3–11, comparable levels of decline were observed among non-Hispanic White (percentage change: 41.2 percent) and Mexican American (percentage change: 39.0 percent) youth, but a lesser decline was observed among non-Hispanic Black youth (percentage change: 19.8 percent) (Ref. 141). A more recent analysis of NHANES data also indicated that, between 2011 and 2018, the percentage of people who do not use cigarettes with detectable serum cotinine levels increased among non-Hispanic Black youth ages 12–19 but remained stagnant among non-Hispanic White youth of the same ages (Ref. 142).

Moreover, there is also some scientific evidence supporting disparities in secondhand smoke exposure by sexual orientation. An analysis of NHANES data from 2003–2010 found that secondhand smoke exposure (defined as a serum continine [17] levels ≥0.05 nanogram per milliliter) differed by sexual orientation among women 20–59 years of age (Ref. 143). This study found that among women 20–59 years of age, secondhand smoke exposure was higher among non-smoking women who identified as lesbian (56.2 percent) or who reported a lifetime experience with a same-gender partner (47.7 percent) than those women who identified as exclusively heterosexual (33.0 percent; $p<0.001$) (Ref. 143). However, among men 20–59 years of age, exposure to secondhand smoke did not significantly differ by sexual orientation.

[16] Cotinine is an alkaloid found in tobacco leaves and is the main metabolite of nicotine. Measuring cotinine in people's blood is a reliable way to determine exposure to nicotine for both people who smoke and those exposed to environmental tobacco smoke (Ref. 140).

Disparities in the secondhand smoke exposure are found across various environmental settings. These disparities speak to the interrelated influences of individual factors (*e.g.,* age, race and ethnicity, sexual orientation, income) and existing inequities in places where members of communities disproportionally impacted by tobacco-related health disparities are likely to reside, spend time, and work (Refs. 53 and 120). For example, an analysis of NHANES data from 2017–2018 found that 87.8 percent of non-smoking persons 3 years of age and older who lived with someone who smoked inside the home was exposed to secondhand smoke based on serum cotinine values of 0.05–10.00 nanogram per milliliter compared to 21.4 percent of non-smoking persons 3 years of age and older not living with someone who smoked inside the home (Ref. 142). In terms of race and ethnicity, findings drawn from the 2013–2016 NHANES data indicate that compared to non-Hispanic White respondents, non-Hispanic Black respondents had higher odds of secondhand smoke exposure in homes other than their own (Ref. 144). An analysis of NYTS data indicates that non-Hispanic Black and non-Hispanic White students both had higher prevalence of secondhand smoke exposure at home and in vehicles than Hispanic and non-Hispanic other race/ethnicity students (Ref. 145). While secondhand smoke exposure in homes and vehicles declined from 2011 to 2018, secondhand smoke exposure in homes among non-Hispanic Black students did not change (Ref. 145). Additionally, a study using data from Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health (PATH) Study found that the odds of exposure to secondhand smoke at home were higher for Black adults (OR=1.12, 95 percent CI:1.00–1.24; p-value=0.042) than White adults; and higher for those adults who self-identified as being LGBT (OR=1.30, 95 percent CI:1.11–1.52; p-value=0.001) than for heterosexual adults (Ref. 146). Home smoking bans (*i.e.,* when people decide to have their own rules that restrict or ban smoking inside their own home)—can reduce secondhand smoke exposure. For example, a study using data from the 2009–2010 National Adult Tobacco Survey (NATS) found the prevalence of exposure to secondhand smoke varied based on the presence (or absence) of smokefree rules in the home (Ref. 147). This study found that overall, 1.4 percent of people who did not smoke and had a smokefree rule at home were exposed to secondhand smoke in their homes in the past 7 days, compared with 43.9 percent of people who did not smoke and did not have a smokefree rule at home (Ref. 147). A similar pattern was observed across age groups, race and ethnicity, and levels of educational attainment. For example, a higher percentage of Black and Hispanic people were exposed to secondhand tobacco smoke in homes with and without smokefree rules than White people. Additionally, a study using 1995–2007 TUS–CPS data found that among two parent households, higher levels of parental educational level and annual household income were associated with the higher reporting of a complete home ban as compared to lower levels of parental educational and annual household income (Ref. 148). Such findings emphasize the degree to which certain aspects of disadvantage (such as lower family income, lack of access to single-family housing, or lack of autonomy over the home environment) may compound tobacco-related health disparities.

Individuals who live in multi-unit housing, including apartments, are particularly susceptible to involuntary secondhand smoke exposure in the home, as secondhand smoke can infiltrate throughout a building along various pathways (Refs. 149 to 153). Exposures to secondhand smoke in multi-unit housing are potentially concerning given a study drawing on the 2013–2014 National Adult Tobacco Survey (NATS) found that tobacco use was higher among adults living in multi-unit housing (24.7 percent) than those in single-family housing (18.9 percent) (Ref. 154). This study also found that smoke-free home rules (*i.e.,* home smoking bans) were higher among adults living in single-family housing (86.7 percent) than those in multi-unit housing (80.9 percent) (Ref. 154). However, more than a third (34.4 percent) of multi-unit housing residents with home smoking bans have experienced secondhand smoke incursions (Ref. 154). Recent estimates indicate that approximately 80 million residents in the United States are currently living in some type of multi-unit housing (Ref. 150). Among those living in multi-unit housing with a home smoking ban, an estimated 27.6–28.9 million are exposed to secondhand smoke incursions from neighboring units and/or shared common areas (Ref. 150). Moreover, a 2013 nationally representative study conducted among U.S. adults living in multi-unit housing found that 25.2 percent of non-smoking residents who had no smoking in the home for at least 3 months and who also

had a child in the home had a recent secondhand smoke incursion into their unit; 99 percent of these residents also reported being bothered by the incursion (Ref. 155). Multi-unit housing secondhand smoke incursions have also been found to be greater among specific populations that are already disproportionately burdened by tobacco-related disease and death, including women, younger adults, and non-Hispanic Black, Hispanic, and lower income populations (Ref. 154).

Workplace secondhand smoke exposure has also been shown to vary across population groups. A study using data from the 2009–2010 NATS show the prevalence of secondhand smoke exposure from employed nonsmoking adults was higher among males, non-Hispanic Black, Hispanic, and AI/AN people compared with White people, and people with low education and low income (Ref. 156). Similarly, data from the 2010 and 2015 NHIS show that exposure to secondhand smoke in the workplace was disproportionately high among non-Hispanic Black respondents, Hispanic respondents, and workers with low education and low income (Ref. 157). Additionally, the study findings indicated that ''blue-collar workers'' (defined as those who performed manual labor such as manufacturing, mining, sanitation, and construction) experienced higher prevalence of secondhand smoke exposure compared to ''white-collar workers'' (defined as those who primarily work in an office, with computer and desk setting, and perform professional, managerial, or administrative work) (Ref. 157).

The disparities observed in tobacco use, as well as disparities in secondhand smoke exposure, contribute to the disparities in tobacco-related morbidity and mortality experienced by some population groups. This proposed product standard is anticipated to reduce smoking-related morbidity and mortality for the population as a whole, including these populations that use tobacco or are exposed to secondhand smoke at disproportionately high levels.

Other combusted tobacco products, particularly those that could serve as alternatives to cigarettes if people who smoke cigarettes no longer had access to normal nicotine cigarettes (NNC), cause similar negative health effects. For example, cigar smoke contains many of the same harmful constituents as cigarette smoke, and cigar smoke may have even higher levels of several harmful compounds compared to cigarette smoke (Refs. 1, 134 and 158). For example, cigar smoke contains higher amounts of carcinogenic, tobacco-specific N-nitrosamines than cigarette smoke due to the relatively high concentration of nitrate in cigar tobacco, which leads to formation of cancer-causing nitrosamines during the fermentation process (Refs. 1; 53 at Chapter 3; and 158). Researchers have found urinary concentrations of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) (a hazardous tobacco-specific nitrosamine) measured in people who smoke cigars daily to be as high as those measured in people who smoke cigarettes daily (Refs. 159 and 160). Like exposure to cigarette smoke, exposure to higher levels of cigar smoke for longer time periods increases the adverse health risks caused by cigar smoking (Ref. 28).

Consequently, there is a long-standing body of research, including reports from the U.S. Surgeon General and National Cancer Institute (NCI), demonstrating that cigar use causes serious adverse health effects (Ref. 53 at p.119–155; Refs. 55; 161, and 162). 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 of risk a function of the amount smoked and depth of inhalation (Ref. 53 at p.119–155). Likewise, a systematic review of the mortality risks associated with cigar smoking that identified 22 studies found that people who regularly smoke cigars are at increased risk for many of the same diseases as people who smoke cigarettes, including oral, laryngeal, esophageal, and lung cancer; cardiovascular diseases; and COPD (Ref. 163).

Research indicates that most people who smoke cigars do inhale some amount of smoke, even when they do not intend to inhale, and are not aware of doing so (Refs. 54 and 55). Even when people who smoke cigars do not breathe smoke into their lungs, they are still subject to the addictive effects of nicotine through nicotine absorption (Refs. 55 and 56). This nicotine absorption occurs because cigar smoke dissolves in saliva, allowing the person smoking the cigar to absorb sufficient nicotine by holding the smoke in their mouths, even if the smoke is not inhaled (Refs. 53, 56, and 164). Cigar and/or pipe smoking causes cancers of the lung and upper aerodigestive tract, including the oral cavity, oropharynx, hypopharynx, larynx and esophagus (Ref. 158). Additional evidence suggests that cigar and/or pipe smoking is causally associated with cancers of the pancreas, stomach, and bladder (Ref. 165). People who smoke cigars also have increased risks for coronary heart disease and COPD compared with people who never used tobacco (Ref. 166).

One study using NATS data from 2009 to 2010 found that regular cigar smoking (defined as 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. 134). A study of healthcare expenditures from 2000 to 2015 found that cigar-attributable healthcare expenditures for adults totaled $1.75 billion per year, with $284 million attributed to exclusive cigar smoking and $1.5 billion attributed to poly tobacco use (*i.e.,* use of multiple tobacco products) involving cigar smoking plus cigarette or smokeless tobacco use (Ref. 167). In addition, overall mortality rates for all people who smoked cigars (*i.e.,* those who report inhaling as well as those who report not inhaling cigar smoke) are higher than rates for those who have never smoked, although they are generally lower than the rates observed for people who smoke cigarettes (Ref. 53 at p. 112). In an analysis of National Longitudinal Mortality Study (NLMS) data, researchers also found that the risk of dying from tobacco-related cancers is higher for people who currently exclusively use pipe tobacco and those who currently exclusively smoke cigars than for those who reported never using combusted tobacco products (Ref. 168). Another similar analysis using the restricted-use National Health Interview Survey-Linked Mortality Files (NHIS–LMF), following participants for mortality from 2000 through 2015, observed that people who currently smoked cigars daily had elevated risk of all-cause mortality compared to those who had never used tobacco (Ref. 169). In addition, researchers studying people who smoke cigars in 2009 and 2010 found that the average person who smokes cigars or pipes loses approximately 15 life years (Ref. 134).

Disparities in cigar-related health outcomes have also been observed by gender and race/ethnicity. Likely due to the greater prevalence of cigar use among men versus women, one analysis observed a significantly greater number of years of potential life lost for men than women (117,440 for men; 22,284 for women) associated with cigar use, as well as disparate monetary losses associated with cigar use ($19.5 billion

for men; $3.4 billion for women) based on the value of a statistical life year (Ref. 134). Studies have shown that levels of nicotine and other carcinogens in cigars can be higher than those in cigarettes and may be at levels that lead to increased risk of morbidity and mortality from conditions such as cancer, cardiovascular disease, and COPD (Refs. 134, 163, and 164). The prevalence of cigar smoking among AI/AN populations is lower than prevalence among Black populations, but higher than among Hispanic and Asian populations (Refs. 120 and 121), contributing to the disproportionate prevalence of lung cancer and cardiovascular diseases in these populations (Refs. 170 and 171).

E. Tobacco Product Marketing Has Contributed to Disparities in Use and Health Outcomes

Tobacco companies have long understood the complexities of nicotine addiction (Ref. 172) and have capitalized on the psychological and sociological aspects of tobacco use to market their products disproportionately to specific populations, such as youth and young adults, some racial and ethnic populations, individuals who identify as lesbian, gay, bisexual, transgender, queer, and intersex (LGBTQI+),[17] those with lower household income and educational attainment, and individuals with behavioral health conditions (Refs. 173 and 174). For example, retail advertising for tobacco products is more common in neighborhoods with greater proportions of Black residents and in lower income neighborhoods (Refs. 175 to 179). Storefront and outdoor tobacco marketing, as well as point-of-sale marketing, are all disproportionately present in Black, Hispanic/Latino, AI/AN, and low-income communities (Refs. 175, 179, 180 to 187). Higher exposure to tobacco advertisements and retailing is associated with tobacco use susceptibility and tobacco use among youth, with observed disparities impacting youth who are Black, Hispanic, or lower socioeconomic status (Refs. 188 to 192). For example, a systematic review of 35 studies found that a higher density of tobacco retailers near the home is associated with increased combustible tobacco product use among youth (Ref. 193).

Industry marketing tactics have also included the incorporation of culture-specific imagery, traditional practices, and events that target specific racial and ethnic groups. For instance, tobacco companies have sponsored cultural events such as Cinco de Mayo celebrations, Chinese New Year celebrations, and activities related to Black History Month (Refs. 173 and 194) and have used the cultural significance of traditional tobacco to validate the authenticity of commercially available cigarettes, exploiting the traditions of Native people to encourage cigarette use (Ref. 195). Tobacco industry documents show that tobacco companies have strategically marketed their products to women with lower income, particularly Black and Hispanic women, (Ref. 196), people experiencing homelessness and people with mental illness (Refs. 197 and 198), and the LGBTQI+ community (Refs. 199 to 201). Research also demonstrates that since at least the 1960s, the tobacco industry has made strategic donations to organizations representing and affiliated with these communities (Refs. 120, 202 to 205). Internal industry documents reveal that at least one tobacco company considered such donations to be a ''quid pro quo,'' because they could result in the normalization of tobacco use, development of brand loyalty, and opposition to health-protective tobacco control policies (Ref. 206).

The industry's practices have resulted in long-term consequences for communities. Tobacco marketing influences social norms around tobacco use, making it more socially acceptable and increasing the likelihood of use (Refs. 207 to 209). In communities where the tobacco industry has disproportionately marketed to historically marginalized populations over decades, these social norms are transferred through peers and family generations, perpetuating the use of harmful combusted tobacco products, and contributing to present-day tobacco-related health disparities in these populations (Refs. 207, 210, and 211). Moreover, recent scientific evidence indicates that tobacco companies continue to target populations that experience tobacco-related health disparities with tobacco marketing (Refs. 178, 180, 191, 207, 212 to 226).

Although targeted marketing is only one factor in the development and perpetuation of combusted tobacco product use and related harms, it contributes to disparities that affect public health and are of great concern to FDA. Advancing health equity is a policy priority and an important component of fulfilling FDA's mission to protect and promote public health. FDA and the Federal Government recognize the advancement of health equity as ''both a moral imperative and pragmatic policy,'' as Executive Order 13995 states. Considerations related to health equity helped inform FDA's decision to prioritize this proposed product standard.

F. Consumer Knowledge, Attitudes, Beliefs, and Perceptions About Nicotine

The science on consumer knowledge, attitudes, beliefs, and perceptions about nicotine demonstrates that a majority of consumers correctly understand that nicotine is the substance in cigarettes that causes addiction. Nationally representative studies that examined nicotine addiction beliefs in the general population reported that the belief that nicotine is addictive was endorsed by approximately 85.8 percent of the population, and the belief that nicotine is responsible for driving continued cigarette use was endorsed by approximately 82.9 percent of the population (Refs. 227 to 233). A nationally representative survey found that 88 percent of people who currently smoke cigarettes and 91 percent of people who use e-cigarettes agreed that nicotine makes people want to smoke (Ref. 227). A nationally representative study of youth suggests that about 77.1 percent of respondents believe that nicotine definitely or probably causes addiction (Ref. 234).

However, in contrast to high rates of correct beliefs about the addictiveness of nicotine, there are high rates of incorrect beliefs about the harms of nicotine. Studies that examined nicotine harm beliefs in the general population reported that the belief that nicotine causes cancer was endorsed by 40 to 78 percent of adult participants (Refs. 227, 228, 232, 233, 235 to 245). Additionally, a nationally representative study of youth suggests that about 74.7 percent believe that nicotine definitely or probably causes cancer (Ref. 234). Multiple nationally representative studies that examined nicotine harm perceptions by tobacco use status found that 52 to 61 percent of people who currently use cigarettes and up to 84 percent of people who do not use cigarettes endorsed the belief that nicotine itself causes cancer or that nicotine is the major contributing constituent in cigarettes that causes cancer (Refs. 228, 241, and 245). A more recent qualitative study of people who currently use little cigars and cigarillos suggests that the misperception that nicotine has significant adverse health

[17] Throughout this document, FDA uses the term ''LGBTQI+'' broadly when referring to lesbian, gay, bisexual, transgender, queer, and intersex communities. When we describe findings from the published literature, we refer specifically to the groups that are studied. For example, some authors examine tobacco-related outcomes for members who identify as lesbian, gay, bisexual, or transgender only; as such, the data are limited to those who identify as LGBT, and authors interpret the findings for those specific groups.

effects is also common among people who use these products (Refs. 228, 241, 245, and 246). Although nicotine creates and sustains addiction and therefore is the driver of the death and disease associated with smoking, it is the repeated exposure to toxicants from tobacco products that directly causes most of the serious health effects among those who use tobacco products, including fatal lung diseases, such as COPD, and cancer (Ref. 28).

Consumer misperceptions regarding the harms associated with nicotine may lead to inaccurate judgments about the risks of using products that contain nicotine, including NRT. For example, individuals who hold a misperception about nicotine may be less likely to use NRT as a smoking cessation aid. Furthermore, there is evidence that misperceptions of nicotine harm vary by gender, ethnicity, and age, and may contribute to unequal health outcomes (Ref. 233). FDA recognizes the importance of addressing nicotine misperceptions in the context of a proposed product standard that limits the level of nicotine in cigarettes and certain other combusted tobacco products in order to make those products minimally addictive or nonaddictive. FDA will continue to conduct research and develop communication tools (*e.g.,* consumer outreach, public education initiatives, engagement with interested parties) to ensure that consumers are informed of the risks of using tobacco products that contain nicotine, including the products covered under this proposed product standard.

V. History and Perceptions of VLNC Cigarettes

A. History of LNC and VLNC Cigarettes

Tobacco companies had the technical expertise to manipulate the nicotine content in tobacco as early as the 1920s and then began to market products that may have met very low nicotine content (VLNC) [18] cigarette levels throughout the late 1970s and early 1980s (Ref. 247). As discussed above, the term ''VLNC cigarettes'' generally refers to combusted cigarettes that have been reported to contain ≤1.0 mg nicotine per gram of total tobacco. For a detailed discussion of the scientific evidence that supports the technical achievability of this proposed product standard, see section VII.E of this document. In this section, we describe some of the industry's early and continuing efforts to develop VLNC cigarettes.

Some of the earliest VLNC cigarettes studied by academic researchers were produced by Philip Morris and marketed under the brand name ''Next,'' which was reported to contain 0.4 mg nicotine per gram of total tobacco (Ref. 248). Later, the National Institute on Drug Abuse (NIDA) contracted with the Ultratech/Lifetech Corporation [19] to produce VLNC cigarettes for research purposes only (Refs. 249 and 250). The two types of cigarettes produced were: (1) 8.0–10.3 mg nicotine per gram of total tobacco and (2) 0.6–0.7 mg nicotine per gram of total tobacco (Ref. 250).

Commercially available Quest cigarettes were produced and marketed by Vector Tobacco in the early 2000s and utilized genetically engineered tobacco to create cigarettes with three distinct nicotine content levels (*i.e.,* Quest 1 (12.7 mg/g), Quest 2 (7.3 mg/g), Quest 3 (0.9 mg/g)) (table 1). These cigarettes were used in much of the VLNC research conducted prior to the development of SPECTRUM Nicotine Research Cigarettes; they are no longer on the market. Philip Morris also manufactured cigarettes with varying nicotine levels for research only (Ref. 251). In a public statement issued on July, 2018, 22nd Century Group, Inc. stated that they were already using genetic engineering and plant breeding to produce VLNC tobacco for cigarettes (Ref. 252). In 2014, the company was granted patents for its process to dramatically reduce the nicotine in tobacco plants (Ref. 253). This tobacco has been used to generate low nicotine content research cigarettes, produced and distributed by RTI International, under a contract with the NIDA Drug Supply Program (Ref. 254). 22nd Century Group, Inc. acts as a vendor for RTI for this contract, manufacturing SPECTRUM Nicotine Research Cigarettes that were reported to contain 0.4 mg nicotine per gram of tobacco (Ref. 254), and they also manufacture cigarettes with other reduced levels of nicotine. These SPECTRUM Nicotine Research Cigarettes are similar in many sensory characteristics to NNC cigarettes, but with VLNC (Refs. 255 and 256).

In 2019, 22nd Century Group, Inc. received FDA marketing authorization and, in 2021, received exposure modification orders for their VLNC cigarettes under the names VLN King and VLN Menthol King. VLN cigarettes are currently being marketed and sold to consumers in select U.S. markets as cigarettes with 95 percent less nicotine than conventional cigarettes. From January 1, 2023, to November 22, 2024, 22nd Century VLN cigarette dollar sales accounted for less than 0.001 percent of total cigarette dollar sales in any 4week period. Menthol flavored 22nd Century VLN cigarettes over the same time accounted for less than 0.001percent of any 4-week menthol flavored cigarette dollar sales.[20]

Currently, these are the only authorized VLNC cigarettes. As we discuss in other parts of this document (see section VII.E), we believe the scientific evidence supports the technical achievability of the proposed standard; additionally, the tobacco industry and consumer product companies have developed a range of brands with differing nicotine levels. Thus, it appears there would be opportunities for any manufacturer who chooses to enter the market for products covered by this proposed product standard.

Although many of the studies discussed in this section investigated the effects of VLNC cigarettes, some studies also investigated the effects of cigarettes with higher levels of nicotine, often as comparators. Table 1 displays the reduced nicotine content cigarettes that were administered in studies summarized in this document and their reported nicotine levels. The nicotine content values in table 1 are approximate, and they are primarily based on published reports from the peer-reviewed scientific literature. Most studies that investigated the clinical effects of reduced nicotine content cigarettes did not chemically analyze the study cigarettes. For example, many studies that examined the effects of VLNC SPECTRUM Nicotine Research Cigarettes did not chemically characterize these cigarettes, but the authors of these studies reported that the nicotine content of the cigarettes was 0.4 mg nicotine per gram of

[18] As previously noted in footnote 7, the term VLNC should not be confused with the cigarette brand name ''VLN;'' ''VLN'' refers to cigarette products authorized for marketing by FDA in 2019. See *https://www.fda.gov/media/133633/download?attachment* and *https://www.fda.gov/media/133635/download?attachment.*

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

[20] FDA's own analyses, calculations and conclusions informed in part by the NielsenIQ Retail Measurement Service (RMS) data through NielsenIQ's RMS for the tobacco product category ''Cigarettes'' for the time period January 1, 2023 through November 2, 2024 for Total US Expanded All Outlets Combined (xAOC) and convenience stores are those of FDA and do not reflect the views of NielsenIQ. NielsenIQ is not responsible for, had no role in, and was not involved in analyzing and preparing the results reported herein, or in developing, reviewing, or confirming the research approaches used in connection with this report. NielsenIQ RMS data consist of weekly purchase and pricing data generated from participating retail store point-of-sale systems in all U.S. markets. See *https://NielsenIQ.com/global/en/* for more information.

tobacco. The actual nicotine content of these cigarettes is expected to vary around this value. For example, the results of one study that chemically characterized SPECTRUM Nicotine Research Cigarettes showed that the nicotine content of the sampled VLNC cigarettes ranged between 0.28 and 0.33 mg nicotine per gram (Ref. 256), which is lower than the 0.4 mg nicotine per gram level typically reported in the literature. In 22nd Century Group, Inc.'s modified risk tobacco product applications, the company reported that after 9 years of sampling by the company, the average nicotine content of its genetically engineered VLNC tobacco is 0.6 mg nicotine per gram of total tobacco, with a range of 0.4 to 0.7 mg nicotine per gram of total tobacco. It is likely that the Quest and SPECTRUM Nicotine Research Cigarettes, used throughout the scientific literature, also contained between 0.4 to 0.7 mg nicotine per gram of total tobacco (Ref. 257).

TABLE 1—NICOTINE CONTENT FOR NORMAL, LOW, AND VERY LOW NICOTINE CONTENT CIGARETTES USED IN THE RESEARCH STUDIES CITED IN THIS DOCUMENT

Brand	Manufacturer	Nicotine content category	Nicotine content (mg/g)
Magic [1]	22nd Century Group, Inc	VLNC	*1.0
Next [2]	Philip Morris International	VLNC	*0.4
Philip Morris 1 mg [3]	Philip Morris Tobacco Company	VLNC	*0.7–0.9
Philip Morris 2 mg [3]	Philip Morris Tobacco Company	LNC	*2.1–2.4
Philip Morris 4 mg [3]	Philip Morris Tobacco Company	LNC	*5.0–5.6
Philip Morris 8 mg [3]	Philip Morris Tobacco Company	LNC	*9.3–10.6
Philip Morris 12 mg [3]	Philip Morris Tobacco Company	NNC	*14.4–14.7
Quest 1	Vector Group Ltd	NNC	*12.7
Quest 2	Vector Group Ltd	LNC	*7.3
Quest 3	Vector Group Ltd	VLNC	*0.9
SPECTRUM 0.4 mg (NRC102–NRC105) [4]	22nd Century Group, Inc	VLNC	0.4–0.7
SPECTRUM 1.3 mg (NRC200, NRC201) [5]	22nd Century Group, Inc	LNC	0.9–1.3
SPECTRUM 2.4 mg (NRC300, NRC301) [5]	22nd Century Group, Inc	LNC	1.9–2.4
SPECTRUM 5.2 mg (NRC400, NRC401) [5]	22nd Century Group, Inc	LNC	4.6–5.2
SPECTRUM 15.8 mg (NRC600, NRC601) [5]	22nd Century Group, Inc	NNC	15.5–17.3
Ultratech/Lifetech denicotinized [6]	Ultratech Inc./Lifetech Corp	VLNC	*0.6–0.7
Ultratech/Lifetech nicotine [6]	Ultratech Inc./Lifetech Corp	LNC	*8.0–10.3
Xodus [7]	22nd Century Ltd., LLC	LNC	*1.2–1.7

Abbreviations: VLNC: ≤1.0 mg nicotine per gram of total tobacco; LNC: >1.0 mg and <11.4 mg nicotine per gram of total tobacco; NNC: ≥11.4 mg nicotine per gram of total tobacco.
[1] Nicotine content from (Ref. 31).
[2] Nicotine content from (Ref. 248).
[3] Nicotine content from (Refs. 258 and 259).
[4] Nicotine content from (Ref. 257).
[5] Nicotine content from (Ref. 29) (supplement).
[6] Nicotine content estimated by FDA based on nicotine yield data from (Ref. 250).
[7] Nicotine content from (Ref. 41).
* For these cigarettes, FDA calculated milligrams of nicotine per gram of total tobacco based on reports of milligrams of nicotine per cigarette. Calculations were based on an estimate of 0.7 grams of tobacco per cigarette.

B. Consumer Knowledge, Attitudes, Beliefs, and Perceptions Regarding VLNC Cigarettes and FDA Regulation of Levels of Nicotine in Tobacco

In this section we describe the science related to consumer knowledge, attitudes, and beliefs about reduced nicotine content (RNC) [21] cigarettes and consumers' perceptions about a hypothetical policy reducing nicotine levels in cigarettes and certain combustible tobacco products. These concepts are important because they are associated with the behavioral responses consumers believe they would take if such a policy is in effect.

The science on consumer knowledge, attitudes, beliefs, and perceptions about RNC cigarettes demonstrates that a majority of consumers perceive that RNC cigarettes are equally or more harmful than NNC cigarettes. Nationally representative studies suggest that 50 to 71 percent of consumers perceive RNC cigarettes to be as or more harmful to health than NNC cigarettes, while 25 to 35 percent perceive them to be less harmful than NNC cigarettes (Refs. 260 to 262). Recent nationally representative findings estimate that between 12 and 25 percent of people who smoke or use e-cigarettes believe RNC cigarettes are less harmful than NNC cigarettes (Refs. 227 and 236). In studies where participants actually use VLNC cigarettes, they tend to perceive them as significantly less harmful to health and less likely to cause cancer than NNC cigarettes (Refs. 230, 263 to 265). Furthermore, there is evidence that perceptions about the harms of VLNC cigarettes relative to NNC cigarettes vary by race and age (Refs. 236, 266 to 268). The science on consumer knowledge, attitudes, beliefs, and perceptions about RNC cigarettes also demonstrates that there are widespread misperceptions about the addictiveness of RNC cigarettes relative to NNC cigarettes. Studies that use nationally representative surveys report that 60 to 77 percent of consumers incorrectly believe that RNC cigarettes are equally or more addictive than NNC cigarettes (Refs. 260 and 261). Tobacco use status does not appear to significantly change misperceptions about the addictiveness of RNC cigarettes (Ref. 228).

A 2019 nationally representative study of consumer support for a policy ''requiring cigarette makers to lower the

[21] RNC cigarettes in this context refers to any cigarette with a lower amount of nicotine than NNC cigarettes. FDA notes that studies focusing on consumer perceptions of RNC cigarettes typically do not differentiate between RNC, LNC, and VLNC cigarettes. However, when describing studies that focus on consumer behavior and perceptions of VLNC cigarettes specifically, FDA uses the term VLNC cigarettes. FDA notes that studies in this domain typically use consumer perceptions of RNC cigarettes to form conclusions about consumer perceptions about VLNC cigarettes and FDA's proposed reduction of nicotine more broadly.

nicotine levels in cigarettes so that they are less addictive'' reported that 81 percent of study participants favored the policy (52.4 percent strongly favored, 28.6 somewhat favored) and 19 percent opposed the policy (10.3 percent somewhat opposed, 8.7 percent strongly opposed) (Ref. 269). However, consumer misperceptions about the harm and addictiveness of reduced nicotine content combustible tobacco products impact understanding of the purpose of a reduced nicotine product standard. For example, respondents in some studies did not understand why FDA would choose to remove nicotine from cigarettes or little cigars and cigarillos but not remove other chemicals that are harmful (Ref. 229, 270, and 271). Respondents also stated that they believed other chemicals besides nicotine make cigarettes addictive, and that removing nicotine from cigarettes would not eliminate their addictiveness (Refs. 229 and 270). Misperceptions may also serve as potential determinants of consumer responses to a reduced nicotine product standard. For example, one study suggests that misperceptions among people who smoke regarding the harm of RNC cigarettes is correlated with quit intentions in responses to a hypothetical government policy reducing most of the nicotine in cigarettes (Ref. 267). FDA recognizes the importance of addressing consumers' misperceptions about the relative harm and addictiveness of VLNC cigarettes as compared to other products. FDA will continue to conduct research (*e.g.,* assess changes over time in knowledge, attitudes, and perceptions relative to tobacco product characteristics including nicotine content) to inform regulatory decisions and other actions.

VI. Rationale for Products Covered by the Proposed Product Standard

FDA has reviewed and closely considered the comments to the Nicotine ANPRM, as well as additional evidence and information not available at the time of the ANPRM, in developing the scope of products for this proposed product standard. Specifically, we considered several factors, such as the strength and breadth of the available data on the likely effects of reducing nicotine derived from studies of VLNC cigarettes; current prevalence and initiation rates for different classes of tobacco products; the available data on product toxicity, addictiveness, and appeal; product use topography [22] (including quantity, intensity, and duration of use); and the potential for migration to different products. These data indicate that reduction of nicotine in cigarettes would reduce addiction potential, dependence levels, number of cigarettes smoked per day, and increase quit attempts among people who currently smoke cigarettes. In light of these data, FDA also expects that reduction of nicotine would prevent people who experiment with cigarettes and cigars from developing an addiction to tobacco and progressing to regular tobacco use.

This proposed product standard is intended to address one of our nation's greatest public health challenges: the death and disease caused by combusted tobacco use. Approximately 480,000 people die every year from smoking cigarettes (Ref. 1 at p. 659) and another 9,000 die from smoking cigars (Ref. 1 at p. 659; Ref. 134). Cigarettes are the tobacco product category that causes the greatest amount of harm to the public health as a result of the prevalence of cigarette use among adults and cigarette toxicity and addictiveness. This proposed product standard is expected to increase cessation and switching to potentially less harmful tobacco products and prevent people who are experimenting with use—mainly youth and young adults—from transitioning to regular use of cigarettes. However, if the product standard were only to cover cigarettes, it would likely be less effective. Specifically, a significant number of people who are addicted to smoking cigarettes would likely migrate to similar combusted tobacco products after the standard went into effect to maintain their nicotine exposure, thereby undermining the significant health benefits of the proposed product standard (Ref. 5) (see also section VI.B of this document for further discussion of the potential for non-cigarette combusted tobacco product switching). Therefore, to increase public health benefits, FDA also is proposing to cover certain other combusted tobacco products in addition to cigarettes.

Based on these considerations, FDA is proposing to cover the following products under this product standard:

- Cigarettes (other than noncombusted cigarettes, such as HTPs that meet the definition of a cigarette),
- Cigarette tobacco,
- RYO tobacco,
- Cigars (including little cigars, cigarillos, and large cigars but excluding premium cigars), and
- Pipe tobacco (other than waterpipe tobacco).

FDA has determined that research regarding the public health impacts of potential maximum nicotine level policies applies across the tobacco products covered under this proposed product standard. As discussed in greater detail in section VII.B.12 of this document, given that cigarette tobacco, RYO tobacco, and pipe tobacco can be effectively used in cigarettes, the VLNC cigarette research discussed in this proposed rule applies to these products, and any expected benefits that would accrue as a result of instituting the proposed product standard for cigarettes would also be expected to accrue for these product categories. FDA also concludes that the VLNC cigarette research applies to cigars, given the similarities between cigarettes and most cigars (*e.g.,* use topography). For further discussion of FDA's findings that VLNC cigarette research applies to other covered products under this proposed product standard, see section VII.B.12 of this document. In addition, as discussed in section VI.A.3 of this document, FDA finds that the non-cigarette combusted products within the proposed scope of this rule (*i.e.,* RYO tobacco, cigars, pipe tobacco) could function as acceptable substitutes for many people who smoke cigarettes while exposing them to similar risks and toxicity as cigarettes.

As discussed in section VIII of this document, FDA finds that the proposed product standard, with this scope, is appropriate for the protection of the public health and would provide substantial benefits for people who currently use cigarettes and certain other combusted tobacco products and for people who experiment with cigarettes and cigars and people who do not use such tobacco products. FDA seeks comments on this proposed scope, particularly on how it may affect youth initiation and use of combusted tobacco products.

A. Prevalence and Abuse Potential of Cigarettes and Other Combusted Tobacco Products

Cigarettes, the most frequently used tobacco products, are the tobacco product category that causes the greatest burden of harm to public health given that approximately 28 million adults and 380,000 youth currently smoke cigarettes (Ref. 3); the toxicity and addictiveness of these products; and the resulting tobacco-related disease and death across the population, including among people who do not smoke. Cigarettes are highly addictive and harmful tobacco products; however, the other combusted tobacco products

[22] Smoking topography measures provide data on various aspects of smoking behavior, including number of puffs per cigarette, total time spent smoking, puff volume (*i.e.,* puff size), puff velocity (*i.e.,* puff intensity), puff duration, and inter-puff interval (*i.e.,* length of time between puffs).

covered in this proposed product standard are similarly addictive and harmful. If the proposed product standard covered only cigarettes, some number of people who smoke cigarettes and are addicted to nicotine would likely migrate to similar combusted tobacco products to maintain their nicotine exposure (or engage in dual use with other similar combusted tobacco products), thus reducing the positive public health impact of this proposed product standard.

Regulating the nicotine yield of cigarettes and certain other combusted tobacco products through setting a maximum nicotine level for them would make these dangerous combusted products minimally addictive or nonaddictive, making cessation easier and helping to prevent people who are experimenting with smoking from developing nicotine dependence and progressing to regular use. As stated elsewhere in this document, FDA's approach in proposing this product standard for cigarettes and certain other combusted tobacco products protects public health by reducing combusted tobacco product use (and therefore reducing exposure to harmful toxicants created through combustion) by making it considerably easier for people who want to quit cigarette use to quit all tobacco products or switch to potentially less harmful, noncombusted tobacco products which remain available. Therefore, to increase the public health benefits, FDA is focusing this proposed rule on nicotine levels in cigarettes and certain other combusted tobacco products because combusted products are responsible for the majority of death and disease due to tobacco use.

1. Cigarettes

Data from the 2024 NYTS indicate that 1.7 percent of high school students (approximately 250,000) and 1.1 percent of middle school students (approximately 120,000) reported current use of cigarettes (*i.e.,* smoked at least once during the past 30 days) (Ref. 3). In addition, 11.6 percent of adults reported that they currently smoked cigarettes in 2022 (*i.e.,* smoked at least 100 cigarettes during their lifetime and now smoke cigarettes every day or some days); this means an estimated 28.8 million adults in the United States currently smoke cigarettes (Ref. 4). Although cigarette smoking is present in all population groups in the United States, the prevalence of cigarette use differs based on sociodemographic characteristics.

Findings from the 2024 NYTS show that, among middle and high school students, 1.4 percent of non-Hispanic White students, 0.9 percent of non-Hispanic Black students, and 1.6 percent of Hispanic students currently smoked cigarettes (Ref. 3). Additionally, data from the 2022 NHIS show differences in smoking prevalence on the basis of race/ethnicity among adults (age 18 and over). Specifically, 4.6 percent of non-Hispanic Asian, 8.0 percent of Hispanic, 12.7 percent of non-Hispanic White, 14.2 percent of non-Hispanic Black, 19.3 percent of non-Hispanic AI/AN, and 11.9 percent of non-Hispanic Other participants reported current cigarette smoking (Ref. 272). Data from the 2005 and 2015 NHIS also indicate that the prevalence of cigarette smoking has statistically significantly declined over this time period for non-Hispanic white, Black, Asian, and AI/AN adults and Hispanic adults (Ref. 273).

Data from an analysis of the 2005 and 2015 NHIS indicate that the prevalence of smoking has declined significantly over that time period among both adult male and female participants (29.9 and 25.2 percent relative decrease, respectively) (Ref. 273). Currently, according to data from the 2022 NHIS, smoking remains more prevalent among males (13.2 percent) as compared to females (10.0 percent) in the United States (Ref. 272).

Study findings indicate that individuals who identify as lesbian, gay, or bisexual are more likely to report smoking cigarettes as compared to those who identify as heterosexual (Refs. 274 to 277). Among adults in the 2022 NHIS, cigarette smoking among persons identifying as lesbian, gay, and bisexual was 12.8 percent and among those identifying as heterosexual/straight it was 11.6 percent (Ref. 272), and smoking was more prevalent among youth identifying as lesbian, gay, and bisexual (7.0 percent) in the 2020 NYTS than among those ''not sure'' of their sexual identity (3.5 percent) or youth identifying as heterosexual (2.7 percent) (Ref. 275). Current tobacco use for lesbian, gay, bisexual, and transgender youth in the 2022 NYTS was reported for ''any'' tobacco use (*i.e.,* current use of one or more of the following: e-cigarettes, cigarettes, cigars, smokeless tobacco, hookah, HTPs, nicotine pouches, pipe tobacco, or bidis), but not for individual tobacco products (Ref. 278). Pooled data from the 2015 to 2019 NSDUH indicate that compared to heterosexual/straight respondents, respondents who identified as gay males, lesbian/gay females, or bisexual females reported higher prevalence of past 30-day smoking (Ref. 279). Additionally, in data from the 2015/2016 NSDUH, relative to same-age heterosexual men, lifetime rates of daily cigarette smoking were significantly elevated among gay men ages 18–25 (30 percent versus 23 percent) and ages 35–49 years (44 percent versus 38 percent) (Ref. 277). Similarly, relative to same-age heterosexual women, lifetime daily cigarette smoking was significantly greater among lesbian/gay women ages 18–25 (37.7 percent versus 16.3 percent), ages 26–34 (42.2 percent versus 30.3 percent), and ages 35–49 (42.7 percent versus 32.6 percent) (Ref. 277).

As evidenced in a systematic review and meta-analysis (Ref. 280), studies have consistently shown a relationship between socioeconomic status and the prevalence of cigarette smoking, such that greater levels of educational attainment and greater total family income are inversely associated with the prevalence of smoking. Specifically, in 2021 NHIS data, the prevalence of cigarette smoking was 18.3 percent for adults with a low income, 12.3 percent for those with a medium income, and 6.7 percent for those with a high income (Ref. 274). Similarly, by and large, there is an inverse relationship between educational attainment and the prevalence of smoking. For instance, according to the 2021 NHIS, the prevalence of smoking was 20.1 percent among adults with some high school education but no degree, 30.7 percent among persons with a general equivalency degree, 17.1 percent among those with a high school diploma, 13.7 percent among persons with an associate's degree, 5.3 percent among those with an undergraduate degree, and 3.2 percent among persons who had received a graduate degree (Ref. 274).

The prevalence of cigarette smoking is also higher among adults with mental health symptoms or substance use disorder (Refs. 281 to 284). Findings from the 2022 NHIS show that 27.2 percent of persons reporting severe generalized anxiety disorder (GAD) currently smoke cigarettes, as compared with 10.1 percent who report no or minimal GAD (Ref. 272). Similarly, 27.1 percent of adults who report severe depression currently smoke cigarettes, versus 10.1 percent among those who report no or minimal depression (Ref. 281). Additionally, findings from the 2021 NHIS show that 28.1 percent of persons reporting serious psychological distress also reported smoking cigarettes, compared to 10.9 percent of persons not reporting serious psychological distress (Ref. 274). Analyses of data from the 2015 NSDUH for individuals aged 12 years and over also show that cigarette smoking is significantly more prevalent among

persons who use cannabis (daily cannabis use: 54.6 percent; nondaily cannabis use: 40.2 percent) as compared to those who do not use cannabis (15.1 percent) (Ref. 282). An analysis of 2016 NSDUH data indicates that cigarette smoking is more than twice as prevalent among persons with alcohol use disorder, as compared to those without (37.8 percent versus 16.3 percent) (Ref. 283), while data from the 2014 NSDUH show that the prevalence of cigarette smoking is also more than twice as high among persons with mental health and/or substance use problems than among persons without (38.5 percent versus 15.4 percent) (Ref. 284).

2. Cigars

Cigar smoke contains many of the same constituents as cigarette smoke, including nicotine, many of which can cause significant harm to those who use cigars (Ref. 53). According to the 2024 NYTS, 330,000 middle and high school students,[23] including 1.5 percent (an estimated 230,000) of high school students (grades 9–12) and 0.8 percent (an estimated 80,000) of middle school students (grades 6–8), had smoked a cigar (cigar, cigarillo, or little cigar) on at least 1 day during the past 30 days (Ref. 3). Overall, the prevalence of cigar smoking among middle and high school students is comparable to the prevalence of cigarette smoking, with 1.7 percent (an estimated 250,000) of high school students and 1.1 percent (an estimated 120,000) of middle school students having smoked cigarettes on at least 1 day during the past 30 days (Ref. 3). Cigars are also a popular tobacco product among adults. In the 2022 NHIS, 3.7 percent of adults aged 18 or older reported currently using cigars some or every day, behind cigarettes (11.6 percent) and e-cigarettes (6.0 percent) (Ref. 272).

Evidence from national surveys—including the Monitoring the Future study and NSDUH—indicate that, similar to cigarettes, cigar use has been on the decline among U.S. youth and adults in recent years (Refs. 285 to 287). However, among youth, this decrease has not been equitably experienced. The popularity of cigar use is disproportionately high among groups such as lesbian, gay, and bisexual youth and young adults (3.2 percent among transgender youth, 3.2 percent among sexual minority females, and 3.9 percent among sexual minority males) (Ref. 288), and youth with disabilities (7.0 percent among those who reported using little cigars and 2.6 percent among those who reported using large cigars) (Ref. 289). Cigar smoking also occurs disproportionately among specific populations of adults as well, with greater prevalence of cigar smoking reported among non-Hispanic Black adults (5.1 percent) (Ref. 274), individuals of lower educational attainment and lower annual household income (Refs. 290 and 291), and LGBTQI+ adults (Refs. 292 to 296).

Additionally, when comparing data from 2011 to 2019, while past month cigarette smoking and cigar use were both statistically significantly lower in young adults (ages 18–25), the absolute and relative declines in cigar use were less than the declines in cigarette use (33.5 percent in 2011 to 17.5 percent in 2019 for cigarettes; 10.9 percent in 2011 to 7.7 percent in 2019 for cigars) (Ref. 286). For adults (ages 26 or older), cigarette use in 2011 was statistically significantly higher compared to in 2019; however, cigar use remained relatively stable and did not significantly change (21.9 percent in 2011 to 18.2 percent in 2019 for cigarettes; 4.2 percent in 2011 to 4.0 percent in 2019 for cigars) (Ref. 286). The 2023 NSDUH found that among adults ages 26 or older in 2019, 1,847 individuals initiated cigar use each day, considerably more than the 282 who initiated cigarette smoking each day in that year (Ref. 86).

While these data indicate a high burden of current cigar smoking, the true prevalence of cigar use is likely higher. Little cigars often closely resemble cigarettes, given their shape, size, filters, and packaging, and are perceived by many as being healthier than cigarettes (Refs. 297 and 298). Several studies have shown that youth tend to underreport cigar smoking if brand name identifiers are not provided (Refs. 299 to 301). For example, in one study of Virginia high school students, the reported prevalence of cigar use nearly doubled after accounting for students who reported smoking Black & Mild (a brand name of cigarillos); in the original survey results, more than half of the students who used Black & Mild cigarillos did not report using cigars, cigarillos, or little cigars (Ref. 299).

Research indicates that most people who smoke cigars unknowingly inhale some amount of smoke, including people who smoke cigars who report that they do not inhale (Refs. 54 and 55). Youth more commonly use cigarillos and little filtered cigars that are designed to be inhaled, which may increase their risk of poor health outcomes as well as addiction (Refs. 53 and 163). Even if people who smoke cigars do not breathe or inhale smoke into their lungs, they are still subject to nicotine's addictive effects through buccal (oral) absorption of nicotine or nicotine absorption through the lips due to cigar tobacco's alkalinity, as well as other harmful health effects (Refs. 55, 56, 302 and 303). Cigar smoke dissolves in saliva and makes it possible for people who smoke cigars to absorb sufficient amounts of nicotine to create dependence even if the user does not inhale (Ref. 56).

Nicotine can exist in protonated and freebase (unprotonated) forms. In the freebase form, it is most addictive because it is readily absorbed by the buccal mucosa, respiratory tissues, skin, and the gastrointestinal tract (Refs. 28 and 57). Freebase nicotine amounts are generally higher in cigars than cigarettes due to the higher pH of cigar smoke (Ref. 53). Nicotine absorbed across the buccal mucosa, the mouth's membrane lining, can provide sustained amounts of freebase nicotine to the person using the tobacco product (Ref. 53). Cigars can deliver nicotine much like chewing tobacco or oral snuff, with nicotine extraction absorbed directly through the buccal mucosa and lips (Ref. 53).

A 1998 NCI Monograph chapter (NCI Monograph 9) on cigar pharmacology and abuse potential concluded that the nicotine delivery characteristics and daily patterns of smoking among people who smoke cigars indicate that cigars produce dependence (Refs. 53 and 164). Since the publication of NCI Monograph 9, several in-person laboratory studies, where participants use products under observation and have outcome measures assessed, have provided additional evidence to support that nicotine exposure from cigar smoking is sufficient to create or sustain nicotine dependence among people who use cigars. Through cigar smoke, nicotine can be absorbed by inhalation (like cigarettes) or through the buccal mucosa (like smokeless tobacco). Multiple studies found that people who smoke cigars inhale (as evidenced by carbon monoxide (CO) levels and smoking topography) and that plasma nicotine levels are similar to those of people who smoke cigarettes (Refs. 304 to 308). Furthermore, using the Questionnaire of Smoking Urges, a commonly used measure of tobacco craving, several studies found that cigars reduce craving and urge to smoke to a similar magnitude as cigarettes (Refs. 306 to 308). Cigars have also been shown to decrease acute nicotine withdrawal

[23] The weighted population estimate reported in the scientific publication is 500,000 students. As noted in the scientific publication, overall population estimates might not sum to corresponding population estimates because of rounding or inclusion of students who did not self-report sex, race and ethnicity, or grade level.

symptoms (*e.g.,* craving, anxiousness) (Ref. 304).

Several additional studies have used epidemiological data to compare nicotine dependence levels among people who use multiple tobacco products (*i.e.,* poly tobacco use), people who exclusively use cigarettes, and people who exclusively use cigars (Refs. 309 to 311). The data show that a significant proportion of people who exclusively use cigars display characteristics of tobacco dependence such as craving (Ref. 309); however, people who use multiple tobacco products and people who exclusively use cigarettes showed the highest levels of dependence, followed by people who exclusively use cigars (Refs. 309 to 311).

3. Loose Tobacco (Pipe and RYO Tobacco)

Laboratory and survey studies have provided evidence to conclude that RYO and pipe tobacco smoking is sufficient to create or sustain nicotine dependence among people who use RYO or pipe tobacco (Ref. 312). Studies show that people who use RYO and pipe tobacco inhale (as evidenced by smoking topography) (Refs. 312 to 314) and plasma nicotine levels are similar to those of people who smoke factory-made cigarettes (Ref. 313). Furthermore, RYO tobacco reduces craving and urge to smoke at a similar magnitude and is rated similarly with regard to subjective appeal as factory-made cigarettes (Ref. 313). Evidence also suggests that RYO tobacco is at least as harmful to health as factory-made cigarettes (Refs. 315 to 318).

According to data from the 2024 NYTS, 0.5 percent of high school students (or approximately 70,000 students) reported using pipe tobacco within the previous 30 days and 0.5 percent of middle school students (or approximately 50,000 students) reported pipe tobacco use in the prior 30 days (Ref. 3). Data from the 2021 NHIS indicated that 0.9 percent of adults ages 18 and older (or approximately 2.3 million adults) currently used pipes (Ref. 274). However, FDA notes that pipe tobacco prevalence data are likely an underestimate, as the NIHS survey does not include the number of people who use pipe tobacco to roll their own cigarettes.[24] There is also evidence that young adults who smoke cigarettes are engaging in RYO use for financial reasons (Ref. 319). Studies of RYO tobacco use among youth are limited, but prevalence of RYO tobacco use among U.S. middle and high school students in the 2012 NYTS was 3.4 percent (Ref. 320).

The lack of data on RYO and pipe tobacco use and the limitations in how national surveys assess loose tobacco use impact our ability to draw conclusions regarding appeal of loose tobacco among youth and adults at this time. However, if such products were not included within the scope of this proposed product standard, some number of people who smoke cigarettes and/or cigars and are addicted to nicotine would likely easily migrate to such products to maintain their nicotine exposure given that RYO and pipe tobacco have the same addictive properties and health consequences as factory-made cigarettes (Refs. 168 and 321). For example, more people who smoke cigarettes could use RYO or pipe tobacco to make NNC cigarettes (or engage in dual use with certain other combusted tobacco products), reducing the positive public health impact of this proposed product standard (see section VI.B.1 of this document) (Ref. 322).

Taken together, these data demonstrate that if FDA did not include certain other combusted tobacco products within the scope of this proposed product standard, many people who smoke cigarettes likely would migrate to, or increase use of, such other tobacco products in an attempt to replace or supplement the reduction of nicotine in their VLNC cigarettes.

B. Potential for Non-Cigarette Combusted Tobacco Product Switching

Nicotine can be delivered through products that represent a continuum of risk, with combusted tobacco products at the most harmful end of this continuum. FDA's approach in proposing this product standard for cigarettes and certain other combusted tobacco products protects public health by reducing combusted tobacco product use (and therefore reducing exposure to harmful toxicants created through combustion) while potentially less harmful, noncombusted tobacco products remain available for people who have not quit all tobacco products. FDA expects that, if this proposed rule is finalized and a nicotine product standard for cigarettes and certain other combusted tobacco products is in place, many people who smoke cigarettes will either quit smoking or switch to a noncombusted tobacco product. Those who switch completely to use of a noncombusted tobacco product may sustain their nicotine dependence and may significantly reduce their risk of tobacco-related death and disease to the extent that the products they switch to result in less harm. That is, while dependence on any tobacco product remains a health concern, nicotine alone is not directly responsible for tobacco-related cancer, lung disease, and heart disease (Ref. 323). Switching completely to a noncombusted tobacco product would reduce exposure to the chemical constituents created through combustion, which are the primary contributors of combusted tobacco-related harm (Refs. 28 and 324).

However, as discussed throughout this document, if a nicotine tobacco product standard were to apply to cigarettes only, it likely would have substantially less impact on improving health outcomes for people who use tobacco products. Specifically, FDA expects that, to maintain their nicotine exposure, some people who smoke cigarettes and are addicted to nicotine would likely migrate to other combusted tobacco products (or begin to engage in dual use with such other products) with similar toxicological risks after such a cigarette-only standard was in effect. FDA also would expect that people who use non-cigarette combusted tobacco products would continue their existing use patterns, thereby maintaining their risk of tobacco-related death and disease. To ensure maximum benefits for this nicotine tobacco product standard, FDA is proposing that it apply to cigarettes and certain other combusted tobacco products.

1. Tobacco Product Switching in Behavioral Intention and Clinical Studies

Studies involving people who currently use cigarettes predict a range of tobacco use behaviors in response to a nicotine product standard. When presented with a hypothetical nicotine reduction policy, most people who use cigarettes report that they would continue to smoke VLNC cigarettes or use other combusted tobacco products, or that they would quit; only a small portion report that they would consider switching to a noncombusted tobacco product (Refs. 262 and 264). One experimental study using a nationally representative sample examined the intended behaviors of people who currently smoke cigarettes if a nicotine product standard were put in place; overall, 30.5 percent of the participants intended to quit using all tobacco products, 5.8 percent intended to switch to noncombusted tobacco products, and 61.0 percent indicated they would

[24] People who smoke RYO and pipe tobacco are susceptible to similar negative health consequences as people who smoke traditional cigarettes. While there is a paucity of research examining RYO and pipe tobacco use, FDA is not aware of any data indicating that RYO cigarettes or pipe tobacco are associated with fewer adverse health consequences than traditional cigarettes.

smoke VLNC cigarettes or other combusted tobacco products (Ref. 262). An in-depth qualitative study assigned a small number of people who use cigarettes to use VLNC cigarettes for 5 days, then examined their intended behaviors in response to a nicotine product standard (Ref. 264). Most participants reported that if a product standard was put in place, they would use VLNC cigarettes if they were the only cigarettes available, and a few said that they would use VLNC cigarettes to reduce their smoking over time to eventually quit. Some participants discussed the possibility of switching to ENDS or other combusted products if a product standard was put in place. Self-reported intentions to use tobacco products are a useful predictor of individuals' future tobacco use behavior (Refs. 325 and 326) and these two studies support FDA assessments of the likelihood of switching in response to the nicotine product standard.

In clinical studies that investigated the effects of VLNC cigarettes, researchers typically instructed participants assigned to VLNC cigarette groups to use only study-provided cigarettes (*i.e.,* to refrain from using usual brand cigarettes or other tobacco products during experimental conditions). Noncompliance with these instructions during a clinical trial may also indicate the likelihood that people who smoke VLNC cigarettes would use alternative nicotine-containing products if a nicotine product standard is implemented. Several studies reviewed in this document assessed biochemical or self-reported measures of VLNC cigarette noncompliance (*i.e.,* ongoing NNC cigarette or other tobacco product use) and showed high levels of noncompliance with smoking only VLNC cigarettes during the study. Since participants were provided with VLNC cigarettes at no cost and continued to use non-study provided tobacco products (particularly NNC cigarettes), these data suggest that VLNC cigarettes have lower appeal and abuse potential compared to NNC cigarettes (Refs. 327 to 331). These findings suggest that once a nicotine product standard covering solely cigarettes is in place and VLNC cigarettes are the only cigarettes available, people are likely to use alternative nicotine-containing products including other combusted products. However, if cigarettes and certain other combusted products are covered by a product standard, people who use combusted products are likely to use non-combusted products, therefore benefitting public health.

A clinical study conducted to compare the use of alternative nicotine-containing products (*i.e.,* smokeless tobacco, ENDS, NRT, cigars, cigarillos) and smoking behavior in 136 people who smoked cigarettes and were unwilling to quit randomly assigned participants to one of three conditions and instructed them to use only study-assigned tobacco products for 8 weeks (Ref. 5). The ''LNC1'' group received LNC cigarettes combined with noncombusted tobacco products (*i.e.,* smokeless tobacco, ENDS, NRT) and combusted non-cigarette tobacco products (*i.e.,* cigars, cigarillos), the ''LNC2'' group received LNC cigarettes combined with only noncombusted tobacco products, and the NNC cigarette group received NNC cigarettes combined with noncombusted and combusted non-cigarette products. Participants who received LNC cigarettes (both the LNC1 and LNC2 groups) used more alternative combusted tobacco products and more noncombusted tobacco products (the LNC2 group) than participants in the NNC cigarette group. However, these participants also smoked fewer total combusted tobacco products and had more quit attempts than participants in the NNC cigarette group. The findings from this study demonstrate that when people who smoke cigarettes are switched to LNC cigarettes and provided with alternative sources of nicotine, they will readily use the alternative sources of nicotine. Moreover, the LNC cigarette group (the LNC2 group) that had access to noncombusted nicotine sources only (*i.e.,* smokeless tobacco, ENDS, NRT) had statistically significantly lower biomarker levels of certain harmful constituents (N-Nitrosonornicotine (NNN) and NNAL) than those who continued to smoke NNC cigarettes and had access to noncombusted and combusted non-cigarette products (the LNC1 group) (Ref. 5). The NNN and NNAL biomarker levels in the LNC1 group with access to both combusted and noncombusted tobacco products resembled the NNC group (Ref. 5).

Taken together, these findings suggest that if the proposed product standard reduces the nicotine level in cigarettes only, but people who smoke cigarettes still have access to other NNC combusted tobacco products, they likely would substitute with the NNC combusted tobacco products. This behavior would negate a significant proportion of the public health impact of the product standard. If other combusted tobacco products also are covered by this proposed product standard, however, data suggest that people who smoke cigarettes would likely switch from combusted tobacco product use to potentially less harmful tobacco products. For further discussion of switching to a potentially less harmful nicotine delivery product, see section VIII.D.3 of this document.

2. Cigarette Price Increases

Studies investigating the effects of changes in cigarette prices on product substitution may also be used as an indicator of potential product switching in response to the proposed nicotine tobacco product standard, because a reduction in nicotine content could be conceptualized as an increase in the unit price of nicotine, as the cost to consumers is increased per unit of nicotine (Ref. 332). Therefore, studies assessing cigarette taxation may be useful because they are assessing the influence of changes in the unit price of cigarettes, through increases in cost, on behavior among people who use the products. Price increases, including taxation, represent one of the most effective tobacco control policies associated with significant declines in overall tobacco consumption as well as reductions in youth initiation rates (Ref. 333). However, taxation and price increases are also associated with a range of tax avoidance behaviors, such as substitution with a less expensive product, purchasing from low or untaxed sources, or purchasing in bulk (Ref. 334), and this behavior is more likely to occur among people who smoke and are of lower socioeconomic status (Ref. 335). It is this potential substitution that FDA is seeking to mitigate by proposing to cover certain other combusted tobacco products in addition to cigarettes. FDA expects that by reducing the nicotine in cigarettes and certain other combusted tobacco products through this proposed product standard, the effect on people who smoke will be similar to increasing the price, and, as is seen in examples of taxation and price increases, people who smoke would likely turn to alternative sources of nicotine.

An epidemiological study used data from the 2001 and 2002 New Jersey Adult Tobacco Survey (NJATS) to determine whether people who smoke cigarettes switched to cigars following an increase in the state cigarette excise tax (U.S. $0.80 to U.S. $1.50 per pack) (Ref. 336). In 2001, the cigarette smoking prevalence in New Jersey was 22.1 percent. Following a large cigarette excise tax increase, the cigarette prevalence decreased to 18 percent (Ref. 336). There were no statistically significant differences in the cigar smoking prevalence between 2001 and 2002; however, ever cigar use increased

statistically significantly for people who currently smoked cigarettes (50.9 percent versus 60.3 percent, respectively) and increased slightly for people who recently quit smoking (48.4 percent versus 56.4 percent, respectively). In 2001, people who currently smoked cigarettes had the highest prevalence of current cigar use (13.9 percent), while people who had recently quit cigarette use had the lowest prevalence (2.6 percent). In contrast, in 2002, while people who currently smoked cigarettes again reported the greatest prevalence of current cigar use (13.2 percent), people who had recently quit cigarette smoking had the second highest prevalence of current cigar use (11.1 percent). The authors concluded that after a cigarette excise tax increase, a small but notable proportion of people who had recently quit cigarette smoking tried cigars, substituted cigars for cigarettes, or continued using combusted tobacco products in the form of cigars (Ref. 336). Additional indirect evidence assessing trends in internet searches following the 2009 U.S. Federal tobacco tax increase showed that after the tax was announced, search queries increased for both combusted and noncombusted non-cigarette tobacco products (Ref. 337).

Similarly, several studies assessed changes in loose tobacco sales following a large tax increase in RYO tobacco and found decreases in RYO tobacco sales and increases in pipe tobacco sales as soon as the tax rate changed (Refs. 322, 338 to 340). Researchers analyzing publicly available Federal excise tax data from 2000 to 2015 found that total RYO tobacco sales statistically significantly decreased by 70.0 percent; however, total pipe tobacco sales increased by 556.4 percent (Ref. 340). Another study found a similar increase in pipe tobacco sales and decrease in RYO tobacco sales in response to tax differences between the products; however, self-reported pipe tobacco use, assessed via the NSDUH, remained consistent, and RYO consumption increased (Ref. 338). The authors suggested that people who smoke cigarettes may have bought loose tobacco labeled as pipe tobacco for use as RYO cigarettes as a tax avoidance strategy. These data suggest that following the implementation of a new tobacco control policy, manufacturers may modify their products and a significant proportion of consumers may modify their behavior to adapt to the changes (*e.g.,* switching to a similar combusted tobacco product if a final nicotine tobacco product standard covered cigarettes only), which would reduce the rule's potential public health effects. If cigarettes were the only product covered by the proposed product standard, a proportion of people who smoke cigarettes would likely to turn to certain other combusted products, thereby reducing the significant public health impact of this rule. Similarly, people who use certain other combusted products would not be affected by the reduction in nicotine in cigarettes and would also not benefit. Further, if cigarettes were the only product covered by the proposed product standard, the negative health effects of second- and thirdhand smoke from these other combusted products would still affect other non-smoking individuals exposed to these combusted products. However, if these certain other combusted products are covered, then the alternative products for those who switch (instead of quitting) likely would not be combusted, therefore benefitting public health.

3. Behavioral Economics Data

Behavioral economics utilizes principles of psychology and economics to predict purchasing behavior as a function of different market constraints (Ref. 341). Several studies have used real or hypothetical scenarios to investigate the impact of a change in price or availability of a given tobacco product on subsequent purchasing or use of another tobacco product. Purchasing behaviors observed in behavioral economics studies have been shown to be concordant with actual tobacco consumption and real purchase estimates (Refs. 342 to 344).

Studies have used retail sales data to investigate tobacco substitution as a function of price (Refs. 345 to 347). One study investigated relationships between purchasing patterns and price of cigarettes and little cigars. In 2013, a pack of little cigars was approximately 32 to 37 percent less expensive than a pack of cigarettes (Ref. 345). A 10 percent increase in the price of little cigars was associated with a 31.7 percent decrease in per capita little cigar sales, while a 10 percent increase in the price of cigarettes was associated with a 27.3 percent increase in per capita little cigar sales. The authors concluded that people who smoke cigarettes are price sensitive and avoided the higher cost of cigarettes by switching to little cigars. Another study estimated demand for cigarettes, little cigars/cigarillos, large cigars, e-cigarettes, smokeless tobacco, and loose tobacco using Nielsen's Convenience Track retail scanner database (Ref. 347). In this study, a 10 percent increase in the price of cigarettes resulted in an 18.6 percent increase in e-cigarette demand, showing that e-cigarettes substituted for cigarettes (Ref. 347). Although, in this study, large cigars, smokeless tobacco, and loose smoking tobacco were not associated with increased use in response to increasing cigarette prices, Nielsen retail sales data that were analyzed in another study showed that little cigars, RYO tobacco, and pipe tobacco each serve as substitutes for cigarettes (Ref. 346).

Studies have also used hypothetical purchase tasks to investigate responses by people who smoke cigarettes to potential tobacco policy changes or price increases (Refs. 348 and 349). One study used a simulated tobacco marketplace to measure purchasing behaviors among people who smoke cigarettes (Ref. 349). Participants could purchase cigarettes, e-cigarettes, cigarillos, gum, dip, lozenges, and snus. When cigarette prices increased, e-cigarette purchasing statistically significantly increased (Ref. 349). A study conducted in the Netherlands utilized a similar hypothetical tobacco marketplace to investigate hypothetical purchases for VLNC cigarettes as a function of varying scenarios (Ref. 348). Most relevant was the scenario where participants made hypothetical purchases for VLNC cigarettes, e-cigarettes, and NRT in a marketplace where NNC cigarettes were unavailable. VLNC cigarettes had the highest rate of purchase, followed by e-cigarettes, and then NRT. Approximately 20 percent of participants reported that they would not purchase any of the products if NNC cigarettes were unavailable (Ref. 348).

These data demonstrate that people who smoke cigarettes are willing to shift consumption toward both noncombusted and combusted non-cigarette tobacco products in times of economic or product constraint. Moreover, this evidence supports the conclusion that many people who smoke cigarettes likely would switch to other combusted tobacco products that contain nicotine if a nicotine product standard covered only cigarettes. Of additional concern is the potential for increased combusted non-cigarette tobacco product substitution among certain populations that may be price sensitive, such as individuals with low socioeconomic status compared to those with higher socioeconomic status (Ref. 335). One study showed that individuals of low socioeconomic status are 85 percent more likely to report using discount brands/RYO compared to participants with higher socioeconomic status (SES) in order to avoid an increase in the cost of their

preferred product, combusted cigarettes, and therefore, these individuals have a history of and comfort with switching to alternative combusted products when available at a lower cost (Ref. 335). Given that the research highlighted above has shown that a change in the availability of a tobacco product influences subsequent purchasing or use of other tobacco products, FDA is concerned that if the proposed nicotine product standard is limited to cigarettes, a large portion of individuals will seek out alternative sources of nicotine by using other combusted tobacco products if those products are not included within the scope of this rule.

VII. Discussion of Nicotine-Related Topics

A. Approach To Limiting User Exposure to Nicotine

Nicotine is the primary addictive constituent in all tobacco products, including cigarettes. FDA is proposing a tobacco product standard that would limit nicotine yield by establishing a maximum nicotine level in cigarettes and certain other combusted tobacco products to make these products minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health.

After consideration of the scientific literature, comments submitted in response to the Nicotine ANPRM, and the measured levels of nicotine content in research cigarettes (as reported in the literature, as well as in information submitted to FDA from industry), FDA is proposing that the maximum nicotine level in cigarettes and certain other combusted tobacco products not exceed 0.70 mg of nicotine content per gram of total tobacco in order to limit user exposure to nicotine.

Nicotine ''yield'' is the amount of nicotine in smoke, in other words, the amount of nicotine to which a smoker potentially is exposed. Nicotine yield is measured by a machine-generated protocol where the product is smoked by a machine in a prescribed manner and the smoke is collected in order to measure nicotine with another instrument, such as a gas chromatograph. Nicotine content refers to the total amount of nicotine present in the tobacco filler and is typically conveyed as either milligrams of nicotine per gram of total tobacco or milligrams of nicotine per product. The nicotine content of a tobacco product serves as a ceiling on nicotine yield, as it denotes the maximum amount of nicotine that a user can be exposed to when they smoke the cigarette or other tobacco product, and it cannot be manipulated by user behavior.

Setting a limit on nicotine content and measuring that content is more effective in reducing yield (*i.e.,* the amount of nicotine the user is exposed to) than setting a limit based on a direct measurement of yield under standardized smoking-machine protocols. This is because the way yield is measured by smoking machines does not accurately capture the amount of nicotine that is taken in by a person using the tobacco products. For example, manufacturers have developed ''low-yield'' cigarettes designed to markedly reduce yield results as measured by the Federal Trade Commission (FTC) testing method (Ref. 350). They decreased yields by manipulating various characteristics of the cigarettes (*e.g.,* decreasing the length of the available tobacco column, increasing the burn rate of the column, increasing filter efficiency, increasing air dilution in mainstream smoke, decreasing density of tobacco, or changing the concentration of nicotine in the tobacco) (Ref. 350 at Table 2–2). Many of these design changes led to the amount of nicotine measured in the machine-generated yield being different from—and less than—the amount of nicotine received by the smoker (Ref. 350). This disconnect is a result of smoking compensatory behaviors, such as smoking more cigarettes per day, increasing the number of puffs (with a smoker's last few puffs on a cigarette delivering disproportionately more nicotine than delivered in a smoking machine's standardized number of puffs), increasing puff volume and frequency, inhaling more deeply, and covering ventilation holes with fingers or lips, that enable smokers to overcome, intentionally or unintentionally, many of these design changes and, thereby, increase the amount of their nicotine intake compared to the machine-generated yield. They often do this to obtain adequate nicotine to satisfy their nicotine cravings (Ref. 350).

While standardized smoking machine puffing regimes in a controlled laboratory environment are effective in producing reproducible measurements of nicotine yield, as noted above, human behavior—how people smoke, including in response to cigarette-design features—influences the nicotine intake from a cigarette and can overcome features of a cigarette that lowered the machine-generated nicotine yield. For example, combusted cigarettes that were once referred to as ''light'' cigarettes achieved a reduction in machine-measured nicotine yield (*e.g.,* ISO machine smoking method, CI smoking method, FTC smoking method) through a variety of design changes to the cigarette, including the use of ventilation holes—although the actual nicotine content of the tobacco filler was not low. These design changes led to lower tar and nicotine yields in machine-generated smoke, and therefore, these products were labeled and marketed as low nicotine yield or ''light,'' ''low,'' or ''mild'' cigarettes. However, often unconsciously cigarette users could and did modify their use behaviors to compensate for these design changes and extract more nicotine from the products compared to the machine-generated yields, often to levels comparable to conventional cigarettes. For example, cigarette makers generally design cigarettes with ventilation holes far enough down the cigarette that they are not blocked during the FTC smoking test, but are easily blocked by users' fingers or mouths, and larger or more frequent puffs could be taken by consumers (Ref. 351). Through such compensatory smoking behaviors, cigarette users were able to overcome the changes in ventilation in these products, resulting in no benefit to public health (Ref. 350). There is ample research demonstrating that people who use ventilated cigarettes change their smoking behavior to increase their smoke intake, including taking larger puffs, inhaling more deeply, taking more frequent puffs, or increasing the number of cigarettes they smoke per day [25] (Refs. 350 to 361). As a result, evidence shows that many people are exposed to higher yields of smoke constituents, including nicotine, than the yields estimated by standardized smoking machine methods (Refs. 362 to 364). Further, researchers have reviewed the extensive body of literature on filter ventilation and health effects and concluded that there is strong evidence to suggest that filter ventilation has contributed to the rise in lung adenocarcinomas among people who smoke (Ref. 365). Studies that measure nicotine pharmacokinetics have also found that the relative percentage of free nicotine in smoke may increase with percent of filter ventilation (Ref. 366), which suggests that greater filter ventilation may expose smokers to greater free nicotine levels that can lead to greater total nicotine exposure while smoking as this form of nicotine is more easily absorbed by the body.

[25] See section VII.B 4., Smoking Topography, of this document for further discussion of compensatory smoking and VLNC cigarettes.

In contrast, reducing the nicotine content in cigarettes and certain other combusted tobacco products places an absolute maximum limit on the amount of nicotine that can be extracted (*i.e.,* yielded) by the user. VLNC cigarettes, in contrast to low nicotine yield cigarettes generated by other design changes, are associated with minimal and transient compensatory smoking because people who smoke these cigarettes are unable to obtain adequate amounts of nicotine through these behaviors; therefore, they stop trying to do so. In sum, limiting nicotine yield through a maximum nicotine content level would be more effective in achieving the public health benefits that come from reducing the amount of the nicotine to which a user is exposed than would setting a limit based on a measurement of the maximum yield of tobacco products.[26]

B. Scientific Evidence Supports the Target Level of Nicotine

Many studies have investigated the effects of VLNC cigarettes on behavioral outcomes, including smoking cessation, use behaviors, biomarkers of exposure, and physiological effects. Findings from these studies are discussed in this section, and they suggest that individuals who smoke VLNC cigarettes with nicotine levels similar to what FDA is proposing here are more likely to make a quit attempt, reduce smoking, demonstrate reduced exposure to harmful and potentially harmful constituents (HPHCs), and demonstrate similar or reduced physiological responses to cigarettes relative to individuals who smoke usual brand or NNC cigarettes. Results from these and other studies suggest that switching to VLNC cigarettes does not lead to compensatory smoking (see this section and VII.B.4 of this document for further discussion of compensatory smoking).

Therefore, the data reported in the scientific literature support a tobacco product standard limiting nicotine yield by setting a maximum nicotine content level in cigarettes and certain other combusted tobacco products to a maximum of 0.70 mg of nicotine per gram of total tobacco. FDA believes that this maximum nicotine level would provide the appropriate flexibility to account for variations in tobacco growing seasons and variations in analytical testing. FDA requests comments, data, and research regarding this proposed maximum nicotine level.

1. Origin of the Proposed Product Standard

In 1994, Benowitz and Henningfield proposed the idea of Federal regulation of nicotine content in combusted tobacco products to a level too low to sustain addiction (Ref. 367). They considered the smoking habits of a small population of people who smoke cigarettes intermittently and who demonstrate reduced nicotine dependence (a group sometimes referred to as tobacco ''chippers'') to inform indirect estimates of a nicotine level that they proposed would be too low to sustain addiction in most people who smoke cigarettes. Chippers are typically characterized by smoking five or fewer CPD, with limited or no withdrawal symptoms, and by being able to skip smoking for days at a time (Ref. 368). Based on their estimates of nicotine exposure among chippers, the researchers proposed a level of nicotine per cigarette—approximately 0.5 mg of nicotine per cigarette—that should be low enough to prevent or limit the development of nicotine addiction in most young people. The nicotine level proposed by Benowitz and Henningfield was an initial estimation based on observational data, and there is individual variability in dose sensitivity to all addictive substances; however, the initial estimate posed by Benowitz and Henningfield paved the way for subsequent prospective clinical studies designed to evaluate the addiction potential of VLNC cigarettes.

Several brands of commercial and research cigarettes were manufactured to contain a nicotine content similar to that originally proposed by Benowitz and Henningfield (see table 1 of this document). Using these cigarettes, researchers have consistently demonstrated that VLNC cigarettes have reduced addiction potential compared to NNC cigarettes.

22nd Century Group Inc., the company that developed SPECTRUM Nicotine Research Cigarettes and whose genetically engineered tobacco was used to make Quest cigarettes, submitted modified risk tobacco product applications to FDA that reported that the actual average value of nicotine content in its genetically engineered VLNC tobacco is 0.6 mg nicotine per gram of total tobacco, with a range of 0.4 to 0.7 mg nicotine per gram of total tobacco (see section V.A of this document for a discussion of the history of LNC and VLNC cigarettes, including the SPECTRUM Nicotine Research Cigarettes).[27] The natural variation of this agricultural product resulted in the slight variation in the nicotine content of the tobacco filler within the company's internal range of acceptable values. The average value and range were compiled by the company from 9 years of sampling data of the genetically engineered tobacco that was used to make SPECTRUM and Quest cigarettes. It is likely that the cigarettes used throughout the scientific literature, reported as having 0.4 mg nicotine per gram of total tobacco, may have, in actuality, been between 0.4 and 0.7 mg of nicotine per gram of total tobacco. This range is consistent with the scientific evidence to support a minimally addictive or nonaddictive level of nicotine content in cigarettes and certain other combusted tobacco products, and FDA took these data from 22nd Century Group Inc.'s VLNC cigarettes into consideration when determining the appropriate, technically feasible maximum level of nicotine content to propose in this product standard.

2. Smoking Cessation

A number of studies investigated the effects of VLNC or LNC cigarettes alone or in combination with NRT on smoking cessation among people who smoke but are interested in quitting (Refs. 32, 35, 41, 369 to 373) and those uninterested in quitting (Refs. 31, 40, 258, and 374). As stated throughout this document, most adults who use tobacco products wish to quit but are unsuccessful because of the highly addictive nature of these products (Refs. 1, 13, 28, 58, and 61) (see section IV.A of this document for a discussion of the addictiveness of nicotine). Taken together, results from these studies demonstrate that people who smoke and are interested in quitting who are given VLNC cigarettes are more likely to achieve initial smoking abstinence compared to those who continue to smoke their usual brand or NNC cigarettes. In addition, provision of NRT and/or behavioral intervention with VLNC cigarettes may further increase smoking cessation among individuals interested in quitting (Ref. 19).

Research demonstrates the benefits of VLNC cigarettes for those people who smoke and are interested in quitting. In one of the clinical trials that has examined the effects of VLNC cigarettes

[26] Consistent with the proposed limit on nicotine content, FDA is also proposing testing for nicotine content only, rather than both content and yield. This testing requirement is less burdensome yet still effective in measuring the maximum nicotine yield, *i.e.,* the maximum amount of nicotine to which a user can be exposed.

[27] On December 23, 2021, FDA issued exposure modification orders to 22nd Century Group Inc. for VLN King and VLN Menthol King combusted, filtered cigarettes. See *https://www.fda.gov/tobacco-products/advertising-and-promotion/22nd-century-group-inc-modified-risk-tobacco-product-mrtp-applications.*

alone on smoking cessation in people who smoke cigarettes who were interested in quitting, 165 people who smoke were randomized to use LNC cigarettes, VLNC cigarettes, or 4 mg nicotine lozenges for 6 weeks (Ref. 32). While there were no statistically significant differences between groups in CO-verified point prevalence abstinence (*i.e.,* quit) rates at 1–4-week followup visits, abstinence rates at the week 6 followup visit were statistically significantly higher in the VLNC cigarette group (47.2 percent) and nicotine lozenge group (36.7 percent) relative to the LNC cigarette group (23.1 percent) (Ref. 32). In another randomized clinical trial (RCT), 346 people who smoked and were interested in quitting were randomized to receive 6 weeks of (1) a combination of VLNC cigarettes (nicotine was gradually reduced from NNC to LNC to VLNC cigarettes every 2 weeks) and nicotine patch (VLNC cigarettes + NRT); (2) VLNC cigarettes and a placebo patch (VLNC cigarettes only); or (3) NNC cigarettes and NRT after their quit date (NNC cigarettes + NRT) (Ref. 369). Following their quit date at week 7, the VLNC cigarettes + NRT group continued to receive NRT, the VLNC cigarettes only group received placebo patches, and the NNC cigarettes + NRT group was provided with NRT during weeks 7–10. Biochemically confirmed continuous abstinence rates were 32.8 percent in the VLNC cigarettes + NRT group, 16.4 percent in the VLNC cigarettes only group, and 21.9 percent in the NNC cigarettes + NRT group (Ref. 369), suggesting that the combination of VLNC cigarettes and NRT is more effective at promoting continuous abstinence than VLNC cigarettes alone. However, abstinence at 3- and 6-month followups could not be adequately assessed due to attrition (Ref. 369).

Many other studies conducted in individuals interested in quitting investigated the effects of LNC or VLNC cigarettes combined with NRT (Refs. 41, 35, 371 to 373, and 375). For example, in a study conducted in New Zealand, 1,410 callers to a quitline were randomized to receive VLNC cigarettes with usual quitline care (8 weeks of NRT and behavioral support via a quitline) or usual care alone (Ref. 373). Six months after the quit date, 7-day point-prevalence abstinence rates [28] were statistically significantly greater in participants using VLNC cigarettes with usual quitline care (33 percent) compared to the group who received usual quitline care alone (28 percent). Continuous abstinence rates at month 6 also were statistically significantly higher for participants who received VLNC cigarettes with usual quitline care (23 percent) compared to those who received usual quitline care alone (15 percent). Likewise, in another study, 98 persons who reported heavy smoking (*i.e.,* greater than or equal to 20 CPD) received either VLNC cigarettes and a 21 mg nicotine patch or NNC cigarettes for 2 weeks prior to quitting (Ref. 372). After the quit date, all study participants wore nicotine patches for up to 8 weeks. Participants who smoked VLNC cigarettes and received patches reported less frequent and less intense cravings during the 2 weeks before and after the quit date, suggesting that use of VLNC cigarettes plus NRT may aid in cessation by reducing cigarette craving during a quit attempt. Participants in the VLNC cigarettes + NRT group had a higher self-reported quit rate compared to those in the NNC cigarettes + NRT group at 3 months (43 percent vs. 34 percent, respectively) and 6 months (28 percent vs. 21 percent, respectively), but these quit rates did not differ statistically significantly between groups, likely due to a small sample size precluding sufficient statistical power.

Several other studies have investigated the effects of VLNC or LNC cigarettes on smoking cessation among individuals uninterested in quitting (Refs. 31, 40, 258 and 374). In an RCT, participants received either NNC cigarettes or VLNC cigarettes (double-blinded, *i.e.,* neither the participants nor the researchers knew which type of cigarette participants received), and either received or did not receive a transdermal nicotine patch (open-label, *i.e.,* participants and researchers were aware of whether participants received NRT) for 7 weeks. At week 7, participants were provided a daily descending monetary bonus for refraining from using any cigarettes. Participants randomized to receive NRT were encouraged to continue using their patches. Although participants who received VLNC cigarettes smoked statistically significantly fewer total CPD than participants who received NNC cigarettes, during the abstinence period, no groups differed statistically significantly from the NNC cigarette-only group in time to lapse or number of days abstinent; however, these results were likely influenced by low adherence to VLNC cigarette use in this study (Ref. 376). In another series of studies, participants received gradually reduced nicotine content cigarettes over a period of 6 months, beginning with NNC cigarettes and ending with VLNC cigarettes (Refs. 258 and 374). In the first study, a statistically significantly greater proportion of participants who received VLNC cigarettes considered quitting at the end of the study, compared to those in a control group who smoked their usual brand cigarettes throughout the study (Ref. 258). In a followup study in which a subset of participants was followed for 2 years, cotinine levels in the gradual nicotine reduction group rose to baseline levels or levels similar to those of the control group after 12 months during which both groups could freely smoke usual brand cigarettes (Ref. 374). Although 7.5 percent of participants in the gradual reduction group quit smoking, compared to only 2 percent of participants in the usual brand control group, this difference was not statistically significant (Ref. 374). In another study, 33 participants were randomized to receive VLNC cigarettes or to continue to smoke their usual brand cigarettes for 12 weeks (Ref. 31). The availability of VLNC cigarettes increased quit attempts in people who smoked cigarettes and had no intention of quitting (Ref. 31).

Furthermore, several extended duration VLNC studies demonstrated how VLNC cigarettes can increase cessation by assessing self-reported quit attempts as a secondary study aim. While one study showed no statistically significant differences in quit rates among people who smoke cigarettes on a nondaily basis who used VLNC or NNC cigarettes for 10 weeks (Ref. 377), other studies showed that participants who smoked VLNC cigarettes were more likely to report a quit attempt after 6 weeks of use (Ref. 29) and had a greater number of cigarette-free days after 12 (Ref. 378) and 18 weeks (Ref. 379) compared to those who smoked NNC cigarettes. However, a secondary analysis of the 18 week study (Ref. 379) found that there were no significant differences in quit rates or intention to quit at the 6-month followup timepoint (Ref. 380).

Among the studies evaluating smoking cessation following VLNC cigarette use, few utilized a randomized controlled trial design, and results were sometimes inconsistent, particularly related to long-term followup. However, the weight of evidence from these studies suggests that among people who smoke and are interested in quitting, using VLNC cigarettes can facilitate initial smoking abstinence, particularly when used along with NRT and/or behavioral intervention. Among people

[28] Seven-day point prevalence abstinence is a measure of, in this case, tobacco cessation outcomes for quitlines. At a given point in time (in this case, 6 months after the quit date), study participants are asked whether they have used cigarettes or other forms of tobacco in the past 7 days.

who smoke but are uninterested in quitting, VLNC cigarette use did not increase quit rates; however, it did increase quit attempts. It is important to note that studies evaluating smoking cessation following VLNC cigarette use took place in an environment where NNC cigarettes and other combusted tobacco products remained readily available. For this reason, the available data likely underestimates the likelihood of increased cessation rates following the implementation of a nicotine product standard because NNC cigarettes would no longer be available, making relapse to these cigarettes no longer possible.

3. Cigarettes Per Day (CPD)

One concern raised by some with regard to a reduced nicotine policy is whether people who smoke might alter their smoking behavior by smoking additional cigarettes in order to attempt to compensate for the lower amounts of nicotine, but studies show that extended use of VLNC cigarettes does not produce increases in CPD. Researchers typically assess CPD via participant self-reporting or by counting cigarette filters or packs returned by participants. By measuring CPD during an extended exposure trial, researchers can determine whether switching to VLNC cigarettes produces changes in CPD compared to usual brand or NNC cigarette conditions. Research conducted in the absence of the proposed standard shows that switching to LNC or VLNC cigarettes can produce modest decreases in CPD. However, as noted previously, studies evaluating changes in CPD following VLNC cigarette use took place in an environment where NNC cigarettes and other combusted tobacco products remained readily available, likely underestimating the potential reductions in CPD following implementation of a nicotine product standard because NNC cigarettes and other combusted tobacco products would no longer be legally available. These findings suggest that, if the proposed product standard were finalized and implemented, people who smoke VLNC cigarettes would not increase CPD to compensate for reduced nicotine exposure, and FDA expects that for many CPD would decrease over time.

Many studies measured VLNC CPD under conditions of extended exposure (*e.g.,* several consecutive weeks or longer). These studies varied in sample size, duration of exposure, average CPD requirements to enter the study, participants' intentions to quit smoking, and the method in which participants transitioned from usual brand cigarettes to VLNC cigarettes (*i.e.,* gradual versus immediate reduction in nicotine content). Despite these differences in study methods and participant characteristics, nearly all the studies came to a similar conclusion: relative to usual brand or NNC cigarette conditions, CPD was similar (*i.e.,* there was no compensatory smoking) (Refs.31, 35, 329, 369, 374, 381 to 385,) or lower in VLNC cigarette conditions (Refs. 29, 32, 41, 265, 386, and 387). Notably, studies that found lower CPD while participants smoked VLNC cigarettes tended to have larger sample sizes (Refs. 29 and 379), which may have had more statistical power to detect relatively small but consistent differences in CPD across conditions.

One limitation of some studies that examined the effects of VLNC cigarette smoking on CPD is that comparisons between VLNC CPD and usual brand or NNC CPD were made without taking into account the number of non-study cigarettes smoked per day in experimental conditions. A measure of ''total CPD'' in VLNC cigarette conditions would include the number of study-assigned VLNC cigarettes plus the number of usual brand or non-study cigarettes smoked by participants who were not fully compliant with study procedures. Few studies have compared total CPD across VLNC and usual brand or NNC cigarette conditions. However, one study found that, relative to usual brand and NNC cigarette conditions, the combination of study- and non-study-assigned CPD was lower in VLNC and LNC cigarette conditions when nicotine content was less than or equal to 2.4 mg nicotine per gram of total tobacco, and that those participants who used VLNC cigarettes (*i.e.,* 0.4 mg nicotine per gram of total tobacco), demonstrated reduced use and dependence with minimal evidence of withdrawal-related discomfort or safety concerns (Ref. 29). Another study found that fewer combusted tobacco products were smoked during LNC cigarette conditions relative to an NNC cigarette condition (Ref. 5). A study where participants were confined to a hotel in order to limit their access to non-study products assessed the potential effects of VLNC cigarettes on compensatory smoking behaviors (Ref. 388). Participants completed two 4-night stays; during their first stay, they were randomized to receive either NNC or VLNC cigarettes and were randomized to the other group during their second stay. Furthermore, participants were given an ''account balance'' where they could purchase study cigarettes from a ''cigarette store'' during the study. Investigators found that by the end of the four night stays the number of cigarettes participants smoked did not differ statistically significantly between the NNC and VLNC cigarette groups, indicating that people who smoke may not engage in compensatory smoking behavior when only VLNC cigarettes are available (Ref. 388). Another study compared the effects of VLNC and NNC cigarettes on CPD in people who smoke who inhabited a residential research facility throughout the study. The results showed that when participants had access to only VLNC cigarettes for 11 days, they smoked statistically significantly fewer CPD than those who had access to only NNC cigarettes (Ref. 64).

Taken together, these studies indicate that extended use of VLNC cigarettes does not produce increases in CPD in an attempt to compensate for the reduced nicotine levels. FDA expects that this may result in reductions in CPD among people who do not quit, particularly in an environment where NNC cigarettes are not legally available.

4. Smoking Topography

Smoking topography refers to various aspects of smoking behavior, including number of puffs per cigarette, total time spent smoking, puff volume (*i.e.,* puff size), puff velocity (*i.e.,* puff intensity), puff duration, and inter-puff interval (*i.e.,* length of time between puffs). Although some of these outcomes (*e.g.,* puffs per cigarette) can be measured via direct observation, smoking topography is typically assessed with an electronic puff topography unit attached directly to a cigarette. Smoking topography measures that indicate more intense smoking behavior may be attributed to compensatory smoking. A concern raised by some with regard to a nicotine reduction policy is whether people who smoke might engage in compensatory smoking behavior to try to extract more nicotine from the cigarettes, thus increasing exposure to tobacco-related toxicants. Smoking topography study results are mixed, but the majority of studies show that individuals who smoke VLNC cigarettes demonstrate no statistically significant differences in smoking topography relative to those who smoke usual brand or NNC cigarettes, or they demonstrate changes in smoking topography measures that are associated with reductions in tobacco smoke exposure (*e.g.,* lower total puff volume) rather than increased compensatory smoking.

Some studies found no differences in smoking topography between VLNC and NNC or usual brand cigarette conditions (Refs. 389 to 391). However, many other

studies found that smoking topography differed between cigarette conditions. Some of the more reliable findings replicated across studies were the effects of VLNC cigarettes on total puff volume and number of puffs per cigarette. Under conditions of both brief (*e.g.,* several hours) and extended (*e.g.,* several weeks) exposure, studies found that total puff volume was lower (Refs. 29, 34, 383, 384, and 392) and number of puffs per cigarette was lower (Refs. 329, 384, 392, and 393) when participants smoked VLNC cigarettes, relative to usual brand or NNC cigarettes. However, two brief exposure studies showed higher puff volumes (Refs. 393 and 394) and puff duration (Ref. 394) when participants smoked VLNC cigarettes in short laboratory sessions. Another brief exposure study conducted in adolescents showed that VLNC cigarettes produced higher numbers of puffs relative to NNC cigarettes; however, additional measures were not collected to determine whether this was a transient or lasting effect (Ref. 395). An extended exposure study showed initial decreases in puff volume when participants smoked VLNC cigarettes relative to NNC cigarettes, but these differences dissipated over the course of 7 days (Ref. 383). Finally, limited evidence suggests that VLNC cigarettes are smoked faster (Refs. 259 and 396), are smoked with increased peak velocity (Ref. 384) and may decrease inter-puff intervals when compared to NNC cigarettes (Ref. 392).

In all, while smoking topography study results are mixed, the majority of studies show that individuals who smoke VLNC cigarettes demonstrate no statistically significant differences in smoking topography relative to those who smoke usual brand or NNC cigarettes, or they demonstrate changes in smoking topography measures that are associated with reductions in tobacco smoke exposure (*e.g.,* lower total puff volume) rather than increased compensatory smoking.

5. Abuse Potential

Abuse potential refers to the ability of a product to promote continued use and the development of dependence. Choice studies are commonly used to measure abuse potential, where preference for one tobacco product over another indicates greater abuse potential. When participants are asked to make a real or hypothetical choice between VLNC cigarettes and NNC cigarettes in research studies, they reliably choose NNC cigarettes (Refs. 391, 397 to 401). Combined with data showing that VLNC cigarettes are associated with significantly lower plasma nicotine exposure (Ref. 402) and decreased positive subjective effects compared to NNC and usual brand cigarettes (Ref. 391), these data indicate lower abuse potential of VLNC cigarettes. However, research has also shown that the choice between VLNC and NNC cigarettes can be influenced by factors such as cost or effort, such that when the effort required to obtain NNC cigarettes increases, some people who smoke cigarettes will switch their preference from NNC cigarettes to VLNC cigarettes (Ref. 398). For example, one laboratory study investigating tobacco product choice when participants were provided with an experimental income found that, although participants rated VLNC cigarettes as less satisfying than both LNC and NNC cigarettes, they purchased statistically significantly more puffs of the VLNC cigarettes when LNC and NNC cigarettes were more expensive (Ref. 403). Thus, if the proposed product standard is implemented and the cost, effort, or risk associated with obtaining NNC cigarettes increases, individual preference may shift to VLNC cigarettes or more readily available tobacco products rather than attempting to seek out illicitly marketed NNC products. If the proposed product standard were to apply only to cigarettes, these findings also indicate that people who smoke cigarettes who do not quit after a final rule goes into effect would likely be willing to switch to other NNC combusted tobacco products rather than using VLNC cigarettes. If this were the case, the public health benefit of the proposed product standard would be reduced.

Hypothetical choice tasks (*e.g.,* cigarette purchase task, multiple choice questionnaire) are used to characterize reinforcing efficacy by determining how changes in the cost of a commodity affect its consumption. These tasks typically involve prior experience with the product or brief laboratory exposure, followed by a series of questions asking participants to either (1) report how many cigarettes they would consume at a variety of escalating prices; or (2) choose between cigarettes or money at a variety of prices. Studies that used hypothetical choice tasks to assess VLNC cigarette reinforcement showed that participants find VLNC cigarettes to be less reinforcing than NNC cigarettes (Refs. 265, 343, and 391). In one study, the reinforcing efficacy of cigarettes varying in nicotine content following 6 weeks of access to the products was examined (Ref. 343). Compared to the NNC cigarette group, those in the VLNC cigarette group estimated that they would smoke fewer cigarettes even if the cigarettes were free, spend less for the VLNC cigarettes, and quit smoking VLNC cigarettes at a lower price point (*i.e.,* a price point at which participants would continue to pay for NNC cigarettes). Responses on the hypothetical choice task were highly correlated with the actual number of cigarettes smoked during week 6 of the study.

Hypothetical choice tasks can also be used to investigate the substitutability of tobacco products. For example, another study employed a cross-price elasticity task in which the price of VLNC cigarettes was held constant while the price for usual brand cigarettes was manipulated (Ref. 404). When usual brand cigarette price increased, demand for VLNC cigarettes increased and demand for usual brand cigarettes decreased, indicating that VLNC cigarettes are a partial substitute for usual brand cigarettes (Ref. 404).

Rather than directly assessing choice between tobacco products, some studies evaluate how much people who smoke are willing to work to earn puffs from cigarettes when the number of responses required to earn a puff progressively increases (*i.e.,* a progressive ratio task). One study that used this method found that participants assigned to an NNC cigarette group were willing to work statistically significantly harder to earn puffs from their NNC cigarette than participants assigned to a VLNC cigarette group, indicating greater abuse liability (*i.e.,* ability to promote continued use and the development of dependence) of the NNC cigarette (Ref. 64).

These studies demonstrate that VLNC cigarettes are consistently shown to be of lower abuse potential compared to NNC cigarettes, as evidenced by responses to behavioral and hypothetical choice procedures. Behavioral and hypothetical choice research has also shown that the choice between VLNC and NNC cigarettes can be influenced such that some people will switch their preference from NNC cigarettes to VLNC cigarettes when the price or effort required to obtain the products increases. See section VI.B of this document for further discussion on the impact of cigarette price on switching behavior.

6. Biomarkers of Exposure

Research demonstrates that, following VLNC cigarette use, some biomarkers of exposure (*e.g.,* CO, measured as breath CO or carboxyhemoglobin (COHb)) are typically similar to those observed following NNC cigarette use, while other biomarkers (*e.g.,* total nicotine

equivalents (TNE), which are a combination of nicotine, cotinine, and other nicotine metabolites collected through plasma, saliva, or urine) are typically lower following VLNC cigarette use. However, no biomarkers of exposure are reliably observed to be higher following VLNC cigarette use relative to NNC cigarette use, meaning that study participants are not engaging in compensatory smoking behaviors.

Some of the most commonly measured biomarkers of tobacco smoke exposure are CO, plasma nicotine, cotinine (collected through plasma, saliva, or urine), TNE, and other HPHCs or their metabolites (*e.g.,* NNN, NNAL, Benzo[a]pyrene (BAP), 3-hydroxypropyl mercapturic acid (3–HPMA), S-phenylmercapturic acid (S–PMA)). While nicotine and its metabolites would be expected to decrease in individuals who switch from NNC to VLNC cigarettes, other biomarkers of exposure would be expected to remain the same if smoking behavior remained unchanged. Thus, any changes in biomarker levels observed between NNC and VLNC cigarette conditions in clinical studies may indicate differences in smoking behavior (*e.g.,* changes in CPD or smoking topography) between these two groups. Notably, due to the short half-lives of some biomarkers (*e.g.,* breath CO), decreases in smoking can produce decreases in these biomarkers during brief exposure studies. However, decreases in smoking may not produce decreases in some biomarkers (*e.g.,* NNAL) under such conditions due to the prolonged half-lives of these biomarkers.

Most studies have found no differences in CO exposure between participants who smoke VLNC cigarettes and those who smoke usual brand or NNC cigarettes (Refs. 5, 29, 32, 34, 40, 258, 374, 376, 383, 387, 388, 390, 391, 393, 395, 396, 402, 405 to 417,). This finding may be somewhat unexpected as many studies have found that participants smoke fewer CPD when they smoke VLNC cigarettes relative to NNC or usual brand cigarettes. However, although CO is positively associated with CPD, research has shown that the correlation may only be of moderate strength (Ref. 418). Furthermore, CO may be impacted by noncompliance with study cigarettes (see section VI.B of this document for a discussion about noncompliance).

Nevertheless, differences were observed between VLNC and NNC cigarette conditions in a few studies. Two brief exposure studies in which participants were given limited access to reduced nicotine content cigarettes over the course of several hours under controlled laboratory conditions found increases in breath CO following VLNC cigarette use relative to NNC cigarette use (Refs. 419 and 420). In addition, an extended exposure study (over the course of 35 days) showed that CO levels initially increased when participants switched from usual brand cigarettes during baseline to VLNC cigarettes; however, these effects dissipated over time as CO levels eventually returned to baseline levels (Ref. 384). As discussed in section VIII.D.7 of this document, these limited increases in CO exposure may be due to changes in smoking topography. At least one extended exposure study found decreases in CO boost (the difference between measured CO levels before and after smoking a cigarette) after VLNC cigarette use compared to usual brand cigarettes (Ref. 329). In another study, one group of participants smoked NNC cigarettes throughout the study, a second group smoked study cigarettes with gradually reduced nicotine contents, and a third group immediately switched to VLNC cigarettes (Ref. 421). This study found that subjects in the immediate VLNC cigarette group had statistically significantly lower CO than did the NNC cigarette or gradual reduction groups. Breath CO for participants in the NNC cigarette and gradual reduction groups did not differ statistically significantly from each other (Ref. 421). Moreover, the only study to date that examined the effects of VLNC cigarettes on breath CO in people who smoke who inhabited a residential research facility found that when participants only had access to study cigarettes for 11 days, those who were assigned VLNC cigarettes had statistically significantly lower breath CO than those who were assigned NNC cigarettes. Furthermore, these differences increased over the course of each day such that they were much larger in the afternoon than in the morning (Ref. 64).

Notwithstanding the differing CO studies, studies that examined nicotine, cotinine, or TNE levels had overwhelming concurrence regarding the effects of either brief or extended exposure to VLNC cigarettes compared to usual brand or NNC cigarettes. VLNC cigarette use resulted in substantially lower levels of nicotine, cotinine, and TNE than usual brand or NNC cigarettes (Refs. 5, 29, 32 to 34, 40, 258, 329, 370, 374, 376, 382 to 384, 387, 388, 390, 402, 403, 406, 407, 410, 413, 417, and 419 to 425). One within-subjects laboratory study compared the nicotine pharmacokinetic profile of VLNC, LNC, NNC, and usual brand cigarettes in 12 participants who smoked cigarettes daily (Ref. 402). While each of the four cigarettes produced statistically significant increases in plasma nicotine boost (*i.e.,* peak plasma nicotine level minus baseline level) after smoking, the VLNC and LNC cigarettes had statistically significantly lower plasma nicotine boost and $AUC_{0–120}$ (*i.e.,* plasma nicotine area under the curve calculated for the first 120 minutes following product use, indicating extent of exposure to nicotine and its clearance rate from the body) compared to the NNC and usual brand cigarettes. These data show that although VLNC cigarettes are associated with significantly lower nicotine uptake compared to NNC and usual brand cigarettes, the cigarettes still deliver a measurable amount of nicotine.

The effects of VLNC cigarette exposure on other HPHCs were less reliable across studies. Nevertheless, studies consistently found that VLNC cigarette exposure either reduced or did not change exposure to NNN, NNAL, urinary 1-hydroxypyrene, or BAP relative to NNC or usual brand cigarettes (Refs. 5, 29, 32, 40, 258, 382, 384, and 329). Two studies also examined 3–HPMA and S–PMA levels and found that these biomarkers decreased in VLNC cigarette conditions compared to LNC and NNC cigarette conditions (Ref. 32). Another study found that an immediate switch to VLNC cigarettes statistically significantly reduced exposure to acrolein and phenanthrene tetraol (both are biomarkers of smoke exposure) throughout a 20-week study duration compared to a gradual reduction approach (Ref. 379). The reductions in biomarkers that were observed in some of these studies following VLNC cigarette exposure were typically correlated with decreases in CPD or other smoking behaviors. Thus, as expected, VLNC cigarette use resulted in fewer CPD, which resulted in overall reductions in HPHC exposure. Importantly, none of the studies found that VLNC cigarette use resulted in increases in any of these other HPHCs or their biomarkers. Taken together, these studies support that VLNC cigarette use is associated with biomarker exposure that is similar to or lower than NNC cigarette use.

7. Physiological Effects

Physiological measures may be proxy measures for the stimulant effects of nicotine. Pharmacodynamic effects of nicotine include central and peripheral nervous system stimulation, arousal, and increased heart rate or blood pressure. Nicotine is a known stimulant, but physiological effects may occur in

response to combusted tobacco products even in the absence of nicotine in those who regularly use cigarettes and certain other combusted tobacco products due to behavioral conditioning or other psychoactive chemicals in tobacco smoke. Data show that physiological effects related to VLNC cigarettes are similar or less pronounced than those produced by NNC cigarettes, suggesting that the nicotine in the VLNC cigarettes is able to produce physiological effects.

There is slight variability in the data assessing the physiological effects of VLNC cigarettes. Some studies show that, regardless of nicotine content, acute cigarette smoking is associated with an increase in baseline heart rate (Refs. 259, 407, 411, and 419); however, these increases were either less pronounced following VLNC cigarette use compared to NNC cigarette use (Refs. 259 and 407) or were less consistent (*i.e.,* observed at some but not all time points following use) (Ref. 411). Some research has shown that escalations in heart rate dissipate after repeated exposure to VLNC cigarettes but not usual brand cigarettes (Ref. 407). In contrast, other studies did not observe increases in heart rate when participants smoked VLNC cigarettes (Refs. 250, 413, 417, and 426), and several studies showed statistically significantly reduced escalations in heart rate compared to acute LNC, NNC, or usual brand cigarette administration (Refs. 64, 249, 265, 390, 405, 415, 427, and 428).

Some studies also investigated the effects of VLNC cigarettes on blood pressure. Several studies found no differences in blood pressure after smoking a VLNC cigarette compared to an LNC cigarette (Refs. 249 and 419), NNC cigarette (Ref. 259), or usual brand cigarette (Refs. 249, 259, and 419). However, other studies showed statistically significantly greater increases in blood pressure after smoking NNC or usual brand cigarettes relative to VLNC cigarettes (Refs. 265 and 390).

A small number of studies examined the effects of VLNC cigarettes on skin temperature and skin conductance (a measure of sympathetic nervous system activity indicating psychological or physiological arousal). Although one study showed that skin temperature decreased to a greater extent with NNC cigarettes compared to VLNC cigarettes (Ref. 259), another study found no differences in skin temperature as a function of nicotine content in cigarettes (Ref. 426). Another study found no statistically significant differences in skin conductance between VLNC and NNC cigarettes (Ref. 429).

Taken together, findings from these studies suggest that VLNC cigarettes produce physiological responses that are similar to or less pronounced than those produced by NNC cigarettes. These data suggest that the nicotine in the VLNC cigarettes is able to elicit physiological responses in people who smoke cigarettes, although a portion of the response may also be due to sensorimotor cues, or other stimuli associated with smoking, that may have conditioned participants to produce these physiological effects due to the historical repeated pairings with nicotine.

8. Neurological Effects

The main target of nicotine in the central nervous system is the nicotinic acetylcholine receptor (nAChR). Positron emission tomography (PET) and magnetic resonance imaging (MRI) data obtained from humans who smoke using an nAChR-specific radiotracer indicates that after smoking a VLNC cigarette, nAChR receptors located in numerous areas of the brain are occupied despite the lower nicotine content of VLNC cigarettes (Ref. 430).

Nicotine also activates the dopaminergic brain reward system, which results in dopamine release and a pleasure response. The release of dopamine also initiates an adaptive process in which an individual forms learned associations between the subjective state (*e.g.,* pleasure) and the object or context that led to that state (*e.g.,* the act of smoking a cigarette) (Ref. 389). Through this process, both nicotine administration and smoking stimuli (*e.g.,* a cigarette, a lighter) contribute to the cycle of nicotine dependence (Ref. 38). Smoking NNC cigarettes to satiety results in near-complete occupancy of nAChRs in the brain (Refs. 431 and 432). In contrast, although studies have shown there is enough nicotine in VLNC cigarettes to bind to nAChRs in the brain (Ref. 430) and to release dopamine (Ref. 389), results from these studies have also shown the effects are smaller than those observed from smoking NNC cigarettes. These differences in nAChR occupancy and dopamine release between VLNC and NNC cigarettes may explain, in part, why many studies have shown smoking VLNC cigarettes does not consistently produce the same magnitude of subjective craving and withdrawal responses observed following use of NNC cigarettes (Refs. 398, 406, 407, 411, 413, 415, 417, 419, 422, 433 to 439). Taken together, these findings demonstrate that nicotine from smoking VLNC cigarettes binds to nAChRs located in numerous areas of the brain; however, nAChR receptor occupancy and the magnitude of craving and withdrawal responses observed following use of VLNC cigarettes are not as high as those following use of NNC cigarettes.

9. Dependence

Combusted tobacco product use can lead to symptoms of nicotine dependence, which may include tolerance to the effects of nicotine, withdrawal upon cessation of use, craving, and unsuccessful efforts to quit smoking. Because dependence may take time to develop or change, it is often measured under conditions of extended exposure. Studies typically assess dependence with questionnaires, including the Fagerström Test for Nicotine Dependence (FTND), Fagerström Test for Cigarette Dependence (FTCD), Nicotine Dependence Syndrome Scale (NDSS), and Wisconsin Inventory of Smoking Dependence Motives (WISDM). Although some studies found no evidence of a change in dependence when the nicotine content of cigarettes was gradually reduced, most studies found evidence indicating that switching to VLNC cigarettes decreases dependence. Moreover, the evidence suggests that immediate nicotine reduction is more likely to lead to decreases in dependence than gradual reduction. These findings support the hypothesis that lowering the nicotine levels in cigarettes and certain other combusted tobacco products would reduce nicotine exposure and, thereby, nicotine dependence in people who do not to switch to another nicotine-containing tobacco product.

In studies that gradually reduced the nicotine content of cigarettes over the course of weeks or months, the effects of VLNC cigarettes on dependence were somewhat mixed. In a study wherein nicotine content was gradually reduced (using NNC, LNC, and VLNC cigarettes) over the course of 4 weeks, there was a trend towards statistical significance (*i.e.,* if more participants had been tested, the results may have become statistically significant) in overall reduction of dependence scores across conditions (Ref. 329). Another gradual reduction study found no difference in dependence when comparing data from baseline to week 26 in 135 participants who smoked either gradually reduced nicotine content cigarettes over the course of 6 months or their own brand cigarettes for the same duration (Ref. 258). However, when comparing only data from week 14 to week 26, while participants were primarily smoking VLNC cigarettes, there was a statistically

significant decrease in dependence in the group that received gradually reduced nicotine content cigarettes (Ref. 258). A secondary analysis of data from 51 people who smoke demonstrated that participants with higher FTND scores at baseline were more likely to demonstrate signs of dependence during the study, regardless of the nicotine content of their study cigarettes (Ref. 381). In a followup study, participants assigned to receive gradually reduced nicotine content cigarettes were given VLNC cigarettes for an additional 6 months, and no statistically significant changes in dependence were observed (Ref. 374).

In studies that immediately reduced the nicotine content of cigarettes by switching participants from usual brand cigarettes to LNC or VLNC cigarettes, dependence decreased in people who smoked cigarettes who were not interested in quitting compared to those who smoked NNC or usual brand cigarettes for 6 weeks (Ref. 29), 10 weeks (Ref. 30), or 12 weeks (Ref. 31). In smoking cessation studies in which participants endorsed wanting to quit, VLNC cigarettes were also associated with reductions in nicotine dependence over time (Refs. 32 to 35). Conversely, a trial in which people with serious mental illness who smoke and were not seeking smoking cessation treatment were randomized to use either VLNC or NNC cigarettes for 6 weeks showed no statistically significant differences in FTCD scores across VLNC and NNC cigarette groups (Ref. 440). However, these results may be explained by the high level of noncompliance (*i.e.,* ongoing use of NNC cigarettes or other tobacco products) reported in the VLNC cigarette condition (Ref. 440) (see section VI.B of this document for further discussion of noncompliance).

To date, one study compared the effects of gradual versus immediate nicotine reduction on FTND and WISDM dependence scores (Ref. 379). In a 20-week double-blind, parallel design study, adults who smoke cigarettes (n=1,250) were randomized to an immediate reduction group that received VLNC cigarettes, a gradual reduction group that received cigarettes containing progressively decreased nicotine content every 4 weeks (15.5, 11.7, 5.2, 2.4, and 0.4 mg nicotine per gram of total tobacco, respectively), or a control group that received NNC cigarettes. At the conclusion of 20 weeks, the immediate reduction group showed statistically significantly lower FTND and WISDM dependence scores compared with the gradual reduction group and the NNC cigarette control group; no statistically significant differences in dependence scores were observed between the gradual reduction and control groups. These results suggest that immediate nicotine reduction is associated with reduced nicotine dependence compared to gradual reduction or continued use of NNC cigarettes (Ref. 379).

The delay to smoking the first cigarette of the day is a strong predictor of dependence. In the only study to date that examined the effects of VLNC cigarettes on latency (*i.e.,* delay) to smoke in participants inhabiting a residential research facility, time to first cigarette was statistically significantly longer among people who smoke who only had access to VLNC cigarettes for 11 days compared to those who only had access to NNC cigarettes, supporting the potential for less dependence over time among those who switch to VLNC cigarettes (Ref. 64).

Accordingly, despite some mixed results in studies using a gradual decrease in nicotine content, most evidence shows that switching to VLNC cigarettes decreases dependence among people who smoke cigarettes. The evidence also suggests that immediate nicotine reduction is more likely than gradual reduction to lead to decreases in dependence. For more discussion of the scientific evidence supporting an immediate nicotine reduction approach, see section VII.C of this document.

10. Subjective Effects of VLNC Cigarettes

Self-reported subjective effects (*e.g.,* drug ''liking,'' ''satisfaction'') are widely used measures of reinforcing efficacy and abuse liability of drugs and tobacco products. Drug ''liking'' is associated with drug self-administration and has been shown to be the most sensitive and reliable subjective effects measure of abuse liability (Ref. 441). Many studies have compared the subjective effects of VLNC, LNC, NNC, and participants' usual brand cigarettes using self-reported measures of drug effects (*e.g.,* Cigarette Evaluation Scale, Smoking Effects Questionnaire, Visual Analogue Scale items). These studies typically found that VLNC cigarettes are ''liked'' less than NNC and usual brand cigarettes and, therefore, subject to lower abuse potential than NNC cigarettes.

Under conditions of brief exposure when participants were given limited access to cigarettes that varied in nicotine content, typically over the course of several hours under controlled laboratory conditions, studies generally found that VLNC cigarettes were rated lower in cigarette ''liking'' compared to NNC or usual brand cigarettes (Refs. 265, 383, 398, 399, 403, 410, 413, 428, 435, 437, 440, 442 to 448). However, a few studies found no statistically significant differences in ''liking'' as a function of nicotine content in cigarettes (Refs. 415, 419, 420, and 449). Many studies also have evaluated other subjective effects (such as ''good'' or ''positive'' effects and ''bad'' or ''negative'' effects) and found that they vary together with drug ''liking.'' A number of studies have shown that VLNC cigarettes were rated lower on other positive subjective effects items (*e.g.,* ''satisfaction,'' ''pleasure,'' ''taste,'' ''strength,'' ''stimulation'') compared to LNC cigarettes (Refs. 265, 412, 419, and 450), NNC cigarettes (Refs.265, 394, 396, 437, and 451) and usual brand cigarettes (Refs. 390, 407, 413, and 452). VLNC cigarettes were also rated lower on effects such as ''aversiveness,'' ''sickness,'' and ''dizziness'' (Refs. 390, 396, 414, 453, and 454), and higher on items such as ''dislike'' and ''unpleasant'' compared to NNC or usual brand cigarettes (Refs. 265 and 383). These seemingly contradictory findings are likely due to the constructs that these subjective effects measure; ''aversiveness,'' ''sickness,'' and ''dizziness'' are used to measure direct sensory and physical effects of nicotine, while ''dislike'' and ''unpleasant'' are used to measure general product liking.

Although often assumed, recent findings confirm that greater immediate positive subjective effect ratings (*e.g.,* ''liking,'' ''satisfaction'') predict greater acute reinforcing effects of cigarettes of varying nicotine content (Ref. 455). Several factors have been shown to influence subjective effects ratings of VLNC and NNC cigarettes. These factors include participants' ability to discriminate the nicotine content of cigarettes. For example, NNC cigarettes have increased ratings of positive subjective effects when participants are able to discriminate them from VLNC cigarettes (Refs. 400 and 401). Individuals who smoke menthol cigarettes rated both VLNC and NNC cigarettes higher in positive subjective effects compared to people who smoke nonmenthol cigarettes (Ref. 456). In addition, positive subjective effects ratings are higher when participants are told that they are receiving a nicotine-containing cigarette, regardless of the actual nicotine content of the cigarette (Refs. 428, 435, 444, 445, and 457).

Several studies assessed subjective effects of VLNC cigarettes following extended exposure when participants were given less restricted access to cigarettes of varying nicotine content in their natural environments (*e.g.,* homes, workplaces), typically over the course of

several weeks. Findings from these studies were relatively similar to findings from brief exposure studies. On average, VLNC cigarettes were rated as less appealing (*e.g.,* lower ratings of ''liking,'' ''satisfaction,'' or ''pleasure'') compared to LNC and NNC cigarettes (Refs. 249 and 384). However, at least one study found no differences in subjective effects as a function of cigarette nicotine content (Ref. 258). Positive subjective effects ratings for VLNC cigarettes were shown to remain constant or decrease over time (Refs. 249 and 373).

In a study where people who smoke inhabited a residential research facility, during 11 days of exposure, participants who received NNC cigarettes rated positive subjective effects lower and negative subjective effects higher than baseline subjective effects of usual brand cigarettes (indicative of a general dislike of research cigarettes); however, subjective ratings of NNC study cigarettes increased and were similar to usual brand cigarettes by the end of the study (Ref. 64). In contrast, participants assigned to the VLNC cigarette group rated positive subjective effects of cigarettes (*e.g.,* ''enjoyable'') lower and negative subjective effects (*e.g.,* ''unpleasant'') higher than baseline subjective effects of usual brand cigarettes throughout the entire study period (Ref. 64).

Finally, gender may influence differences in subjective effects. In one study, women rated all cigarettes as more flavorful than men, and an interaction was observed between gender and nicotine content such that women demonstrated less sensitivity than men to the differential subjective effects of NNC and VLNC cigarettes (Ref. 447). Another study found that women reported increased satisfaction with VLNC or LNC cigarettes alone, while men reported greater satisfaction when these cigarettes were combined with NRT (Ref. 458). Finally, one study found that women reported higher psychological reward than men across all nicotine contents tested (Ref. 459).

In sum, subjective effects data consistently show that VLNC cigarettes have equal or lower abuse potential compared to NNC and usual brand cigarettes under conditions of brief and extended exposure. FDA is not aware of any studies that found that VLNC cigarettes had greater abuse potential than NNC or usual brand cigarettes.

11. The Effects of VLNC Cigarettes on Relief From Craving and Withdrawal Symptoms

Symptoms of nicotine and tobacco withdrawal may include irritability, depression, insomnia, headache, and increased craving. Although craving is often characterized as a symptom of nicotine and tobacco withdrawal, it is also a symptom of dependence, and it can occur in the absence of other withdrawal symptoms. Thus, craving is usually measured and reported separately from withdrawal. Studies typically assess craving and withdrawal using the Questionnaire of Smoking Urges (QSU), QSU-Brief, Minnesota Nicotine Withdrawal Scale (MNWS), Shiffman-Jarvik Withdrawal Scale, and Visual Analogue Scale items. Despite their lower nicotine content, VLNC cigarettes typically do not produce greater reports of craving or other withdrawal symptoms. Although findings from some brief exposure studies are mixed, the results of many studies suggest that brief and extended exposure to VLNC cigarettes can suppress craving and withdrawal just as effectively as NNC and usual brand cigarettes. The ability of VLNC cigarettes to suppress craving and withdrawal in people who smoke cigarettes is likely at least partially due to the long history of pairings between nicotine and the sensorimotor stimuli associated with smoking. Through conditioning, these stimuli can suppress craving and some other withdrawal symptoms even in the absence of nicotine (Ref. 38).

In brief exposure studies where participants were given limited access to reduced nicotine content cigarettes, typically over the course of several hours under controlled laboratory conditions, VLNC cigarettes suppressed craving and withdrawal relative to baseline measures that were typically assessed following overnight abstinence (Refs. 452, 460 to 467). Furthermore, many studies showed that VLNC cigarettes can reduce craving and withdrawal as much as usual brand or NNC cigarettes (Refs. 391, 406, 407, 411, 413, 415, 417, 419, 422, 433 to 439). However, some studies observed that suppression of craving and withdrawal was lower after smoking VLNC cigarettes compared to usual brand or NNC cigarettes (Refs. 265, 396, 388, 402, 427, 440, 453, 454, 468, and 469). In addition, results from a few studies suggest that VLNC cigarettes influence craving more than withdrawal. One study found that VLNC cigarettes suppressed craving similarly to NNC cigarettes, but also produced an increase in other withdrawal symptoms (Ref. 470). Other studies have found no effects of VLNC cigarettes on withdrawal symptoms (Refs. 414, 428, and 448). Notably, some of these brief exposure studies reported differences between genders and generally found that females who smoke experienced greater reductions in craving (Refs. 265, 463 and 464) or withdrawal (Refs. 436 and 462) compared to males who smoke after smoking VLNC cigarettes. However, another study found that, after smoking VLNC cigarettes, males who smoke had greater reductions in craving compared to females who smoke (Ref. 435).

During extended exposure studies, when participants smoked VLNC cigarettes from 4 days to 1 year, ratings of withdrawal (Refs. 249 and 258) and craving (Refs. 249 and 383) were generally similar to ratings observed in usual brand and NNC cigarette conditions. In one study, researchers found that, after switching to VLNC cigarettes from usual brand cigarettes for 1 week, withdrawal symptoms increased with no reported change in craving (Ref. 32). However, these effects were relatively brief, and, within 6 weeks, withdrawal symptoms returned to baseline levels, and craving steadily decreased below baseline levels. Results from another study showed that VLNC cigarettes can produce persistent reductions in craving characterized by participants as ''moderate'' or ''a lot'' after 3 and 6 weeks of exposure; however, some participants reported that no relief from craving occurred during the 6-week study (Ref. 373). In addition, one study demonstrated that 6 weeks of exposure to LNC and VLNC cigarettes resulted in less craving and no difference in other withdrawal symptoms compared to NNC cigarettes (Ref. 471). Finally, during week 1 of a 20-week trial, people who smoke and were randomized to immediately reduce nicotine with VLNC cigarettes reported statistically significantly more withdrawal symptoms compared to those who gradually reduced nicotine content every 4 weeks (15.5 (NNC), 11.7 (NNC), 5.2 (LNC), 2.4 (LNC), and 0.4 (VLNC) mg nicotine per gram of total tobacco, respectively) and compared to a control group using NNC cigarettes (Ref. 379). However, at the conclusion of 20 weeks, the immediate reduction group reported statistically significantly lower smoking urges compared with the gradual reduction group and the NNC cigarette control group. No statistically significant differences in smoking urges were observed between the gradual reduction group and the NNC cigarette control group, suggesting that gradual reduction may be less effective than immediate reduction in reducing urge to smoke. Similar to findings from brief exposure studies, female participants

experienced a reduction in craving after switching to LNC cigarettes for 1 week, whereas male participants showed no change in craving upon switching. Overall, withdrawal symptoms increased in both males and females who smoke cigarettes after 1 week. However, these differences from baseline were short-lived. Ratings of both craving and withdrawal symptoms were no different than baseline over the remaining 6 weeks of the study (Ref. 458).

Craving and withdrawal were also assessed in several smoking cessation studies wherein participants were provided VLNC cigarettes along with pharmacotherapies (*e.g.,* NRT, varenicline) before a designated quit date. In these studies, participants who received VLNC cigarettes plus a nicotine patch experienced less severe cravings, with no statistically significant difference in withdrawal (Ref. 472), a greater reduction in craving and withdrawal (Ref. 35), and less frequent and less intense cravings before and after the quit date (Ref. 372) compared to those who received NNC cigarettes before the quit date. Another study found that LNC cigarettes plus either varenicline or NRT resulted in decreases in craving compared to pharmacotherapy alone, with no differences in withdrawal across groups (Ref. 371).

Accordingly, findings from these studies suggest that the maximum nicotine level in this proposed product standard, consistent with VLNC cigarette levels, would not result in substantial increases in craving or other withdrawal symptoms.

12. VLNC Cigarette Data Applies to Other Covered Products Under This Proposed Product Standard

Research regarding the public health impacts of this proposed maximum nicotine level applies across the tobacco products covered under this proposed product standard. People who smoke cigarettes who have lower SES have a greater likelihood of choosing to use RYO tobacco as a cheaper alternative to factory-made cigarettes (Ref. 312, Ref. 319). Also, literature shows that tobacco manufactures reformulate or re-label pipe tobacco as ''dual purpose'' and sell it for RYO use to capitalize on disparities between tax rates on different types of tobacco products (Ref. 322). Given that cigarette tobacco, RYO tobacco, and pipe tobacco can be effectively used in cigarettes, the VLNC cigarette research applies to these products, and any expected benefits that would accrue as a result of instituting the proposed product standard for cigarettes also would be expected to accrue for these product categories.

While the current published literature regarding very low nicotine products discusses only cigarettes, the many similarities between cigarettes and most cigars (in both appearance and use topography) support the application of VLNC cigarette research to the coverage of these cigars. For example, little cigars are often indistinguishable from cigarettes given their shape, size, filters, and packaging, and are perceived as being healthier than cigarettes (Refs. 297 and 298). Little cigars and certain cigarillos also ''are packaged and consumed in a manner similar to cigarettes'' (Ref. 473 at p. 584). The close resemblance of little cigars and many cigarillos to cigarettes have led consumers, particularly children and young adults, to mistake them for cigarettes (Ref. 474). Because they are physically similar to cigarettes, little cigars are generally smoked the same way as cigarettes, with deeper inhalation than large cigars (Refs. 53 and 475). Secondhand smoke from cigars also contains many of the same toxins and carcinogens as cigarette smoke, including carbon monoxide, nicotine, ammonia, benzene, nitrosamines, and formaldehyde, all of which are on FDA's list of HPHCs (HPHC Established List, 77 FR 20034 (2012)). Moreover, people who smoke cigarettes who switch to products like cigars to sustain their addiction tend to engage in deeper inhalation, making them even more susceptible to the dangers associated with tobacco product use (Ref. 53).

Studies also suggest that people smoke some cigarillos like cigarettes, inhaling and smoking them every day (Refs. 53 and 475). Research has found that little cigars deliver nicotine levels similar to, and sometimes higher than, cigarettes, as well as similar or higher levels of carcinogens compared to cigarettes (Refs. 476 and 477). Large cigars can deliver as much as ten times the nicotine of a filtered cigarette (Ref. 53). Even if people who smoke cigars do not breathe or inhale smoke into their lungs, they are still subject to nicotine's addictive effects through buccal absorption of nicotine or nicotine absorption through the lips due to cigar tobacco's alkalinity (Refs. 54 to 56, 302 and 303). Cigar smoke dissolves in saliva and makes it possible for people who smoke cigars to absorb sufficient amounts of nicotine to create dependence (Ref. 56). People who smoke cigars regularly are at increased risk for many of the same diseases as people who smoke cigarettes, including oral, esophageal, laryngeal, and lung cancer; cardiovascular diseases; and COPD (Ref. 163). Accordingly, FDA believes it is appropriate to bridge these VLNC cigarette studies to cigars.

C. An Immediate Nicotine Reduction Approach Is Strongly Supported by Scientific Evidence

Two approaches have been suggested for implementing a nicotine product standard that would limit nicotine yield by establishing a maximum level of nicotine content in cigarettes and certain other combusted tobacco products. One is a gradual reduction approach, which decreases the nicotine content in the tobacco products over time until it reaches minimally addictive or nonaddictive levels. The other is an immediate reduction approach, or single target approach, which would immediately reduce the nicotine content to minimally addictive or nonaddictive levels. Available research indicates that both approaches are associated with noncompliance (*i.e.,* use of NNC cigarettes) when participants reach the VLNC cigarette phase of the intervention, which supports findings from other studies that show people who use VLNC cigarettes are more likely to use alternative nicotine-containing products when such products are concurrently available. However, the available scientific evidence suggests that the gradual approach can lead to compensatory smoking during the intermediate steps when people are smoking products with low to moderate nicotine content.

Based on scientific evidence, as well as comments and information submitted in response to the Nicotine ANPRM, FDA is proposing an immediate reduction approach to reach the maximum nicotine level in this proposed product standard. We expect that there would be very little compensatory smoking with an immediate reduction approach and that any compensatory smoking would be self-limiting and transient (*i.e.,* research shows that people who smoke would be unable to obtain their nicotine dose from VLNC cigarettes no matter how they smoked them and would quickly stop trying to do so), which would increase the benefits of the proposed product standard. We anticipate most people who smoke will maintain usual smoking behavior during these 2 years. An attempt to taper nicotine intake could involve switching to VLNC cigarettes already on the commercial market (*i.e.,* VLN® cigarettes), reducing the number of cigarettes smoked per day, or switching to another tobacco product. Tapering nicotine intake while

NNC cigarettes are on the market may facilitate abstinence in smokers by increasing motivation to quit and quit attempts. However, we do not expect most people who smoke to switch to VLNC cigarettes while NNC cigarettes are available. We request comments, data, and information regarding the selection of an immediate reduction approach.

Several studies have investigated the effects of a gradual approach to reducing cigarette nicotine content on compensatory smoking (Refs. 40, 258, 329, and 384). In these studies, participants were not interested in quitting and did not receive NRT or alternative tobacco products. For example, a pilot study and a clinical trial examined whether a gradual reduction in cigarette nicotine content would increase exposure to tobacco smoke toxins due to compensatory smoking (Refs. 40 and 258). Participants smoked their usual brand cigarettes during baseline and then were switched to five types of research cigarettes containing gradually reduced nicotine content (*i.e.,* 10.3 (NNC), 6.5 (LNC), 3.9 (LNC), 1.7 (LNC), and 0.5 (VLNC) mg nicotine per cigarette). In the 10-week pilot study, participants were switched weekly, and in the 6-month trial, participants were switched monthly (Refs.40 and 258). Little change in smoking behavior was observed; however, plasma cotinine concentration (a biomarker of nicotine exposure) decreased as a function of cigarette nicotine content, such that cotinine was lowest while participants were smoking VLNC cigarettes. The smaller pilot study showed little evidence of compensation, as calculated based on cigarette consumption, CO, and polycyclic aromatic hydrocarbon (PAH) metabolites (Ref. 40); however, the 6-month trial showed a slight increase in compensatory smoking, as measured by CO and CPD, while participants were in the intermediate phase of the study. This increase was no longer evident once participants reached the VLNC cigarette phase of the study (Ref. 258).

Another study showed that compensatory smoking may increase when participants smoke cigarettes with intermediate levels of nicotine (*e.g.,* LNC cigarettes) compared to usual brand cigarettes (Ref. 384). Taken together, these studies demonstrate that people who smoke cigarettes may engage in compensatory smoking during the early stages of a gradual reduction approach by smoking more intensely in an attempt to obtain their desired level of nicotine (Refs. 258, 329, and 369).

Several studies have investigated whether an immediate reduction approach to nicotine reduction would increase compensatory smoking (Refs. 29 and 31). Like the gradual reduction studies discussed in this section, participants in these immediate reduction studies were not interested in quitting and did not receive NRT or alternative tobacco products. In the most comprehensive immediate nicotine reduction study to date, 839 participants were randomized to one 6-week condition, during which they smoked their usual brand cigarettes or immediately switched to research cigarettes containing either 15.8 (NNC), 5.2 (LNC), 2.4 (LNC), 1.3 (LNC), or 0.4 (VLNC) mg nicotine per gram of total tobacco (Ref. 29). Participants assigned to the LNC or VLNC cigarette groups, who received cigarettes with nicotine content less than or equal to 2.4 mg nicotine per gram of total tobacco, smoked statistically significantly fewer CPD than participants assigned to the usual brand and NNC cigarette groups. Those who received LNC or VLNC cigarettes containing 5.2 mg nicotine per gram of total tobacco or less had statistically significantly lower urinary TNE than those who received NNC cigarettes. There were no differences in breath CO measures, an indicator of compensatory smoking, between the cigarette groups. The total puff volume at week 6 was statistically significantly lower among participants who smoked VLNC cigarettes compared to those who smoked NNC cigarettes. However, much like the gradual reduction studies, a secondary analysis showed that noncompliance (*i.e.,* ongoing use of NNC cigarettes or other tobacco products) was high in participants randomized to the VLNC cigarette group, suggesting that VLNC cigarettes have lower appeal and abuse liability compared to NNC cigarettes and that people who smoke VLNC cigarettes are likely to obtain nicotine from other tobacco product use (Ref. 330).

In another study, 33 participants were randomized to receive VLNC cigarettes at no charge or to continue smoking their usual brand cigarettes for 12 weeks (Ref. 31). Overall, participants in both groups smoked a similar total number of CPD, even though only the participants in the VLNC cigarette group received free cigarettes. These data demonstrate that an immediate reduction in cigarette nicotine content is unlikely to lead to significant compensation or increased toxicant exposure.

A secondary analysis pooled data from five clinical studies to examine the relationship between compensatory smoking and gradual versus immediate nicotine reduction approaches (Ref. 387). Two of the studies utilized a gradual reduction approach, and three of the studies utilized an immediate reduction approach. CPD, breath CO, and cotinine levels were compared between the immediate reduction group, the gradual reduction group, and a control group that received usual brand cigarettes. Relative to baseline, statistically significant decreases in CPD were observed in participants in the gradual reduction groups (5 percent decrease in CPD) and immediate reduction groups (11 percent decrease in CPD), whereas statistically significant increases in CPD were observed in participants in the usual brand groups (12 percent increase in CPD). Although statistically significant changes in breath CO were not observed relative to baseline in any group, statistically significant decreases in cotinine were observed among both gradual and immediate reduction groups, but not in the usual brand group.

The largest study designed to directly investigate gradual versus immediate nicotine reduction on toxicant exposure was a 10-site, randomized, double-blind clinical study in 1,250 adults who smoke and had no intention to quit (Ref. 379). Participants were randomly assigned to an immediate reduction group that received VLNC cigarettes for 20 weeks, a gradual reduction group that received cigarettes containing progressively decreased nicotine content every 4 weeks (15.5, 11.7, 5.2, 2.4, 0.4 mg nicotine per gram of total tobacco) for 20 weeks, or a control group that received NNC cigarettes for 20 weeks. Notably, in this study (and virtually all clinical studies of reduced nicotine content cigarettes), research cigarettes were free to participants. Any changes in biomarker levels observed between these two groups would indicate differences in smoking behavior (*e.g.,* CPD, smoking topography). Completion rates were statistically significantly lower for the immediate reduction group (68 percent) compared to the gradual reduction group (81 percent) and control group (86 percent). The immediate reduction group had statistically significantly lower levels of three primary biomarker outcomes (*i.e.,* CO, 3–HPMA, and r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4 tetrahydrophenanthrene) compared to the gradual reduction group, which did not differ from the control group. In addition, statistically significantly lower levels of other biomarkers (*i.e.,* TNE, NNAL, 2-cyanoethylmercapturic acid, 3-hydroxy-1-methylpropylmercapturic acid, S–PMA) were observed in the immediate reduction group compared to the gradual reduction and the control

groups. The immediate reduction group smoked cumulatively fewer CPD over the course of the 20-week study and had lower nicotine dependence scores compared to the gradual reduction group, with no statistically significant differences in CPD or dependence in the gradual reduction versus control groups. While there was no statistically significant difference between the immediate and gradual reduction groups in the proportion of participants with any ''cigarette-free days'' during the study, the immediate reduction group had a statistically significantly higher number of ''cigarette-free days'' compared to the gradual reduction group. The immediate reduction group had statistically significantly higher withdrawal scores at week 1 compared to the gradual reduction group; however, these differences dissipated after the first week. The immediate reduction group had higher rates of noncompliance with non-study cigarette use and a higher drop-out rate, which may have impacted the various outcome measures (*e.g.,* biomarkers of exposure). Additionally, the immediate reduction group had an increased number of adverse events (predominantly related to withdrawal) compared to the gradual reduction group. Nevertheless, this study provides further evidence that immediate nicotine reduction is associated with reduced toxicant exposure and nicotine dependence and increased smoking abstinence compared to gradual nicotine reduction. This suggests that with immediate nicotine reduction, the potential health benefits could occur sooner than gradual nicotine reduction. While the immediate reduction group had increased levels of nicotine withdrawal, this effect was time-limited, dissipating after 1 week (Ref. 379).

Higher study attrition and noncompliance with study cigarettes are common within VLNC cigarette conditions in clinical studies (Refs. 327, 329, and 330), especially studies such as the one described above (Ref. 379), wherein participants are not interested in quitting smoking, and they are asked to refrain from using alternative sources of nicotine. Because of the lower abuse liability of VLNC cigarettes, participants in these studies may drop out or use non-study cigarettes that contain nicotine. These conditions would not exist if the proposed product standard is implemented. People who smoke would not be able to readily obtain NNC cigarettes, but they would be able to obtain alternative noncombusted products with nicotine content that they could switch to or use with VLNC cigarettes.

In sum, evidence from studies involving VLNC cigarettes suggests it is likely that there would be very little or no compensatory smoking with an immediate reduction approach to a maximum nicotine level, which would increase the public health impact of a nicotine reduction policy. Additionally, FDA believes an immediate reduction approach would have a lesser impact on manufacturers as compared to a gradual approach by limiting any changes necessary for compliance to a single occasion. Although FDA believes this is a benefit of the immediate reduction approach, it is not a determinative factor given the strength of the scientific evidence.

D. Scientific Evidence Supports the Use of an Analytical Test Method To Determine Nicotine Level

In its considerations regarding the use of an analytical test method, FDA determined that any analytical method to measure compliance must accurately and reliably detect nicotine at low concentrations (*i.e.,* below 0.70 mg nicotine per gram of total nicotine). In addition, FDA determined that it is important that the proposed product standard permit comparison of test results among finished tobacco products and testing facilities. FDA also concluded that it is important that the test method demonstrate its suitability and reliability in accurately measuring a range of nicotine concentrations across a wide variety of tobacco blends and products. Accordingly, FDA is proposing to require manufacturers use an analytical test method that would satisfy these preceding factors and demonstrate that the test method was validated in an analytical test laboratory. In lieu of requiring a specified test method, we are recommending manufacturers consider using one of the three following analytical test methods FDA has determined satisfy the preceding factors: FDA's Tobacco Products Laboratory method (Ref. 478), Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) Recommended Method (CRM) No. 62 (Determination of nicotine in tobacco and tobacco products by gas chromatographic analysis; (Ref. 479)), or CRM No. 87 (Determination of nicotine in tobacco products by gas chromatography-mass spectrometry (GC–MS); (Ref. 480)). However, an analytical test method that meets the requirements of the regulation, even if it is not one of the recommended methods, would be acceptable.

FDA's Tobacco Products Laboratory, located in Atlanta, Georgia, has developed an analytical test method, entitled ''Quantitation of Nicotine in Tobacco Products—Update to LIB No. 4550'' (LIB #4692), that is capable of quantifying nicotine levels that include concentrations well above and below the proposed nicotine standard level and also meets formal intralaboratory validation criteria (Ref. 478). The method utilizes GC–MS with a run time of 4.1 minutes. Analysis is conducted on extracted tobacco or spiked surrogate matrix samples treated with a base (sodium hydroxide) to obtain the total nicotine content for each sample. Quinoline is used as the internal standard. Tomato leaves are used as a surrogate matrix for tobacco to examine recovery amounts for spiked samples. Validation was performed using Moonlight brand VLN Menthol King ground tobacco and NIST 1573a (Tomato Leaves) as a blank spiking matrix. The range of the method was 0.1 to 2.0 mg of nicotine per gram of total tobacco, meaning nicotine concentrations in this range can be accurately measured. Tobacco samples with nicotine concentrations expected to be higher than 2.0 mg nicotine per gram of total tobacco were analyzed after dilution of the extraction sample by a factor of ten. The method detection limit is 0.05 mg nicotine per gram of total tobacco, which is more than an order of magnitude below the proposed maximum nicotine concentration of 0.70 mg per gram of total tobacco. The limit of quantitation is 0.1 mg nicotine per gram of total tobacco, which is also well below the limit of the proposed product standard. Furthermore, this method was proven to be applicable to a wide range of tobacco products. Tobacco filler and total tobacco from various marketed tobacco products including cigarettes, large cigars, cigarillos, little cigars, RYO cigarettes and pipe tobacco were analyzed successfully using FDA's Tobacco Products Laboratory method.

CORESTA updated CRM No. 62 (Determination of Nicotine in Tobacco and Tobacco Products by Gas Chromatographic Analysis) in December 2021 and CRM No. 87 (Determination of Nicotine in Tobacco Products by Gas Chromatography-Mass Spectrometry (GC–MS)) in April 2020 to extend the scope of the methods to include VLNC tobacco by lowering the calibration range for these analytical test methods (Refs. 479 and 480). A study determined that the updated versions of CRM No. 62 and CRM No. 87 are suitable for the analysis of nicotine content in VLNC

tobacco and tobacco products (Ref. 481). These methods can reliably measure nicotine content as low as 0.117 mg per gram of total tobacco.

FDA's Tobacco Products Laboratory method, entitled ''Quantitation of Nicotine in Tobacco Products—Update to LIB No. 4550'' (LIB #4692), is publicly available at *https://www.fda.gov/science-research/field-science-and-laboratories/laboratory-information-bulletins.* In addition to the Tobacco Products Laboratory method, CRM No.62 (*https://www.coresta.org/determination-nicotine-tobacco-and-tobacco-products-gas-chromatographic-analysis-29185.html*) and CRM No. 87 (*https://www.coresta.org/determination-nicotine-tobacco-products-gc-ms-33537.html*) are also publicly available methods that include the proposed nicotine level in the range of concentrations that can be accurately measured. FDA recommends manufacturers use one of these analytical test methods to demonstrate compliance with this proposed product standard.

It is reasonable to expect some manufacturers may prefer to use other test methods. If developed and validated, such methods may have different advantages in ease of use, upper and lower bounds of detection, equipment, and expertise. We would evaluate data from analytical test methods as part of a premarket submission in accordance with section 910 of the FD&C Act.

FDA requests comments, including data or other scientific support, regarding FDA's Tobacco Products Laboratory method, CRM No. 62, CRM No. 87, or other available methods, that could test the proposed scope of tobacco products at the proposed maximum nicotine level.

E. Scientific Evidence Supports the Technical Achievability of the Proposed Maximum Nicotine Level Target

While FDA has analyzed various methods of technical achievability for this proposed product standard, section 907(b)(1) of the FD&C Act also requires FDA to consider information submitted in connection with the proposed product standard regarding the technical achievability of compliance. Therefore, pursuant to section 907(d)(2) of the FD&C Act, FDA requests comments by interested parties, including manufacturers and tobacco growers, regarding the technical achievability of compliance with this proposed product standard, including information concerning the existence of patents that may impact the ability to comply by the proposed 2-year effective date of this proposed rule (see section XI of this document).

The tobacco industry has developed a range of brands with differing nicotine levels. Tobacco product manufacturers have extensive experience blending tobaccos with different nicotine levels to ensure that products will have precise levels of nicotine and using continuous quality testing throughout the entire process to ensure that nicotine levels vary only minimally within cigarette packs and from pack to pack (Ref. 482). A cigarette is an inexpensive and extremely effective nicotine delivery system that maximizes the cigarette's addicting and toxic effects (Ref. 61).

In fact, the tobacco industry has had programs in place since the 1960s to obtain ''any level of nicotine desired'' (Ref. 2) (see section V.A for a detailed discussion). Indeed, the tobacco industry conducted research on consumer perceptions of RNC cigarettes to determine the optimal amount of nicotine in cigarettes to maintain appeal. Reviews of industry documents indicate that user experience, such as poor taste and reduced throat sensations, impacted the commercial viability of VLNC cigarettes (Refs. 247, 483, and 484). Internal industry strategies to mitigate these issues and maintain VLNC cigarette appeal to consumers included adding menthol to enhance the flavor of RNC cigarettes (Ref. 484) and maintaining or increasing tar levels to improve taste (Ref. 483).

As discussed in this section, there are numerous methods for altering the concentration of nicotine in cigarettes and certain other combusted tobacco products, and FDA anticipates that manufacturers and tobacco farmers may choose to use a variety of approaches to meet the proposed maximum nicotine concentration. Significant reduction of nicotine in the tobacco products covered by this proposed product standard can be achieved principally through tobacco blending, chemical extraction, or genetic engineering. Other practices such as modified growing conditions (*e.g.,* discontinue the practice of topping where the flowering head of the tobacco plant is removed to produce leaves with a significantly higher nicotine content, increase plant density, decrease nitrogen application), as well as more recent novel techniques, can also help to reduce nicotine levels. One or a combination of these processes can be used to achieve the nicotine target concentration in this proposed product standard.

1. Genetically Engineered Tobacco

Tobacco industry scientists have long recognized the potential for genetic engineering to control nicotine content (Ref. 485). The first practical application of biotechnology by a major tobacco manufacturer was the development of low nicotine content tobacco in the 1980s, which led to the receipt of a patent for biotechnology for altering nicotine in tobacco plants (Refs. 483 and 486). Other tobacco researchers and major manufacturers also recognized the value of biotechnology for developing low nicotine content tobacco for cigarettes, including for use as part of a smoking cessation program (Ref. 487).

In the 1930s, some Havana and Cuban cigar tobacco varieties were discovered to have naturally lower nicotine levels. Genetic analysis of these low nicotine containing plants identified a mutation in the nic1 and nic2 genes that are responsible for the production of reduced nicotine in some tobacco variety leaves (Ref. 488). These varieties of low nicotine content cigar tobacco were crossbred with burley tobacco to produce varieties of cigarette tobacco with low nicotine content to meet the health demands of the time (Ref. 489).

Several American and international tobacco companies genetically engineered low-nicotine strains in the 1960s and 1970s (Refs. 490 to 493), including a strain with a nicotine concentration as low as 0.15 percent (*i.e.,* 1.5 mg nicotine per gram of total tobacco), which was much lower than the 3.15 percent (31.5 mg nicotine per gram of total tobacco) observed in the comparator strain (Ref. 492). During that time period, the Kentucky Tobacco Research Board worked on genetic strains of low nicotine content tobacco (with a nicotine content of 0.2 percent) to be used for experimental studies on the role of nicotine in smoking behavior (Refs. 493 to 497). 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 (Refs. 493, 498, and 499). Although the early strains of low-nicotine tobacco that were developed by these researchers and companies contained far less nicotine than strains that were traditionally used to make cigarettes, the nicotine content is even lower in strains that have been developed more recently through genetic engineering.

Genetic engineering has resulted in up to a 98 percent reduction in nicotine levels (Ref. 483). In 2003, Vector Tobacco began marketing the Quest

cigarette produced from genetically modified tobacco containing only trace amounts of nicotine (this product is no longer on the market) (Ref. 483). In 2014, the U.S. Patent and Trademark Office granted a patent for two genes that may be suppressed to substantially decrease nicotine in tobacco plants (Ref. 500). Additionally, in 2020, the U.S. Patent and Trademark Office granted another patent for methods of manipulating plant metabolism and alkaloid levels by controlling transcription factor NbTF7, which regulates the nicotinic alkaloid biosynthetic pathway in the Nicotiana tabacum plant (Ref. 501). This method appears to be able to introduce very low nicotine traits in any variety of Nicotiana tabacum; therefore, this method may be applicable to other combusted tobacco products that use Nicotiana tabacum (*e.g.,* cigars).

Significant progress has been made in the genetic modification of nicotine and other alkaloid production in tobacco. One powerful gene editing technology, CRISPR-Cas9, has been used to delete or silence various genes involved in the production of nicotine in tobacco plants resulting in several ultra-low nicotine CRISPR tobacco lines that have been grown experimentally (Ref. 502). However, challenges have presented themselves in transitioning these ultra-low nicotine content tobacco plants to fields, such as severely stunted plants and high insect infestation rates (Ref. 503). Studies on the impact of genetically engineered low-level nicotine are ongoing and this method has not been accomplished on a large scale.

FDA is aware that genetically engineered tobacco seed has been created and may be available for purchase on the market. If this proposed rule is finalized, licensing agreements may be needed to support production of VLNC tobacco, at least initially. FDA notes that similar agreements with tobacco manufacturers are common within the tobacco industry.

2. Chemical Extraction

Another method to achieve lower nicotine concentrations in tobacco products is through chemical extraction technology. By the 1970s, tobacco manufacturers were regularly practicing nicotine extraction as a method to control nicotine delivery (Refs. 493 and 504 to 506). Extraction methods include water extraction (coupled with steam or oven drying), solvent extraction, and extractions of nicotine without usable leaf (Ref. 493). For example, one company, Ultratech, Inc., produced VLNC cigarettes by extracting nicotine with an alkaline solution (Ref. 507). Supercritical fluid extraction (which extracts chemical compounds using supercritical carbon dioxide instead of an organic solvent) also yielded success in the 1990s, allowing for optimum extraction times and the elimination of more time-consuming steps (Ref. 508). FDA notes that existing patents for chemical extraction reveal that more than 96 percent of nicotine can be successfully extracted from tobacco while retaining ''a strong characteristic aroma . . . not different from the unextracted blend,'' achieving a product that ''was subjectively rated as average in nicotine characteristics'' (Refs. 509 and 510). A major tobacco manufacturer also 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, and then treated with carbon dioxide/water vapor, to achieve a 95 to 98 percent reduction in nicotine (Refs. 483 and 511).

Water extraction also can be used for nicotine reduction. Although some manufacturers believe that some water extraction practices may have rendered the tobacco ''unsuitable for use'' in cigarettes, other water extraction projects have yielded suitable smoking material with sizeable nicotine reductions (80 to 85 percent reduction in leaf nicotine) (Refs. 493, 505, 512, and 513).

3. Tobacco Farming Practices

Different types of farming practices also can lower nicotine concentrations in tobacco plants. One example is alkaloid-minimizing farming practices. Industry studies have shown that changes to growing and harvesting practices affect the development of tobacco chemistry, including nicotine content (Ref. 493). Some manufacturers have revised their agricultural practices specifically to meet new product development goals, such as the production of low nicotine content tobacco (Ref. 493). For example, one manufacturer evaluated how various experimental agricultural practices including bulk-curing, once-over harvesting, and high plant density could affect the tobacco's chemistry (Refs. 493 and 514). In other cases, chemical agents were observed to reduce nicotine content (Refs. 493, 515 to 517).

Modification of tobacco growth practices can result in reduced levels of nicotine in tobacco plants. In traditional tobacco production, plants are topped and suckered (removing the growth at the apex and axillary buds) to slow the ripening rate of the leaves resulting in increased nicotine content. Therefore, discontinuing these practices results in a significant decrease in nicotine production (Ref. 518). It has been found that plant density is conversely correlated to nicotine production in the plant as increased plant density creates a competition for resources, particularly nitrogen. Therefore, higher plant densities lead to lower nitrogen availability and stunted plant growth, thus resulting in lower nicotine tobacco (Ref. 519).

Nightshades are a botanical family that naturally contain alkaloids, including nicotine. In addition to tobacco plants, tomatoes, eggplants, potatoes, and peppers are in the nightshade category. Nicotine synthesis begins in the root of the tobacco plant and researchers have studied whether replacing tobacco root with other nightshades via grafting could affect nicotine biosynthesis (Ref. 519). Studies have been performed where grafting tobacco shoots on rootstocks of eggplant was shown to reduce nicotine production drastically without significant changes to the development of the plants (Ref. 520). Eggplant grafting results in differential expression of hundreds of genes involved in the nicotine biosynthetic pathway (Ref. 520). In these studies, no significant differences in plant height, leaf length, leaf width, or stalk circumference were observed between the tobacco/tobacco and tobacco/eggplant groups up to 80 days after grafting. However, the grafted tobacco/eggplant leaves resulted in a 95 percent reduction in nicotine content as compared to the tobacco/tobacco control plants (Ref. 520).

4. Tobacco Blending/Crossbreeding

One way to achieve lower nicotine concentrations in tobacco products is to selectively blend the tobacco filler. Most cigarettes sold in the United States are blended from several different types of tobacco (Ref. 359). A tobacco industry executive previously testified that the main component of a cigarette that contributes to nicotine delivery is the tobacco blend, and year-to-year crop variation does not determine the nicotine content in a cigarette (Ref. 521). 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 tobacco grade (Ref. 493). Blend differences can produce significant variations in nicotine concentration in the tobacco rod, leading to differences in smoke composition and yield (Ref. 82 at p. 469).

Many tobacco strains are available, including approximately 1,000 different

tobacco varieties (Ref. 359). 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 (Ref. 522 at 41694). These practices could be used to develop low nicotine content tobacco plants as well. Tobacco industry documents show that in the 1960s, tobacco companies recognized the increasing demand for low nicotine content tobacco and began instituting projects that found low nicotine content cigarettes can be made by selecting grades of tobacco with low nicotine content (Refs. 523 and 524).

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. 525). For example, oriental Turkish-type cigarettes also deliver substantially less nicotine than cigarettes that contain air-cured burley tobacco (Refs. 82 and 526). Even without this selective breeding, manufacturers could use careful tobacco leaf purchasing plans to control the nicotine content in their products (Ref. 522 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 1 percent (despite annual variations of up to 25 percent in the nicotine content of the raw material grown in the same area) (Ref. 522 at 41694).

Grading, which is used to evaluate and identify differences within tobacco types, is a function of both plant position (*i.e.,* higher or lower leaf position on the stalk) and quality (*i.e.,* ripeness), and segregation of grades by nicotine content has become common practice (Ref. 493). The position of leaves on the plant stalk 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 (Refs. 493, 525, and 527). For example, flue-cured tobacco leaves harvested from the lowest stalk position may contain from 0.08 to 0.65 percent nicotine (*i.e.,* 0.8 to 6.5 mg nicotine per gram of total tobacco), whereas leaves from the highest positions may contain from 0.13 to 4.18 percent nicotine (*i.e.,* 1.3 to 41.8 mg nicotine per gram of total tobacco) (Refs. 359, 528 and 529). Therefore, substituting leaves found lower on the plants (commonly called ''priming'') could reduce the nicotine content of tobacco products (Ref. 525).

Internal tobacco industry documents describe the use of leaf blending and tobacco selection to control cigarette nicotine content (Ref. 493). For example, one company project determined that manufacturers could reduce cigarette nicotine content by selecting grades of tobacco with naturally low nicotine content (Ref. 523). Another observed that the demand for low nicotine content tobacco has increased worldwide and necessitated a shift in purchasing standards (Ref. 524).

5. Other Practices

After tobacco is harvested, it is cured and aged before being used in tobacco products. The aging process naturally changes the chemistry of the tobacco, including some reduction in nicotine content (Ref. 493). At least one manufacturer has explored efforts to speed the tobacco aging process, in part to alter or limit the changes in chemistry that naturally occur (Refs. 493 and 530). Other approaches to curing and fermenting tobacco have been explored as methods for altering nicotine content. 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 (Ref. 531). In addition, manufacturers have explored other approaches to identify microbial bacteria that actively degrade nicotine while leaving other components of the leaf intact (Refs. 532 and 533). Consumer product testing showed that the ''product acceptability'' of that tobacco was equal to that of untreated tobacco (Ref. 534).

Researchers also have developed novel approaches to reducing the nicotine in tobacco products in recent years. An example of one such approach is enzymatic digestion utilizing glucose oxidase harvested from the salivary excretion produced by a specific species of herbivorous caterpillar, *helicoverpa zea* (Ref. 535). The extracted enzyme is applied to the harvested tobacco leaves, reducing the nicotine in the tobacco leaf by up to 75 percent, providing 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. 535). Another novel approach is the use of microwave-assisted technology to extract nicotine from tobacco, including cigar filler (Ref. 536), that also could be effective for reducing the nicotine content for other tobacco products such as RYO tobacco and pipe tobacco.

By using one or a combination of methods described above, FDA concludes there is ample evidence of the technical feasibility of complying with this proposed product standard to reduce the nicotine level in cigarettes and certain other combusted tobacco products.

6. Applicability to Other Combusted Tobacco Products and Smaller Manufacturers

FDA anticipates that manufacturers of non-cigarette tobacco products covered by this proposed product standard may also choose to use a variety of approaches to meet the proposed maximum nicotine level. Given the similarities between the tobacco used in cigarettes and in other combusted tobacco products that FDA proposes to include within the scope of this product standard, FDA expects that it is similarly technically feasible for non-cigarette tobacco products to comply with the proposed maximum nicotine level. FDA requests comments, data, and research regarding the feasibility of using the techniques discussed in this section, or other nicotine reduction techniques, for the non-cigarette products covered under this proposed product standard.

Although industry documents contain little information regarding feasibility of VLNC levels for non-cigarette products, an early 1962 patent does indicate a tobacco storage process that dramatically reduced nicotine levels, including in shade-grown Connecticut tobacco used for cigars, from 0.85 percent to 0.075 percent nicotine content (*i.e.,* from 8.5 to 0.75 mg nicotine per gram of total tobacco) (Ref. 537). In 1975, a large tobacco manufacturer also discussed development of a low nicotine cigar or cigarillo, including processed low nicotine content tobaccos such as a burley filler in the range of 0.34 percent nicotine (*i.e.,* 3.4 mg nicotine per gram of total tobacco) and methods for reducing nicotine in the cigar wrapper (Ref. 538).

FDA expects that smaller manufacturers may use a variety of methods to comply with the proposed product standard, including purchasing tobacco blends that are lower in nicotine or have already undergone extraction. FDA believes that the supply chain should be capable of adapting to the purchasing needs of smaller manufacturers as well as larger manufacturers, particularly given the prevalence of genetically engineered tobacco, as discussed in this section. FDA requests comments, including data and research, regarding the methods and

options smaller manufacturers may use to comply with this proposed product standard.

F. Proposal Does Not Seek To Limit Nicotine to Zero

Section 907(d)(3) of the FD&C Act expressly prohibits FDA from requiring the reduction of the nicotine yield of a tobacco product to zero, and consistent with that provision FDA is not seeking to do so. However, section 907(a)(4)(A)(i) of the FD&C Act expressly authorizes FDA to establish product standards with provisions ''for nicotine yields,'' which includes the authority to include a provision, such as the one in this proposed rule, to require reduction of nicotine yield to a level other than zero. The information provided in this section demonstrates that the proposed product standard does not require the level of nicotine to be zero. The level of nicotine proposed in this product standard is measurable in the tobacco filler and in the smoke yield. Research shows that after use of VLNC cigarettes, nicotine is measurable in the body via biomarkers of exposure and neurological receptor occupancy.

1. Nicotine Biomarkers of Exposure

Studies have shown that levels of nicotine biomarkers increase in people who smoke cigarettes containing nicotine equivalent to FDA's proposed nicotine level, thereby demonstrating exposure to nicotine from smoking VLNC cigarettes (Refs. 259, 402, and 539). Short-term studies that measure nicotine exposure in people who smoke cigarettes who smoke one or two VLNC cigarettes have generally found increases in plasma nicotine levels that follow similar, but less dramatic, patterns seen following smoking regular nicotine cigarettes. For example, one study evaluated plasma nicotine exposure before and repeatedly after smoking a single NNC, LNC, VLNC, or usual brand cigarette (Ref. 402). While the LNC and VLNC cigarettes were associated with lower plasma nicotine levels compared to the NNC and usual brand cigarettes, all cigarettes were associated with statistically significant increases in plasma nicotine compared to baseline levels (Ref. 402). Similarly, 22nd Century Group, Inc. submitted modified risk tobacco product applications to FDA containing data from two clinical studies showing that peak plasma nicotine levels following use of a single VLNC cigarette ranged from 0.4–0.5 nanograms of nicotine per milliliter of plasma and total nicotine levels (*i.e.,* plasma nicotine area under the curve calculated using the trapezoidal rule to 180 minutes) ranged from 26.2–30.4 nanograms of nicotine per milliliter of plasma (Ref. 539). Researchers observed similar effects among participants who smoked a single VLNC cigarette made by Philip Morris for research purposes only (Ref. 259).

Studies with longer exposure to VLNC cigarettes have also found evidence of nicotine exposure within study participants. For example, studies showed that after several days or weeks of smoking VLNC cigarettes, biomarkers of nicotine exposure—such as urinary cotinine and TNE (*i.e.,* the sum of nicotine and various nicotine metabolites)—in people who smoke cigarettes were drastically reduced but were still detectable (Refs. 32 and 265). Notably, if participants in these studies were noncompliant with study-assigned cigarettes, then some of the biomarkers of nicotine exposure could be attributed to the use of other tobacco products. However, evidence from studies in which participants were confined to hotels or residential research facilities without access to other tobacco products also demonstrate that extended exposure to VLNC cigarettes produces biomarkers of nicotine exposure and physiological responses consistent with nicotine exposure (Refs. 64 and 423). Taken together, these data consistently show that levels of nicotine biomarkers of exposure in people who smoke VLNC cigarettes are still detectable. For further discussion of biomarkers of exposure, see section VII.B.6 of this document.

2. Receptor Occupancy and Cerebral Response From the Use of VLNC Cigarettes

Studies have shown that the nicotine provided by VLNC cigarettes is enough to occupy sufficient numbers of nicotine receptors in the brain (*i.e.,* α4β2 nAChRs) to mitigate feelings of withdrawal and craving. PET and MRI data obtained from people who smoke cigarettes indicate that after smoking a VLNC cigarette, nicotine receptors located in numerous areas of the brain are occupied despite the lower nicotine content of VLNC cigarettes, and these participants reported a statistically significant reduction in craving compared to before smoking the VLNC cigarette (Ref. 430). In another study that compared VLNC and NNC cigarettes, exposure to both types of cigarettes resulted in the binding of nicotine to receptors in the brain and the release of dopamine (Ref. 425). However, the magnitude of subjective craving or withdrawal responses observed following use of VLNC cigarettes was lower than use of NNC cigarettes (Refa. 425 and 461). For further discussion of receptor occupancy, see section VII.B.8 of this document.

3. VLNC Cigarette Nicotine Smoke Yield

Nicotine ''yield'' refers to the amount of nicotine in tobacco smoke as measured through machine-generated smoking methods (*e.g.,* ISO machine smoking method, CI smoking method, FTC smoking method), and is typically measured and reported in milligrams per cigarette. The maximum level of nicotine set by this proposed product standard would result in nicotine yield in tobacco smoke that is at detectable levels above zero. For example, SPECTRUM NNC cigarettes that contain 15.8–16.6 mg of nicotine per gram tobacco filler have machine-measured nicotine yields of 0.7–0.8 mg of nicotine per cigarette. SPECTRUM VLNC research cigarettes that contain 0.3–0.4 mg of nicotine per gram tobacco filler have quantifiable machine-measured nicotine yields greater than zero, ranging from 0.03–0.04 mg of nicotine per cigarette (Ref. 254). Similarly, Quest® 3 VLNC cigarettes had quantifiable machine-measured nicotine yields of approximately 0.03 mg of nicotine per cigarette (Ref. 540).

In summary, the data indicate that nicotine is measurable in both the tobacco filler and the smoke yield of VLNC cigarettes and therefore does not equal zero. After using VLNC cigarettes, nicotine exposure has been shown to occur as evidenced by studies measuring biomarkers of nicotine exposure and neurological receptor occupancy. Consequently, FDA finds that the proposed product standard would not require the reduction of nicotine yields to zero.

VIII. Determination That the Standard Is Appropriate for the Protection of the Public Health

The Tobacco Control Act authorizes FDA to adopt tobacco product standards by regulation if it finds that such tobacco product standards are appropriate for the protection of the public health (section 907(a)(3)(A) of the FD&C Act). The notice of proposed rulemaking (NPRM) for such a product standard must set forth this finding with supporting justification, which FDA is providing here (section 907(c)(2)(A)) of the FD&C Act.

In order to make this finding, FDA must consider scientific evidence concerning:

- The risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard;

- The increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- The increased or decreased likelihood that those who do not use tobacco products will start using such products.

Section 907(a)(3)(B)(i) of the FD&C Act.

FDA has considered scientific evidence related to all three factors. Based on these considerations, as discussed below, we find that the proposed standard is appropriate for the protection of the public health because it would increase the likelihood that many people who currently smoke cigarettes and/or certain other combusted tobacco products would stop smoking altogether, yielding significant health benefits from smoking cessation. Additionally, we find that the proposed standard is appropriate for the protection of the public health because it would decrease the likelihood that people who do not smoke cigarettes and/or use certain other combusted tobacco products—including youth and young adults—who experiment with combusted tobacco products will become addicted to these products, thereby decreasing progression to regular use, resulting in reduced tobacco-related morbidity and mortality associated with combusted tobacco product use. Increased cessation, as well as decreased initiation, progression to regular use, and consumption would lead to lower disease and death in the U.S. population, due to decreased use of cigarettes and certain other combusted tobacco products. Furthermore, the rule is appropriate for the protection of the public health because the population as a whole would likely experience additional health benefits as a result of reduced secondhand smoke exposure, smoking-related fires, and smoking-related perinatal conditions.

A. Approach To Estimating Impacts to the Population as a Whole

Current evidence shows that, while nicotine itself is not the direct cause of most smoking-related diseases, addiction to the nicotine in tobacco products is the proximate driver of tobacco-related death and disease because it sustains tobacco use (Refs. 1, 28, 58, and 61). The addiction caused by nicotine in tobacco products is critical in the transition of people who smoke cigarettes from experimentation to sustained smoking and in the maintenance of smoking for those who want to quit (Refs. 1 at p. 113 and 28). Combusted tobacco products, including cigarettes, are responsible for the overwhelming burden of disease and death from tobacco product use (Refs. 1 and 28). As a result, FDA expects that making cigarettes and certain other combusted tobacco products minimally addictive or nonaddictive would reduce tobacco-related harms by promoting smoking cessation or complete migration to alternative, potentially less harmful noncombusted tobacco products and by reducing initiation. In this section, we summarize the approach used to estimate the possible impact of a potential nicotine tobacco product standard to the population as a whole and present the findings of this analysis.

To assess the potential public health impacts of a nicotine product standard, FDA developed a population health model using inputs derived from available empirical evidence and expert opinion to estimate the impact of changes in tobacco product initiation, cessation, switching, and dual use on tobacco use prevalence, morbidity, and mortality in the United States. Details of this modeling approach have been previously published in two peer-reviewed publications (Refs. 47 and 48), which describe the overall model in terms of the inputs, transition behaviors, and outputs that it contains, along with results from simulation studies. In preparation for this proposed product standard, FDA updated the model published previously (Ref. 47), which describes the impact of a potential product standard that limits the level of nicotine in cigarettes, RYO tobacco, non-premium cigars, and pipe tobacco so that they are minimally addictive or nonaddictive.[29] The details of this analysis are presented in an updated modeling document, entitled ''Methodological Approach to Modeling the Potential Impact of a Nicotine Product Standard on Tobacco Use, Morbidity, and Mortality in the U.S.'' (Ref. 42). We estimated the potential impacts of a nicotine product standard by modeling a baseline scenario of use of cigarettes and noncombusted tobacco products including smokeless tobacco, e-cigarettes, HTPs, and oral nicotine products. We then compared the baseline scenario to a product standard scenario characterized by the introduction of a potential nicotine product standard that would apply to cigarettes, RYO tobacco, non-premium cigars, and pipe tobacco. FDA's modeling framework and methodological approach and the associated inputs and assumptions have been peer reviewed by independent external experts. Taking into consideration comments from this peer review (Ref. 49), FDA revised the modeling document, and the final modeling document is available in the docket for this proposed rule (Ref. 42). FDA's modeling work informed the development of this proposed product standard. FDA requests comments on the methodology and analysis (including the overall model in terms of the inputs, transition behaviors, and outputs) presented in the scientific modeling document.

FDA's population health model incorporates the following tobacco use transitions to estimate the impact of the policy: (1) cigarette smoking cessation; (2) people who smoke cigarettes switching to noncombusted tobacco products rather than quitting tobacco use entirely; (3) people who continue to smoke cigarettes beginning dual use of cigarettes and noncombusted tobacco products; (4) people who do not smoke initiating regular cigarette smoking; and (5) people who do not smoke who have been dissuaded from smoking cigarettes and certain other combusted tobacco products, who instead initiate use of a noncombusted tobacco product. The model, based on input parameters derived from empirical evidence and expert estimates, projected the impact of a potential nicotine product standard on four main outcomes: (1) prevalence of cigarette smoking and noncombusted tobacco use; (2) tobacco-attributable mortality; (3) life years lost due to tobacco use; and (4) quality-adjusted life years (QALYs) lost due to cigarette smoking-attributable morbidity in the U.S. population over time. The model explores various baseline scenarios via sensitivity analyses, including with and without projections that incorporate implementations of other future tobacco product standards (*e.g.,* flavored cigar and menthol cigarette product standards).

More detailed information regarding modeling study methodology, including descriptions of the model inputs, data sources, and assumptions used to derive estimates of the potential impact of a nicotine product standard on population health can be found in FDA's modeling document (Ref. 42). Briefly, the simulation began with an initial population that reflected the sex and age (based on 2021 U.S. Census Bureau estimates) and cigarette use distribution (*i.e.,* never, current, former

[29] The policy scenario presented in Apelberg et al. 2018 (Ref. 47) did not define a specific level of nicotine as minimally addictive or nonaddictive. Rather, the policy scenario simulated implementation of a hypothetical standard in which cigarettes and certain other combusted tobacco products were made minimally addictive or nonaddictive, informed by a formal expert elicitation process, and used to estimate the impact of decreasing the addictiveness of cigarettes on certain tobacco use behaviors.

use; estimated from the 2020 NHIS data and 2020 NYTS data) in the U.S. population. Next, we incorporated sex-specific rates for smoking initiation and cessation for year 2021 modeled using cigarette smoking histories for birth cohorts reconstructed from NHIS data by Cancer Intervention and Surveillance Modeling Network (CISNET) researchers (Ref. 541). Recent analyses using data from the Population Assessment of Tobacco and Health (PATH) Study (Ref. 542) provide data on initiation of ENDS from Wave 4 (2016–2017) to Wave 5 (2018–2019); however, those estimates are related to transitions from never use to ever use of a specific product at the current wave, rather than transitions to established use, as defined in the population model. In the absence of up-to-date estimates of exclusive noncombusted product initiation rates from the published scientific literature, data regarding exclusive initiation of noncombusted tobacco products and dual use were derived by scaling the sex- and age-specific smoking initiation rates from CISNET using youth (ages 9–17) prevalence estimates from the 2017–2020 NYTS, and young adult (ages 18–24) prevalence estimates from the 2020 NHIS (Ref. 542). NYTS prevalence estimates for noncombusted product use correspond to frequent use, defined as use at least 20 days in the past 30 days.[30] Additional details regarding the estimation of scaling factors to compute noncombusted product initiation rates can be found in FDA's modeling document (Ref. 42). CISNET sex- and age-specific cigarette smoking cessation rates derived from NHIS data were utilized as cessation rates for all product categories, including noncombusted tobacco use. Age-specific rates of switching from cigarettes to noncombusted tobacco products were derived from prior research (Ref. 543). Overall U.S. death rates from 2019 vital statistics data were used to reflect the death rates at baseline for individuals under age 35 who never smoked, since smoking-related mortality is minimal before this age (Ref. 544). For ages 35 and older at baseline, FDA estimated annual death rates from 2019 NHIS–LMF data among participants who have never smoked in NHIS from 1997 through 2018 who were followed for mortality through linkage with the National Death Index from 2002 through 2019 (Ref. 545). NHIS–LMF never-user death rates are adjusted for low mortality in the NHIS's civilian noninstitutionalized population, due to the survey's exclusion of people in institutionalized settings such as long-term care institutions (*e.g.,* nursing homes, hospitals for the chronically ill or physically or intellectually disabled, wards for abused or neglected children), persons in correctional facilities (*e.g.,* prisons or jails, juvenile detention centers, halfway houses), and U.S. nationals living in foreign countries. The adjustment was done by using the ratio of U.S. death rates from the 2019 vital statistics data to NHIS–LMF death rates by sex and age (Ref. 546). Death rates for people who have never smoked cigarettes are projected for the period from 2022 through 2100 using mortality scaling factors obtained from the Lee-Carter mortality forecasting method (Refs. 547 to 549). To estimate mortality for e-cigarettes and other noncombusted tobacco products, we apply the same risks that are used for smokeless tobacco. Our assumptions about all-cause mortality risk among people who use smokeless tobacco in the United States were informed by the first NHANES, Cancer Prevention Study I (CPS–I), and Cancer Prevention Study II (CPS–II). Mortality probabilities for people who currently use and formerly used tobacco are obtained by multiplying never-user probabilities of dying by relative risk according to tobacco use status.

Quantitative inputs for tobacco use transitions following implementation of the proposed product standard were obtained through a formal expert elicitation process that was first conducted in 2015 and then repeated in 2018. FDA is conducting another expert elicitation to obtain updated quantitative inputs for tobacco use transitions and intends to publish the results for public review and comment. For the 2015 and 2018 expert elicitations, the methodology used to identify experts, develop the protocol, conduct the elicitation, and summarize the findings can be found in a previous peer-reviewed publication (Ref. 47) and in FDA's modeling document (Ref. 42). Briefly, the initial 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. 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. This general process was repeated in 2018 to ensure that estimates reflected the experts' current assessment of the research literature and potential effects of a hypothetical product standard. Seven of the original eight experts agreed to participate in the second elicitation. Participants received updated briefing materials, and an online workshop was held in April 2018. The experts, once again, subsequently completed a detailed questionnaire.

To explore the possible impact of a hypothetical policy reducing nicotine levels, 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, non-premium cigars) would be included in the policy, while other tobacco products (*i.e.,* premium cigars, waterpipe/hookah, e-cigarettes, smokeless tobacco) would be excluded. While the policy scenario presented in FDA's modeling document (Ref. 42) is based on a reduction of the nicotine level in cigarettes, cigarette tobacco, RYO tobacco, certain cigars and pipe tobacco, the estimated population impact in the main analysis is solely based on reductions in cigarette smoking. Cigarettes are the only one of these combusted products to be incorporated directly in the model, given that cigarette smoking is responsible for the bulk of morbidity and mortality caused by combusted tobacco product use. Estimates of mortality benefits due to reductions in non-premium cigar and pipe tobacco use are derived from model outputs, as explained below, although these estimates would not include other population health benefits such as reduced morbidity.

The 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 (*i.e.,* premium cigars, waterpipe/hookah tobacco, smokeless tobacco, e-cigarettes or other ENDS); (3) dual use rates; (4)

[30] While past 30-day use is the conventional definition of current use of a tobacco product in the NYTS, we utilized the corresponding definition of frequent use (20 or more days of use in past 30 days) to correspond with initiation of regular use that is more closely associated with longer-term health outcomes. In this context, we have scaled the initiation rates to reflect the initiation of regular, longer-term use. This approach is consistent with that for adult initiation to regular use and long-term cessation as defined by CISNET.

cigarette smoking initiation rates; and (5) initiation rates for other tobacco products excluded from the hypothetical policy scenario. Each of the 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 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 which each expert generated their initial and final estimates. In the updated elicitation, experts were also asked to assess the potential effects of an alternative product standard that would only apply to cigarettes, cigarette tobacco, and RYO tobacco, although they were not required to provide quantitative estimates of the effects of such a standard.

While parameter estimates and their probability distributions varied somewhat among 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 people who smoke cigarettes and decreased initiation among people who do not smoke cigarettes. The experts' parameter estimates fell within a broad range, although the updated estimates were often somewhat more consistent and found greater effects from the potential policy than in the original elicitation. In general, estimates of the effects of a nicotine product standard on use behaviors such as smoking cessation, product switching, and smoking initiation were greater in magnitude in the 2018 expert elicitation than in the previous 2015 elicitation. For example, the median estimates of smoking cessation were 36 percent in the first year following implementation of a nicotine product standard and 34 percent in subsequent years in the 2018 elicitation, compared to 25 and 22 percent, respectively, in 2015. For product switching (from cigarettes to noncovered tobacco products), the median estimates were 56 and 58 percent in the first and subsequent years following implementation in the 2018 expert elicitation and 41 and 40 percent in 2015. Median estimates of reductions in smoking initiation were 63 and 65 percent in the first and subsequent years in the 2018 elicitation, and 46 and 49 percent in 2015. Overall, the experts' estimates indicate that the proposed product standard would introduce substantial changes in tobacco use behaviors which would result in substantial public health benefits. Given the inherent uncertainty associated with projecting the long-term impact of a future regulatory action, FDA conducted a range of analyses to examine the impact of uncertainty around key model inputs and assumptions on tobacco use prevalence and premature mortality. First, in the main analysis, we examined uncertainty in the behavioral responses to a potential nicotine product standard by conducting a Monte Carlo simulation (Ref. 550). For the product standard scenario, a Latin hypercube sampling design with 1,000 simulations was conducted for each set of expert-defined distributions, resulting in a total of 7,000 simulations (Ref. 551 at p. 524). The resulting outputs were aggregated to create an overall set of output distributions, and distribution percentiles were calculated across all 7,000 simulations. For each simulation, the policy scenario was compared to the baseline scenario to estimate changes in the outcomes. Key distribution responses in FDA's modeling document highlight the positive impacts to the public health of the proposed product standard (Ref. 42). More information on this topic can be found throughout this document.

In addition, we conducted sensitivity analyses to assess the impact of specific data input assumptions, including those related to baseline trends in noncombusted product use, noncombusted product mortality risk, dual product use mortality risk, and switching to non-covered combusted products. Specifically, we conducted sensitivity analyses to examine the impact of increased initiation of noncombusted tobacco product use among those who would otherwise not have used tobacco; the impact of an increase in switching from cigarettes to noncombusted tobacco product use; the impact of a varying mortality risk associated with dual use of cigarettes and noncombusted tobacco products; the impact of lower and higher noncombusted tobacco product risk; and the effects of a nicotine product standard, accounting for the emergence of an illicit market for normal nicotine content cigarettes. Additional detailed information concerning these sensitivity analyses can be found in FDA's modeling document (Ref. 42). Overall, the results from FDA's population health modeling, even accounting for the impacts of the factors utilized in FDA's sensitivity analyses, clearly demonstrate the public health benefit of the proposed product standard.

In 2022, FDA issued proposed product standards to prohibit menthol as a characterizing flavor in cigarettes (87 FR 26454, May 4, 2022) and to prohibit all characterizing flavors (other than tobacco) in cigars (87 FR 26396, May 4, 2022). If finalized, these rules are anticipated to reduce overall youth initiation and increase cessation among individuals who smoke cigarettes and non-premium cigars. In sections VIII.E and VIII.F of this document, we describe how we adjusted our model by utilizing estimates of the likely population health impact of these rules, quantified in peer-reviewed publications and discussed in the proposed rules, to adjust the baseline inputs for initiation of combusted and noncombusted products, as well as cessation of combusted products and likelihood of switching to incorporate the impact of the rules in this proposed nicotine product standard.

B. The Likelihood That Nonusers Would Start Using Cigarettes or Other Combusted Tobacco Products

Nicotine is an addictive chemical and the primary constituent in cigarettes and other tobacco products that causes and maintains addiction. It is a significant contributor to youth and young adult initiation of smoking cigarettes and other combusted tobacco products. In section IV.A of this document, we summarize evidence from multiple study designs, incorporating findings from experimental and laboratory-based studies, clinical trials, and pre-clinical research that illustrate the role that nicotine plays in facilitating initiation of and addiction to cigarettes and other combusted tobacco products. As discussed in section IV.B of this document, scientific research demonstrates that adolescence is a period of development when individuals who experiment with tobacco products are more susceptible to developing nicotine dependence and progressing to regular use of such products. Indeed, almost 90 percent of adults who currently and regularly smoke initiated smoking by age 18, and

98 percent initiated smoking by age 26, which is notable given that 25 is the approximate age at which the brain has completed development (Refs. 1 and 17 to 19). The developing brain is more vulnerable to developing nicotine dependence than the adult brain is, and the earlier an individual begins smoking the less likely they are to quit (Ref. 20). Compounding this are the findings described in section IV.C of this document that demonstrate that many youth and adults who smoke want to quit smoking but have difficulty doing so. Further, the scientific literature on relapse in those who try to quit confirms the powerful addictive properties of nicotine in tobacco products, a principal factor limiting a person who smokes' ability to quit, and further underscores the public health importance of decreasing the addictiveness of these products, particularly to reduce susceptibility to addiction for youth and young adults who experiment with smoking. In this section, we discuss how, given this scientific evidence, as well as the findings from our population health model, FDA expects the proposed nicotine product standard for cigarettes and certain other combusted tobacco products would decrease experimentation and progression to regular use of these products among people who currently do not use these products.

Data from the 2023 NSDUH found that, in the United States, approximately 452,000 youth (ages 12–17) smoked their first cigarette and approximately 245,000 youth tried a cigar for the first time during 2023 (Ref. 86 Table A.13A). The 2023 NSDUH also found that approximately 945,000 young adults (ages 18 to 25) initiated with cigarettes and 1,065,000 young adults initiated with cigars in 2021 (Ref. 552 see Table 4.7B). Additionally, nearly 90 percent of U.S. adults who currently smoke cigarettes daily report having smoked their first cigarette by age 18 (Ref. 1). Given that nicotine is highly addictive and present in all cigarettes and cigars, as people who experiment with cigarettes and cigars continue to use these products, there is a substantial risk of the development of nicotine dependence and progression to regular use.

Nicotine is a highly addictive substance, and multiple studies have shown that symptoms of nicotine dependence can arise early after youth start smoking cigarettes, even among people who infrequently use the products (Refs. 24, 93, and 553). Although the majority of adolescents who smoke daily 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 (Ref. 93). Another study found that 19.4 percent of adolescents (initially aged 12–13 years and followed over 6 years) who smoked weekly were dependent on nicotine (Ref. 95). In a study regarding nicotine dependence among adolescents who recently initiated smoking (9th and 10th grade students), adolescents 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. 96). Researchers in a 4-year study of 6th grade students also found that ''[e]ach of the nicotine withdrawal symptoms appeared in some subjects *prior* to daily smoking'' (Ref. 93) (emphasis added). Ten percent of the study participants showed signs of tobacco dependence 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. 93). Moreover, nicotine can disrupt brain development and have long-term consequences for executive cognitive functioning (*e.g.,* decreased attention and working memory and increased impulsivity) and increases the risk of developing a substance use disorder and various mental health problems—particularly affective disorders such as anxiety and depression—as an adult (Refs. 554 to 556). Therefore, progressing to regular use during adolescence can have lasting consequences and signs of nicotine dependence are evident in youth who smoke cigarettes. Taken together, this research suggests that even infrequent experimentation can lead to early signs of dependence, which underscores the public health importance of decreasing the likelihood of cigarette experimentation among youth and young adults in the United States.

If this proposed rule is finalized, cigarettes and the other combusted tobacco products covered would be rendered minimally addictive or nonaddictive, thereby breaking the link between experimentation, nicotine dependence, and progression to regular use. As a result, FDA expects a significant reduction in youth initiation and progression to regular cigarette smoking and use of other combusted tobacco products, which would ultimately protect youth from a lifetime of addiction, disease, and premature death attributable to combusted tobacco use. To the extent that youth and young adults in the United States who would have initiated use of cigarettes and other combusted tobacco products covered by the scope of this proposed rule do not initiate with such tobacco products, the proposed standard would prevent future cigarette- and combusted tobacco product-related disease and death.

Findings from FDA's population health model, previously described in section VIII.A of this document and in the docket (Ref. 42), estimate the likelihood that youth and young adults who do not smoke would initiate regular cigarette smoking use under the proposed standard. Table 2 provides an estimated projection of the cumulative number of youth and young adults who would not initiate regular cigarette use as a result of implementation of this proposed product standard over time (Ref. 42 Appendix J for annual estimates). Since a sustained decrease in smoking initiation rates is expected, the cumulative number of people dissuaded from initiating smoking would continue to increase over time. By 2100, we estimate that, as a result of this proposed nicotine product standard, over 47 million youth and young adults who would have otherwise initiated smoking would not start smoking.

TABLE 2—PROJECTED CUMULATIVE NUMBER OF YOUTH AND YOUNG ADULTS WHO WOULD NOT INITIATE SMOKING AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027

[Millions]

Year	Median	(5th, 95th percentiles)
2028	1.3	(0.4, 1.7)
2030	2.6	(0.7, 3.4)
2040	8.6	(2.3, 11.5)
2050	14.8	(4.0, 19.8)
2060	21.1	(5.6, 28.3)

TABLE 2—PROJECTED CUMULATIVE NUMBER OF YOUTH AND YOUNG ADULTS WHO WOULD NOT INITIATE SMOKING AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027—Continued

[Millions]

Year	Median	(5th, 95th percentiles)
2070	27.5	(7.3, 37.0)
2080	34.1	(9.1, 45.9)
2090	40.8	(10.8, 54.9)
2100	47.6	(12.6, 64.1)

For these reasons, FDA expects that establishing a maximum limit of the nicotine content in cigarettes and certain other combusted tobacco products, as described in this proposed rule, would reduce the likelihood that youth and young adults would initiate with and progress to regular cigarette smoking and use of other combusted tobacco products, thereby protecting many youth and young adults from a lifetime of addiction and disease, and premature death, attributable to the use of combusted tobacco (see section VIII.D of this document for a discussion of life years gained and other public health benefits as a result of decreased initiation). Thus, from the expected impact on people who would not initiate smoking cigarettes, especially youth and young adults, this proposed product standard is appropriate for the protection of public health.

C. The Likelihood That Existing Users Would Reduce Cigarette and Other Combusted Tobacco Product Consumption or Stop Smoking

In addition to the long-term public health benefits that would accrue from the prevention of cigarette smoking and other combusted tobacco use among youth and young adults, FDA anticipates that the proposed standard also would increase the likelihood that many people who currently smoke cigarettes and certain other combusted tobacco products would stop smoking altogether, yielding health benefits from smoking cessation. FDA expects that the proposed standard would result in substantial changes in tobacco use patterns among people who currently use tobacco. Given that tobacco products are addictive primarily due to the presence of nicotine, FDA expects that the proposed standard would lead many people who currently smoke cigarettes and certain other combusted tobacco products to: (1) quit using these tobacco products altogether, (2) transition to dual use of cigarettes or other combusted tobacco products with other potentially less harmful tobacco products, or (3) transition completely to use of other potentially less harmful tobacco products.

As discussed in section IV of this document, the scientific evidence is clear that nicotine is an addictive chemical and is the primary constituent that causes and maintains addiction to cigarettes and other combusted tobacco products. The U.S. Surgeon General has concluded that there is a causal relationship between smoking and addiction to nicotine (Ref. 1), and the earlier that individuals begin smoking, the less likely they are to successfully quit (Ref. 27). FDA expects that, if this proposed rule is finalized, many people who smoke cigarettes will either quit smoking entirely, switch to a noncombusted tobacco product entirely, or transition to dual use. As discussed previously, those who switch completely to a noncombusted product may sustain their nicotine dependence but would significantly reduce their risk of tobacco-related death and disease to the extent that the products they switch to result in less harm. That is, while dependence on any tobacco product remains a health concern, the vast majority of tobacco-related cancer, lung disease, and heart disease is due to exposure to constituents of tobacco smoke (Ref. 323). Switching completely to a noncombusted tobacco product would reduce exposure to the chemical constituents created through combustion (Ref. 8).

There are multiple sources of evidence to inform FDA's analysis of how the proposed standard would affect the likelihood that people who smoke would reduce cigarette and combusted tobacco product consumption or stop smoking altogether. Findings from clinical studies offer insight into tobacco product switching, as well as cigarette smoking cessation behaviors occurring following the implementation of the proposed product standard. As described previously in section VI.B of this document, a clinical trial intended to assess the use of noncombusted and non-cigarette combusted tobacco products among participants randomized to receive LNC and NNC cigarettes found that participants who received LNC cigarettes used alternative combusted and noncombusted tobacco products on a statistically significantly higher percentage of days compared to those who received NNC cigarettes (Ref. 5). Another analysis of switching behavior in the context of a clinical study examined the influence of LNC cigarette use on alternative tobacco product use in participants who did not smoke cigarettes daily. Among participants who did not use e-cigarettes at baseline, new use of e-cigarettes was statistically significantly more prevalent in the LNC cigarette group compared to the NNC cigarette group (Ref. 377). Both findings suggest that people who smoke cigarettes, and do not quit tobacco use altogether, are likely to seek alternative sources of nicotine once a nicotine product standard for combusted tobacco products is in place.

As discussed in section VII.B.2 of this document, numerous studies have investigated the effects of VLNC or LNC cigarettes—alone or in combination with NRT products—on smoking cessation among people who smoke cigarettes and are interested in quitting (Refs. 32, 35, 41, 369 to 373), as well as among samples of people who smoke cigarettes and are not interested in quitting (Refs. 31, 40, 258, and 374). Taken together, results from these studies demonstrate that people who smoke cigarettes and are interested in quitting who are given VLNC cigarettes are more likely to achieve initial smoking abstinence compared to those who continue to smoke their usual brand or NNC cigarettes. In addition, provision of NRT and/or behavioral intervention with VLNC cigarettes can further increase smoking cessation among individuals interested in quitting (Ref. 19).

Estimates from FDA's population health model—described in section VIII.A of this document—indicate that in the first year following the implementation of the proposed standard in 2027, smoking prevalence would decline from 9.1 percent in the baseline scenario to a median of 4.5 percent in the product standard scenario, due to the large increase in

smoking cessation in the first year after implementation. In subsequent years, the difference in smoking prevalence between the scenarios would continue to grow due to sustained increases in cessation and decreases in initiation relative to baseline. The projected smoking prevalence drops to 0.2 percent under the product standard scenario by 2050, compared to 5.3 percent under baseline. By 2100, smoking prevalence is estimated at 0.2 percent in the product standard scenario, compared to 4.6 percent under baseline. Estimates of the projected cumulative number of people who quit smoking are depicted in table 3. Within the first year of the proposed standard implementation, 12.9 million additional people who smoke cigarettes are estimated to either quit tobacco altogether or switch from cigarette smoking to using noncombusted tobacco products, signifying a considerable gain over the estimated 1.6 million people who smoke that would have quit under the baseline scenario. The mortality risk of switching is greater than quitting all tobacco products, therefore the public health model assumes the risk for people who switch to noncombusted products as 8 percent higher than the risk for those who quit tobacco use entirely based on evidence in the literature (Ref. 557), see section VIII.D of this document for a more detailed discussion. The number of additional people who quit smoking would increase to approximately 19.5 million within 5 years after the implementation of the proposed standard, representing a gain of more than the 7.3 million people who quit smoking than would be anticipated under the baseline scenario. The median estimates grow closer to the 95th percentile estimates than to the 5th percentile estimates over time. A closer analysis of this pattern indicates that the 5th percentile estimates are affected by lower estimates given by two experts in the expert elicitation. Those estimates indicate that a lower percentage of people who currently use cigarettes will quit smoking cigarettes, following a nicotine product standard's implementation.

TABLE 3—CUMULATIVE NET PEOPLE WHO QUIT SMOKING [1] (MILLIONS) AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027

Period	Median	(5th, 95th percentiles)
Within 1st year (2027)	12.9	(0.8, 24.8)
Within 2 years (2027–2028)	17.5	(1.2, 24.1)
Within 3 years (2027–2029)	19.3	(1.6, 23.2)
Within 4 years (2027–2030)	19.8	(1.8, 22.3)
Within 5 years (2027–2031)	[2] 19.5	(2.0, 21.4)

[1] Net people who quit smoking cigarettes (including those who switch to noncombusted tobacco products), defined as people who quit smoking cigarettes in addition to baseline, is computed as: (number of people who quit smoking cigarettes under the nicotine product standard scenario) − (number of people who quit smoking cigarettes under baseline scenario).

[2] Cumulative net people who quit smoking declines slightly in year 5 of the simulation because there are more people who quit smoking cigarettes in the baseline scenario compared with the product standard scenario. Since there are millions of fewer people smoking cigarettes in the product standard scenario as the years continue, eventually there are fewer people available to quit smoking cigarettes compared to baseline.

We also examined the potential for an illicit market for NNC cigarettes to develop in response to the proposed product standard (see section IX.D of this document for a discussion on illicit trade). In order to examine the potential impact of such an illicit market, sensitivity analyses were conducted for the effects of diversion from cessation to illicit trade, and initiation into illicit products, on the estimated benefits of a nicotine product standard. These analyses demonstrate that increasing the assumed proportion of people who smoke who may divert to the use of illicit NNC cigarettes (for purposes of illustration, we use a low-end estimate (3.8 percent), a midpoint estimate (5.9 percent), and a high-end estimate (21.0 percent)),[31] and allowing youth and young adults (who would have otherwise initiated NNC cigarette use) to initiate into illicit NNC cigarette use (0 percent, 2.6 percent, and 10 percent) [32] under the proposed nicotine standard, resulted in reductions in the projected cumulative net people who quit smoking following the implementation of the nicotine product standard policy (table 4). However, even in the case of significant diversion to illicit NNC cigarettes, the number of people projected to quit smoking remains substantial.

[31] We use 3.8 percent as a low-end estimate based on 2017 estimates of illicit trade volume in cigarettes from (Ref. 558). This estimate excludes interstate smuggling for purposes of tax avoidance. For a midpoint estimate, using findings from the International Tobacco Control United States Survey (Ref. 559), we estimate that 5.9 percent of U.S. people who use cigarettes last purchased cigarettes from low-tax locations. We use these figures as proxies for the proportions of people who use cigarettes who may actively seek out illicit NNC cigarettes under a nicotine product standard, although we note that the product standard would be implemented nationwide, avoiding disparate pricing/availability between states. We use 21.0 percent as a high-end estimate based on the difference in non-compliance rates between reduced nicotine intervention groups (78 percent) and control groups assigned to NNC cigarettes (57 percent) in clinical trial data from (Ref. 29, Ref. 330). This estimate of 21.0 percent also represents the high-end of the range estimated in (Ref. 560), which reflected the methodology of the pack return survey by (Ref. 561). While FDA uses this 21.0 percent high-end estimate for the purpose of analyzing potential impacts, we note that it represents a highly unlikely upper bound, because for such a substantial percentage of people who use cigarettes to acquire NNC cigarettes, convenient and consistent access to an illicit market would be needed, which is highly unlikely. We also note that basing a high-end estimate on non-compliance rates found in studies (where NNC cigarettes are legally available outside the confines of the study environment) is not equivalent to real-world conditions where NNC cigarettes would not be legally available in the U.S. marketplace.

[32] We use findings from an expert elicitation developed to gauge the impact of a menthol cigarette and cigar prohibition in the United States (Ref. 562), which indicates that among people ages 12–24 who would have otherwise initiated menthol cigarette use, 2.6 percent would initiate illicit menthol cigarette use (estimate ranged from 0 percent to 10 percent).

TABLE 4—CUMULATIVE NET PEOPLE WHO QUIT SMOKING COMBUSTED CIGARETTES (MILLIONS) AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027 UNDER ILLICIT TRADE SCENARIOS. MEDIAN (5TH, 95TH PERCENTILES) ESTIMATES

Period	Illicit trade impact scenarios			
	Main scenario (no impact)	Low Impact [1]	Medium Impact [2]	High Impact [3]
Within 1st year (2027)	12.9 (0.8, 24.8)	12.4 (0.7, 24.6)	12.1 (0.7, 24.4)	9.9 (0.3, 22.6)
Within 5th year (2027–2031)	19.5 (2.0, 21.4)	19.3 (1.7, 21.3)	19.2 (1.5, 21.4)	18.1 (0.3, 21.4)

[1] Low Impact: 3.8 percent people who smoke would divert to use illicit NNC cigarettes, and 0 percent youth and young adults would initiate illicit NNC cigarettes.
[2] Medium Impact: 5.9 percent people who smoke would divert to use illicit NNC cigarettes, and 2.6 percent youth and young adults would initiate illicit NNC cigarettes.
[3] High Impact: 21.0 percent people who smoke would divert to use illicit NNC cigarettes, and 10.0 percent youth and young adults would initiate illicit NNC cigarettes.

The sum of the available evidence—including the current use of cigarettes by millions of Americans, findings from studies assessing the effects of VLNC or LNC cigarettes on smoking cessation, and findings from FDA's population health model—supports FDA's finding that the proposed product standard would increase the likelihood that many people who smoke cigarettes and/or other combusted tobacco products would stop smoking altogether, yielding significant health benefits from smoking cessation. Additionally, we find that the proposed standard is appropriate for the protection of the public health because it would decrease the likelihood that people who do not smoke cigarettes and/or use certain other combusted tobacco products—particularly youth and young adults—who experiment with combusted tobacco products will become addicted to these products, thereby decreasing progression to regular use, resulting in reduced tobacco-related morbidity and mortality associated with combusted tobacco product use. As of 2021, more than 48 million people in the United States ages 12 and older used tobacco products within the past 30 days (Refs. 25 and 274). Further, in 2021, 35.6 million U.S. adults (14.5 percent) and nearly 1 million middle and high school students (3.2 percent) used any combustible tobacco product (Ref. 274). Thus, even small changes in initiation and cessation would result in a significant reduction in the burden of death and disease caused by smoking.

D. Benefits and Risks to the Population as a Whole

We expect that the proposed nicotine product standard, if finalized, would reduce tobacco-related harms. As discussed in section IV of this document, nicotine is the primary constituent in cigarettes and other tobacco products that causes and maintains addiction. By enacting a product standard that would seek to limit the nicotine content in cigarettes and certain other combusted tobacco products to minimally addictive or nonaddictive levels, FDA anticipates that reductions in population harm would be realized through long-term health benefits resulting from prevention of cigarette uptake and progression to regular cigarette smoking among young people, as well as shorter-term health benefits resulting from increased cessation of cigarette smoking among people who currently smoke. Each of these impacts alone would result in significant health benefits to the U.S. population. In totality, they provide overwhelming evidence that the proposed standard would result in substantial health benefits over both the short- and long-term. In this section, we summarize the health benefits of never progressing to regular cigarette smoking and combusted tobacco product use, the health benefits of quitting smoking, the population health benefits of switching from cigarettes to potentially less harmful tobacco products, and the health benefits of not being exposed to secondhand smoke. We also describe additional public health benefits of the proposed standard not addressed in FDA's population health model. Finally, we describe potential risks or limiting effects of the product standard, including risks of compensatory smoking. Based on the available evidence, FDA concludes that any such potential risks or limiting effects would be significantly outweighed by the anticipated substantial benefits of this proposed nicotine product standard.

1. Given the Harmful Effects of Cigarette Smoking and Combusted Tobacco Use, Never Progressing to Regular Smoking Prevents Death and Disease and Improves Quality of Life

Never progressing to regular cigarette smoking prevents death and disease caused by smoking. Any effects of a nicotine product standard in cigarettes and certain other combusted tobacco products on preventing youth, young adult, and even adults who have never smoked from initiating/experimenting and progressing to regular cigarette smoking will have a population health benefit. Youth and young adults would experience the greatest benefits from a nicotine product standard, because it is likely that most of them would not progress beyond experimentation or occasional use and, therefore, may not experience the dangerous and deadly tobacco-related health effects associated with combusted tobacco product use. Fetuses and children also would benefit if their parents quit smoking or using most combusted tobacco products, given the negative health consequences to the fetus of a smoking mother and the dangers of secondhand smoke (Ref. 19). Children of parents who smoke, when compared with children whose parents do not smoke, have an increased frequency of respiratory infections like pneumonia and bronchitis (Ref. 563). Smoking cessation reduces the rates of these respiratory symptoms and of respiratory infections among children (Ref. 63 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. 563). If parents were more readily able to quit because these products were minimally addictive or nonaddictive, the incidence of these health problems among youth would be expected to decline. Additionally, such health problems would not occur in future years, as fewer individuals would initiate and progress to regular smoking.

According to the 2014 Surgeon General's Report, 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. 1). As stated in the 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 ''[t]he burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products'' (Ref. 1). The 2014 Surgeon General's Report estimates that 16 million people live with diseases caused by smoking cigarettes (Ref. 1). Additionally, the burden of tobacco-related addiction and disease disproportionately impacts certain populations, such as individuals experiencing poverty, those of lower educational attainment, in historically marginalized racial and ethnic groups, in the LGBTQI+ community, people living with a mental health condition, in the military, and in certain geographic areas (Ref. 120). In particular, Black individuals experience the highest rates of incidence and mortality from tobacco-related cancers compared to people from other racial and ethnic groups (Refs. 102 and 103). Additionally, mortality related to other tobacco-related diseases such as heart disease, stroke, and hypertension is higher among Black individuals than other racial and ethnic groups (Refs. 105, 106, 108 to 110, and 123).

Moreover, when comparing mortality to morbidity, for every person who dies from smoking, 30 more are living with a smoking-attributable disease (Ref. 1). Smoking is causally associated with a number of diseases affecting nearly all organs in the body, such as numerous types of cancer, heart disease, stroke, lung diseases such as COPD, and diabetes, in addition to putting individuals at increased risk for tuberculosis, certain eye diseases, and immune system issues (Ref. 1). One study estimated that individuals in the United States have had 14.0 million major smoking-attributable medical conditions, including more than 7.4 million cases of COPD, nearly 2.3 million heart attacks, 1.8 million cases of diabetes, nearly 1.2 million stroke events, more than 300,000 cases of lung cancer, and nearly 1 million cases of other smoking-attributable cancers (bladder, cervix, colon/rectum, kidney, larynx, mouth, tongue, lip, throat, pharynx, stomach) (Ref. 564). Therefore, increased smoking cessation, reduced cigarette consumption, and lower progression to regular use would reduce not only the mortality from smoking, but also the enormous burden of cigarette-attributable disease in the United States.

In addition to the years of life gained due to reduced premature mortality from tobacco, the substantial reductions in smoking initiation and increases in smoking cessation will result in improvements in quality of life for those who quit or do not initiate smoking because of the product standard. To estimate the potential impact of the proposed standard on morbidity and mortality, we used estimates from FDA's population health model, which is described in section VIII.A of this document. Table 5 presents cumulative estimates of mortality and morbidity avoided as a result of the proposed nicotine product standard, for certain years in the simulation period (Ref. 42 at Appendix J). By 2060, we estimate that approximately 1.8 million deaths due to tobacco would be avoided, rising to 4.3 million by the end of the century. The reduction in premature deaths attributable to the proposed product standard would result in 19.6 million life years gained by 2060 and 76.4 million life years gained by 2100. Based on previously reported quality of life scores derived for people who do and do not smoke, stratified by age group (Ref. 565), we estimate that the proposed nicotine product standard would result in 24.0 million QALYs gained by 2060 due to reduced smoking morbidity. By 2100, this estimate is projected to increase to 53.1 million QALYs gained due to reduced smoking morbidity (Ref. 42 at Section 2.3).

TABLE 5—PROJECTED NUMBER OF TOBACCO-ATTRIBUTABLE DEATHS AVOIDED, LIFE YEARS GAINED, AND QALYS GAINED DUE TO REDUCED SMOKING AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027

Year	Scenario	Cumulative tobacco-attributable deaths avoided (millions)	Cumulative life years gained (millions)	Cumulative QALYs gained due to reduced smoking morbidity (millions)
2040	Median (5th, 95th)	0.4 (0.1, 0.5)	2.0 (0.2, 2.7)	9.6 (2.7, 10.0)
2060	Median (5th, 95th)	1.8 (0.4, 2.0)	19.6 (3.6, 22.7)	24.0 (10.1, 24.7)
2080	Median (5th, 95th)	3.1 (1.0, 3.4)	47.4 (12.5, 52.5)	38.2 (18.5, 39.2)
2100	Median (5th, 95th)	4.3 (1.6, 4.6)	76.4 (26.5, 82.5)	53.1 (27.5, 54.4)

In addition to the main analyses concerning projected death and disability, we examined the sensitivity of modeled results to underlying assumptions related to baseline product use projections and mortality risk estimates. Sensitivity analyses accounted for the following: an increase in noncombusted product initiation; different assumptions of people who smoke switching to noncombusted products per year; decrease in smoking initiation; lower and higher noncombusted product mortality risk compared to baseline; different assumptions for dual product use mortality risk; changes in baseline mortality rate projections; and the potential impact of a substantial illicit market for NNC cigarettes. Changes to baseline inputs of noncombusted product use trajectories and health risks had minimal impact on smoking prevalence and attributable morbidity and mortality, and the nicotine product standard still resulted in substantial public health benefits. Assuming increasing initiation rates for noncombusted product use until year 2030 implies that the number of people who use tobacco will be higher under the baseline and nicotine product standard scenarios, with a higher proportion being people who use noncombusted tobacco products.

In terms of mortality risk, we applied a relative risk of 1.18 for people who use noncombusted tobacco products as compared with people who have never smoked (*i.e.,* the risk of death associated with noncombusted tobacco use is assumed to be 1.18 times greater than the risk of death associated with never smoking). For combusted cigarette smoking, the relative mortality risk varies with age, but is generally around 2.5, as compared to people who have never smoked (*i.e.,* the risk of death associated with smoking is estimated to be 2.5 times greater than the risk of

death associated with never smoking). Mortality risk for people who have never used tobacco is 1, so the excess mortality risk of using a product beyond that of those who have never used tobacco, and therefore related to the product used, can be calculated by subtracting 1 from the mortality risk (*i.e.,* excess mortality risk for noncombusted tobacco use is $1.18 - 1 = 0.18$, and for combusted cigarette use it is $2.5 - 1 = 1.5$). Thus, in our main modeling projections, we apply an excess risk of using noncombusted tobacco products that is 12 percent that of the excess risk associated with cigarette smoking (*i.e.,* $100 \times (0.18/1.5) = 12$ percent).

TABLE 6—IMPACT OF VARYING BASELINE ASSUMPTIONS ON PROJECTED SMOKING PREVALENCE AND AVOIDED MORTALITY AND MORBIDITY BY 2100. MEDIAN (5TH, 95TH PERCENTILES) ESTIMATES

Scenario	Projections through year 2100			
	Cigarette smoking prevalence (%)	Cumulative tobacco-attributable mortality avoided (millions)	Cumulative life years gained (millions)	Cumulative QALYs gained from reduced smoking morbidity (millions)
Main scenario	0.2 (0.1, 1.9)	4.3 (1.6, 4.6)	76.4 (26.5, 82.5)	53.1 (27.5, 54.4)
Baseline noncombusted tobacco product trajectory				
Increased noncombusted initiation	0.2 (0.1, 1.9)	4.3 (1.6, 4.6)	76.5 (26.7, 82.5)	53.1 (27.5, 54.4)
50% increased complete switching	0.13 (0.06, 1.7)	4.2 (1.7, 4.5)	74.9 (28.6, 80.7)	51.9 (29.0, 52.9)
100% increased complete switching	0.12 (0.06, 1.5)	4.2 (1.8, 4.4)	73.6 (30.3, 79.0)	50.8 (30.2, 51.6)
Baseline smoking initiation trajectory				
25% decrease in smoking initiation during the period 2021–2030	0.13 (0.1, 1.6)	4.1 (1.5, 4.4)	72.9 (24.3, 79.0)	45.2 (22.9, 46.4)
Baseline smoking cessation				
10% increase in smoking cessation	0.15 (0.1, 1.8)	4.0 (1.5, 4.3)	70.9 (24.9, 76.4)	50.1 (26.3, 51.2)
Baseline noncombusted mortality relative risk (RR)				
Higher RR than main scenario (RR = 1.3)	0.2 (0.1, 1.9)	4.3 (1.6, 4.6)	75.0 (26.0, 81.4)	53.1 (27.5, 54.4)
Lower RR than main scenario (RR = 1.1)	0.2 (0.1, 1.9)	4.4 (1.6, 4.7)	77.2 (26.9, 83.2)	53.1 (27.5, 54.4)
Baseline dual use RR				
Dual use RR is 18% greater than for cigarette smoking	0.2 (0.1, 1.9)	4.3 (1.6, 4.6)	75.9 (25.0, 82.4)	53.1 (27.5, 54.4)
Dual use RR is the average of cigarette and noncombusted use RR	0.2 (0.1, 1.9)	4.3 (1.6, 4.6)	77.0 (28.6, 82.6)	53.1 (27.5, 54.4)
Dual use RR is equal to the noncombusted use RR	0.2 (0.1, 1.9)	4.3 (1.6, 4.6)	77.6 (30.7, 82.7)	53.1 (27.5, 54.4)
Baseline mortality rate projections				
Keep mortality rates constant starting at 2060	0.2 (0.1, 2.0)	4.7 (1.9, 5.1)	77.9 (28.2, 83.9)	53.0 (27.4, 54.2)

As shown in table 6, varying baseline input parameter values had very small effects on estimates of the potential population health effects of a nicotine product standard. Assuming a 25 percent decrease in cigarette smoking initiation during the period from 2021 to 2030 resulted in modest decreases in smoking prevalence and health benefits, in particular reductions in morbidity due to smoking, by 2100 in the policy scenario compared to the main analysis. Increases in baseline complete switching to noncombusted tobacco product use resulted in similar small decreases in smoking prevalence and health benefits in terms of life years gained and reduced smoking morbidity by 2100 compared to the main analysis. Different assumptions about baseline relative risks also produced modest changes in differences in life years gained. Additional details regarding the sensitivity analyses can be found in FDA's modeling document (Ref. 42).

Sensitivity analyses were also conducted examining assumptions about the potential effect of the nicotine product standard on smoking cessation. In addition to the modeling results obtained through expert-derived inputs, we also generated projections based on results from clinical studies of VLNC cigarette use and cessation. Based on these studies, we applied a two-fold increase in cessation (estimates ranged from 6.4 percent to 19.8 percent), as compared to the baseline cessation rate (estimates ranged from 3.2 percent to 9.9 percent), as an alternative estimate of the long-term impact of the proposed product standard on cessation, while maintaining the median of the expert-derived values for the other parameters (Ref. 42 at Section 2.3). Given the wide variation in the expert-derived cessation rates, the projected health impacts assuming a two-fold increase in cessation fell within the range of results obtained from expert-derived inputs (see table 6).

Additionally, increasing the assumed proportion of people who smoke who may divert to the use of illicit NNC cigarettes (3.8 percent, 5.9 percent, and 21.0 percent),[33] and allowing youth and

[33] We use 3.8 percent as a low-end estimate based on 2017 estimates of illicit trade volume in cigarettes from Euromonitor International (Ref. 558). This estimate excludes interstate smuggling for purposes of tax avoidance. Using findings from the International Tobacco Control United States Survey, we estimate that 5.9 percent of U.S. people

Continued

young adults (who would have otherwise initiated NNC cigarette use) to initiate into illicit NNC cigarette use (0 percent, 2.6 percent, and 10 percent) [34] under the proposed nicotine standard resulted in reductions in the projected cumulative attributable morbidity and mortality outcomes following the implementation of the policy (table 7). It is noteworthy that significant benefits in terms of reduced morbidity and mortality are realized as a result of this product standard, even in a scenario in which greater proportions of the population who smoke are assumed to divert to use of illicit NNC cigarettes.

TABLE 7—PROJECTED HEALTH BENEFITS AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027 UNDER ILLICIT TRADE SCENARIOS

[Median (5th, 95th percentiles) estimates]

Year	Illicit trade impact scenarios			
	Main scenario (no impact)	Low impact [1]	Medium impact [2]	High impact [3]
Tobacco-Attributable Deaths Avoided (Millions)				
2040	0.4 (0.1, 0.5)	0.4 (0.04, 0.5)	0.4 (0.04, 0.5)	0.4 (0.01, 0.5)
2060	1.8 (0.4, 2.0)	1.8 (0.4, 2.0)	1.8 (0.3, 2.0)	1.7 (0.1, 2.0)
2080	3.1 (1.0, 3.4)	3.1 (0.8, 3.4)	3.1 (0.8, 3.4)	3.0 (0.4, 3.3)
2100	4.3 (1.6, 4.6)	4.3 (1.5, 4.6)	4.3 (1.4, 4.6)	4.2 (0.9, 4.5)
Cumulative Life Years Gained (Millions)				
2040	2.0 (0.2, 2.7)	2.0 (0.1, 2.7)	2.0 (0.1, 2.7)	1.8 (0.01, 2.6)
2060	19.6 (3.6, 22.7)	19.4 (3.2, 22.6)	19.3 (3.0, 22.6)	18.4 (1.2, 22.0)
2080	47.4 (12.5, 52.5)	47.1 (11.4, 52.4)	46.9 (10.7, 52.3)	45.3 (5.3, 51.5)
2100	76.4 (26.5, 82.5)	76.0 (24.6, 82.3)	75.8 (23.4, 82.2)	73.9 (13.7, 81.3)
Cumulative QALYs Gained from Reduced Smoking Morbidity (Millions)				
2040	9.6 (2.7, 10.0)	9.6 (2.5, 10.0)	9.5 (2.4, 10.0)	9.2 (1.5, 9.9)
2060	24.0 (10.1, 24.7)	24.0 (9.6, 24.7)	23.9 (9.2, 24.7)	23.4 (6.5, 24.6)
2080	38.2 (18.5, 39.2)	38.2 (17.7, 39.2)	38.0 (17.0, 39.2)	37.3 (12.6, 39.0)
2100	53.1 (27.5, 54.4)	53.0 (26.6, 54.4)	52.8 (25.5, 54.3)	51.9 (19.3, 54.1)

[1] Low Impact: 3.8 percent people who smoke would divert to use illicit NNC cigarettes, and 0 percent youth and young adults would initiate illicit NNC cigarettes.

[2] Medium Impact: 5.9 percent people who smoke would divert to use illicit NNC cigarettes, and 2.6 percent youth and young adults would initiate illicit NNC cigarettes.

[3] High Impact: 21.0 percent people who smoke would divert to use illicit NNC cigarettes, and 10.0 percent youth and young adults would initiate illicit NNC cigarettes.

As previously discussed, nicotine is the primary driver of addiction in tobacco products and facilitates progression to regular cigarette smoking and other regular combusted tobacco product use. FDA anticipates that establishing a maximum level of nicotine in cigarettes and certain other combusted tobacco products will prevent a substantial number of youth and young adults who experiment with combusted tobacco products from developing an addiction to these products, thereby decreasing progression to regular use, resulting in reduced tobacco-related morbidity and mortality associated with combusted tobacco product use.

2. Given the Harmful Effects of Cigarette Smoking and Other Combusted Tobacco Product Use, Quitting Smoking Reduces Death and Disease

Although the health benefits are greater for people who stop smoking at earlier ages (Refs. 63 and 563), researchers estimate that people who regularly smoke can gain years of additional life expectancy no matter when they quit (Ref. 566). Quitting cigarette smoking and use of other combusted tobacco products substantially reduces the likelihood of tobacco-related death and disease. As stated in the 2004 Surgeon General's Report, ''[q]uitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general'' (Ref. 63). The 2020 Surgeon General's Report also concluded that ''[s]moking cessation is beneficial at any age. Smoking cessation improves health status and enhances quality of life.'' (Ref. 19). As previously noted, FDA expects that, if this proposed rule is finalized, there will be a significant increase in smoking cessation in the U.S. population (see section VIII.C of this document).

The benefits associated with smoking cessation happen quickly (Ref. 63). Within 2 to 12 weeks of quitting smoking, an individual's lung function and blood circulation improve (Ref. 63). During the first 1 to 9 months following cessation, coughing and shortness of breath decrease (Ref. 63). Within several

who use cigarettes last purchased cigarettes from low-tax locations (Ref. 559). We use these figures as proxies for the proportions of people who use cigarettes who may actively seek out illicit NNC cigarettes under a nicotine product standard, although we note that the product standard would be implemented nationwide, avoiding disparate pricing/availability between states. We use 21 percent as a high-end estimate based on the difference in non-compliance rates between reduced nicotine intervention groups (78 percent) and control groups assigned to NNC cigarettes (57 percent) in clinical trial data (Refs. 29 and 330). This estimate of 21 percent also represents the high-end of the range estimated by the National Research Council, which reflected the methodology of the pack return survey by Fix, et al. (Refs. 560 and 561).

[34] We use findings from an expert elicitation developed to gauge the impact of a menthol cigarette and cigar prohibition in the United States, which indicates that among people ages 12–24 who would have otherwise initiated menthol cigarette use, 2.6 percent would initiate illicit menthol cigarette use (estimate ranged from 0 percent to 10 percent) (Ref. 562).

months of quitting smoking, individuals can expect further improvement in lung function (Ref. 63). Additionally, the benefits of cessation continue for those who remain smoke-free. Smoking cessation reduces the risk of cancers and other diseases (Ref. 19). For example, the risk of fatal lung cancer in adults over age 55 is about 25 times higher among people who smoke cigarettes relative to people who have never smoked (Ref. 567). After 10–15 years of abstinence from smoking, the risk of lung cancer is about 50 percent of the risk for individuals who continue to smoke (Ref. 19). The risk of cancer of the mouth, throat, esophagus, stomach, bladder, cervix, pancreas, liver, kidney, colon, and rectum, and the risk of acute myeloid leukemia also decreases (Refs. 19 and 568). The evidence is also sufficient to infer that the risk of stroke decreases after smoking cessation and approaches that of people who have never smoked cigarettes over time (Ref. 569). Furthermore, the evidence is sufficient to infer that the relative risk of coronary heart disease among people who formerly smoked cigarettes falls rapidly after cessation and then declines more slowly (Ref. 19).

In addition, smoking cessation substantially reduces the risk of other dangerous diseases that can lead to death or disability and cause a financial strain on healthcare resources. For example, quitting smoking substantially reduces the risk of peripheral artery occlusive disease (which can cause complications that lead to loss of limbs) (Ref. 563). It also reduces the relative risk of coronary heart disease and stroke morbidity and mortality among people who formerly smoked compared with people who have never smoked (Ref. 19). People who formerly smoked cigarettes also have half the excess risk of experiencing an abdominal aortic aneurysm compared to people who currently smoke cigarettes (Ref. 563). Furthermore, cigarette smoking complicates many diseases (*e.g.,* people who smoke and have 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. 28).

Even people who smoke and quit smoking after the onset of a life-threatening disease experience significant health benefits from cessation. Quitting smoking after a diagnosis reduces the chance of recurrences and future health problems. For example, people who quit smoking after having a heart attack can reduce their chances of having a second heart attack by 50 percent (Ref. 568). For those persons who have already developed cancer, quitting smoking reduces the risk of developing a second cancer (Refs 563, 570 to 572). Additionally, quitting smoking after a diagnosis of lung cancer reduces the risk of cancer progression and mortality (Ref. 573). Researchers also estimate that for people who currently smoke and have been diagnosed with coronary heart disease, quitting smoking reduces the risk of death overall and reduces the risk of recurrent heart attacks and cardiovascular death by 30 to 40 percent (Refs. 19 and 563). The 2020 Surgeon General's Report concluded that quitting smoking reduces the risk of fatal and non-fatal stroke, and earlier reports have also stated that it is reasonable to assume that quitting smoking would reduce the risk of recurrent strokes (Refs.19 and 563). Quitting smoking helps the body tolerate the surgery and treatments, such as chemotherapy and radiation, associated with certain smoking-related diseases, and quitting also improves the likelihood of responding to those treatments (Refs. 63, 563, 570, and 574) and reduces the risk of respiratory infections compared to continued smoking (Refs. 563 and 575).

Given the reduction in risk of smoking-related death and disease associated with cessation, those who successfully quit smoking also increase their life expectancy. Using data from the CPS–II—an ongoing study of 1.2 million adults—scientists have found that, among men who smoke cigarettes, men who smoked at age 35 and continued to smoke until death had a life expectancy of 69.3 years, compared with a life expectancy of 76.2 years for those who stopped smoking at age 35 (Ref. 576). After adjusting for the subsequent quit rate among people who currently smoke cigarettes at baseline (to account for the possibility that some people who currently smoke at baseline quit smoking or some people who formerly smoked relapsed during followup and, thus, were incorrectly classified as people who continue to smoke in the unadjusted analysis), the life expectancy for males who formerly smoked increased to 77.8 years (a life extension of 8.5 years) (Ref. 576). Women who smoked at age 35 and continued to smoke until death had a life expectancy of 73.8 years, compared with a life expectancy of 79.7 years for those who stopped smoking at age 35 (Ref. 576). After adjustment for the subsequent quit rate among people who currently smoke at baseline, the life expectancy for females who formerly smoked increased to 81 years (a life extension of 7.7 years) (Ref. 576). Furthermore, a man aged 60–64 years who smokes 20 cigarettes (one pack) or more per day and then quits smoking reduces his risk of dying during the next 15 years by 10 percent (Ref. 563).

While cessation is beneficial for people of all ages, the health benefits are greatest for people who stop smoking at earlier ages (Refs. 63 and 563). Scientists in the United Kingdom found that people who quit smoking at age 30 reduce their risk of dying prematurely (*i.e.,* dying before their expected average life expectancy) from smoking-related diseases by more than 90 percent (Refs. 544 and 577). Those who quit at age 50 reduce their risk of dying prematurely by 50 percent compared to those who continue to smoke (Ref. 544). Using NHIS data, researchers also estimated that life expectancy in the United States would increase by 4 years among people who smoke who quit at ages 55–64, and 10 years among people who smoke who quit at ages 25–34 (Ref. 566). Scientists using the CPS–II data (while accounting for the possibility that some people who currently smoke at baseline quit smoking and some people who formerly smoked relapsed during followup) found that even people who smoke who quit at age 65 had an expected life increase of 2 years for men and 3.7 years for women (Ref. 576).

The benefits continue for those who remain smoke-free. At year one, an individual's risk of coronary heart disease becomes half that of a person who smokes cigarettes (Refs. 219 and 578). Beginning 2 and 5 years after cessation, an individual's stroke risk is reduced to that of a person who does not smoke cigarettes (Refs. 19 and 578). In addition, the risk of cancers of the mouth, throat, esophagus, and bladder for a person who formerly smoked is halved within 5 years (Ref. 578). By 10 years post-cessation, an individual's risk of cancers of the kidney and pancreas decreases (Ref. 578). The risk of coronary heart disease becomes that of a person who does not smoke after 15 years of abstinence (Ref. 578). FDA anticipates that limiting nicotine yield by setting a maximum level of nicotine in cigarettes and certain other combusted tobacco products would improve smoking cessation outcomes in adults who smoke and result in longer life expectancies for more individuals. Additionally, FDA anticipates that this proposed product standard will benefit populations that use tobacco products at disproportionately high levels by reducing tobacco-related morbidity and mortality by improving quitting and cessation among these populations.

Research has shown that people from specific population groups who smoke cigarettes bear a disproportionate burden of tobacco-related morbidity and mortality. Black individuals, and in particular Black men, experience the highest rates of incidence and mortality from tobacco-related cancers compared to people from other racial and ethnic groups (Refs. 102 and 103). Additionally, mortality due to tobacco-related disease such as heart disease, stroke, and hypertension is higher among Black individuals compared to other racial and ethnic groups (Refs. 105, 106, 108 to 110, 123, and 579). Furthermore, individuals with symptoms of mental health disorders and persons who have substance use disorders smoke cigarettes in disproportionately large numbers (Refs. 128, 580 to 585), resulting in increased risk for tobacco-related morbidity and mortality (Ref. 585). Based on these collective findings, FDA anticipates that the proposed product standard will improve smoking cessation outcomes across the U.S. population, including among populations at increased risk for tobacco-related morbidity and mortality, leading to a reduction in adverse tobacco-related health effects.

3. Given the Harmful Effects of Cigarette Smoking, Switching to a Potentially Less Harmful Nicotine Delivery Product May Reduce Death and Disease

Some people who smoke and who want to quit use NRT products, or other smoking cessation products that do not contain nicotine, that FDA has approved as safe and effective for smoking cessation. These products have been shown to significantly increase the success of smoking cessation (Ref. 586). FDA continues to be committed to enabling the development of safe and effective drug product innovations that help smokers quit combustible cigarettes and improve their health.

FDA also recognizes, however, that other people may seek to switch from cigarette smoking to using other noncombusted tobacco products that deliver nicotine. People who smoke and switch completely to a potentially less harmful noncombusted tobacco product to maintain their nicotine dependence also could, to the extent that use of those products result in less harm, significantly reduce their risk of tobacco-related death and disease (Ref. 8).

As described in section VI.B of this document, studies have reported on the ways in which people who use tobacco have predicted how their patterns of tobacco use would change in response to the implementation of a nicotine product standard. While most people who use tobacco in these studies indicated that they would continue to smoke cigarettes—or other combusted products—or simply quit tobacco use, some participants reported that they would switch to using or increase use of a noncombusted product (Refs. 262, 264, and 587).

One clinical trial compared use of NRT and alternative tobacco products (*i.e.,* smokeless tobacco, e-cigarettes, cigars, cigarillos) among people who smoke cigarettes and were randomized to one of three groups (Ref. 5). One group received LNC cigarettes along with access to NRT, noncombusted tobacco products (*i.e.,* smokeless tobacco, e-cigarettes), and combusted non-cigarette products (*i.e.,* cigars, cigarillos); a second group received LNC cigarettes, and NRT, and noncombusted tobacco products only; and a third group received NNC cigarettes along with NRT, noncombusted tobacco products, and combusted tobacco products. Overall, those who received the LNC cigarettes used more alternative combusted and noncombusted tobacco products as well as NRT. These participants also smoked fewer total combusted tobacco products and had a greater number of quit attempts. Tobacco toxicant levels in participants who received LNC cigarettes and only NRT and noncombusted products were statistically significantly lower than those of participants who received NNC cigarettes, while toxicant levels in those who received LNC cigarettes and had access to NRT, combusted, and noncombusted products did not differ from the NNC cigarette group (Ref. 5). Findings demonstrate that when people who smoke cigarettes are switched to LNC cigarettes and are provided with alternative sources of nicotine, they will readily use the alternative sources of nicotine. Moreover, the LNC cigarette group that had access to NRT and noncombusted nicotine sources only had statistically significantly reduced biomarker levels of certain harmful constituents (NNN and NNAL) compared to those who continued to smoke NNC cigarettes (Ref. 5). The LNC cigarette group with access to NRT and both combusted and noncombusted tobacco products resembled the NNC cigarette group (Ref. 5).

Moreover, in general, the high levels of noncompliance with study-issued VLNC cigarettes in the context of clinical trials, and continued use of non-study provided tobacco products (particularly NNC cigarettes), suggest that VLNC cigarettes have lower appeal and abuse potential compared to NNC cigarettes (Refs. 327 to 331). As a result, these findings suggest that people who smoke VLNC cigarettes are likely to use alternative nicotine-containing products, if such products are concurrently available, once a nicotine product standard for combusted tobacco products is in place.

Under FDA's population health model's product standard scenario, an increase in noncombusted product use would occur concurrently with a dramatic reduction in cigarette smoking. Although the model assumes that noncombusted product initiation would remain constant until the end of the projection period (*i.e.,* 2100), the product standard scenario shows that noncombusted use continues to climb due to higher switching rates from combusted products as compared to the baseline scenario. This is because the number of people who start using noncombusted tobacco products would be much higher compared to the number of people who quit using noncombusted products. That is, there would be more people who currently use noncombusted tobacco products every year than people who quit using noncombusted products, which would cause an increase in noncombusted tobacco use prevalence throughout the projection period. According to the model, adult noncombusted tobacco use would increase from 7.7 percent in the baseline scenario to 12.8 percent in the product standard scenario within 1 year after policy implementation, due to the increase in switching from cigarette smoking and dual use as a result of a nicotine product standard. The prevalence of noncombusted tobacco use would remain higher in the product standard scenario over time due both to increased uptake among people who smoke and increased initiation due to some dissuaded initiation of cigarette use, compared to those individuals taking up noncombusted products instead.

Under the product standard scenario in the model, dual use of cigarettes and noncombusted tobacco products also would increase immediately, since a greater proportion of people who continue to smoke cigarettes would take up noncombusted products than in the baseline scenario, but this pattern would not continue over time with dual use prevalence reaching levels below 0.1 percent by the year 2035. Although the increase in noncombusted tobacco product use trend changes over time (*i.e.,* results showed a spike increase in noncombusted use prevalence within the first 3 years after implementation of a nicotine product standard), the decrease in smoking prevalence becomes greater than the increase in

noncombusted use following the implementation of a nicotine product standard. Consequently, overall tobacco use under the product standard scenario would remain lower than in the baseline scenario.

As described in section VIII.A of this document, in addition to the aforementioned main analyses, FDA conducted a series of sensitivity analyses to examine the impact of key modeling assumptions on the main outcome metrics of interest. In these analyses, we examined the sensitivity of modeled results to underlying assumptions related to baseline product use projections and mortality risk estimates. Sensitivity analyses included examining the impact of increased initiation of noncombusted tobacco product use among those who would otherwise not have used tobacco, the impact of an increase in switching from cigarettes to noncombusted tobacco product use, the impact of a varying mortality risk associated with dual use of cigarettes and noncombusted tobacco products, the impact of lower and higher noncombusted tobacco product risk, and the emergence of an illicit market for full nicotine content cigarettes.

In general, changes to baseline inputs of noncombusted product use trajectories and health risks had minimal impact on smoking prevalence and attributable morbidity and mortality and the nicotine product standard policy scenario still resulted in substantial public health benefits. In the main modeling analysis, we account for people who would have initiated on smoking cigarettes initiating on noncombusted tobacco products instead because of the product standard. It is also possible that there could be increased initiation of noncombusted tobacco use among those who would otherwise not have used tobacco under the product standard scenario; for example, due to increased marketing of noncombusted products because of the policy or changes in public perceptions of the harms of noncombusted products. In a sensitivity analysis, starting at 2027 (year of the proposed standard implementation), we assumed a 20 percent increase in the initiation of noncombusted tobacco products among those who would otherwise have not used tobacco. Table 8 provides the projected impacts on tobacco-related mortality and morbidity through the year 2100. Compared with the main results, a 20 percent increase in initiation of noncombusted tobacco use had minimal impact in mortality outcomes given the substantial reduction in adverse health effects projected under a potential nicotine product standard. For example, by year 2100, cumulative life years gained decreased by less than 1 percent compared with the main results, while cumulative tobacco-attributable deaths avoided remained almost the same. It is important to note that, because we only have data on the effect of cigarette smoking (and not noncombusted product use) on quality of life, the projected changes in QALYs gained from reduced smoking morbidity are not affected by increasing noncombusted product use initiation.

TABLE 8—IMPACT OF INCREASED INITIATION OF NONCOMBUSTED TOBACCO PRODUCTS AS A RESULT OF THE PROPOSED NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027 ON PROJECTED SMOKING PREVALENCE AND TOBACCO-RELATED MORTALITY AND MORBIDITY BY 2100

[Median (5th, 95th percentiles) estimates]

Scenario	Projections through year 2100			
	Noncombusted tobacco use prevalence (%)	Cumulative tobacco-attributable mortality avoided (millions)	Cumulative life years gained (millions)	Cumulative QALYs gained from reduced smoking morbidity (millions)
Main scenario	14.1 (12.7, 14.9)	4.3 (1.6, 4.6)	76.4 (26.5, 82.5)	53.1 (27.5, 54.4)
20% increased initiation of noncombusted products	15.4 (14.0, 16.1)	4.3 (1.6, 4.6)	75.9 (26.1, 82.1)	53.1 (27.5, 54.4)

Taken together, findings from prior research, as well as FDA's population health model, suggest that if the proposed product standard reduces the nicotine yield by setting a maximum level of nicotine in cigarettes only, but people who smoke cigarettes still have access to other NNC combusted tobacco products, they likely would substitute with the NNC combusted tobacco products and negate a significant proportion of the public health impact of the product standard. If other combusted tobacco products also are covered by this proposed product standard, however, data suggest that people who smoke may switch from combusted tobacco product use to potentially less harmful tobacco products. Moreover, findings indicate that switching from combusted cigarette use to noncombusted tobacco product use has the potential to impart significant health-related benefits on a population level. The population health model estimates that on average approximately 50 percent of people who smoke cigarettes will switch to noncombusted tobacco products use per year, and although we estimate that such switching carries an 8 percent higher risk than quitting tobacco use entirely (based on findings from Henley et al. 2007 (Ref. 557)), this is still a significant health-related benefit compared to continuing to use combusted tobacco products.

4. Having Fewer People Smoke Cigarettes and Other Combusted Tobacco Products Will Reduce Death and Disease Associated With Secondhand Smoke Exposure

Cigarettes and other combusted tobacco products also have deadly effects on people who do not smoke because they produce secondhand smoke. It is well-established that secondhand tobacco smoke causes premature death and disease in children and in adults who do not smoke (Ref. 15 at p.11). Secondhand smoke exposure is currently estimated to be responsible for over 41,000 deaths annually in the United States (Ref. 1). For example, an estimated 7,300 lung cancer deaths and nearly 34,000 coronary heart disease deaths annually can be attributed to secondhand smoke (Ref. 1). Additionally, productivity losses due to secondhand smoke-attributable deaths are estimated to cost the United States $5.6 billion each year (Ref. 1).

Children are one group disproportionately exposed to and impacted by secondhand smoke. The 2014 Surgeon General's Report estimated that secondhand smoke is

associated with 150,000 to 300,000 lower respiratory tract infections in infants and children under age 18 months, 790,000 doctor's office visits related to ear infections per year, and 202,000 asthma cases each year (Refs. 1 and 137). In 2014, the U.S. Surgeon General reported that 400 sudden infant death syndrome (SIDS) deaths annually are related to perinatal smoking or exposure to secondhand smoke; the ''Reproductive Outcomes'' section describes the impact of perinatal smoking (Ref. 1). Children of parents who smoke, when compared with children of parents who do not smoke, have an increased frequency of respiratory infections like pneumonia and bronchitis (Ref. 563). Children exposed to tobacco smoke in the home are also more likely to develop acute otitis media (middle ear infections) and persistent middle ear effusions (fluid behind the eardrum) (Ref. 563). More recent data from the 2013–2014 NHANES estimates that approximately 58 million Americans who do not smoke (1 in 4) were exposed to secondhand smoke, including 14 million children (Ref. 588). Approximately half of all U.S. children ages 3–18 are exposed to cigarette smoke regularly at home or other locations that still permit smoking (Ref. 1). In 2019, approximately one-quarter of middle and high school students reported breathing in secondhand smoke in their homes or in a vehicle (Ref. 145).

The burden of secondhand smoke exposure is experienced disproportionately among members of some racial and ethnic groups and lower income groups. Among people who do not smoke and were ages 3 and older, findings from 2011 to 2018 NHANES data indicate that non-Hispanic Black persons and those living below the poverty level had the highest levels of secondhand smoke exposure compared to people of other races and those living above the poverty level, respectively; these disparities persisted across all years of the study analysis from 2011 to 2018 (Ref. 139). From 1999 to 2012, the percentage of people who do not smoke and were age 3 and older exposed to secondhand smoke (defined in the study as levels 0.05–10 nanogram per milliliter) declined across all racial and ethnic groups (Ref. 141). However, a significantly higher proportion of non-Hispanic Black persons who do not smoke continued to have detectable serum cotinine levels compared to Mexican American and non-Hispanic White persons who do not smoke. For example, in 2011–2012, nearly 50 percent of non-Hispanic Black people who do not smoke had detectable serum cotinine levels, compared with 22 percent of non-Hispanic White and 24 percent of Mexican American people who do not smoke (Ref. 141). Additionally, disparities in secondhand smoke exposure are found across various environmental settings, including homes, vehicles, workplaces, and public places. These disparities speak to the interrelated influences of individual factors (*e.g.,* age, race and ethnicity, income) and existing inequities in places where members of communities impacted by tobacco-related health disparities are likely to reside, spend time, and work (Ref. 174). The proposed product standard is anticipated to reduce smoking-related morbidity and mortality for specific population groups that do not smoke that are disproportionately exposed to secondhand smoke, especially youth.

Moreover, there is also some scientific evidence supporting disparities in secondhand smoke exposure by sexual orientation. An analysis of NHANES data from 2003–2010 found that secondhand smoke exposure (defined as a serum continine [17] levels ≥0.05 nanogram per milliliter) differed by sexual orientation among women 20–59 years of age (Ref. 143). This study found that among women 20–59 years of age, secondhand smoke exposure was higher among non-smoking women who identified as lesbian (56.2 percent) or who reported a lifetime experience with a same-gender partner (47.7 percent) than those women who identified as exclusively heterosexual (33.0 percent; $p<0.001$) (Ref. 143). However, among men 20–59 years of age, exposure to secondhand smoke did not significantly differ by sexual orientation.

FDA anticipates that the overall public health benefits of this proposed nicotine product standard would be far greater than those described above once we account for the impacts of reduced cigarette smoking on secondhand smoke exposure. As evidenced by evaluations of smoke-free policies, decreasing exposure to secondhand smoke will decrease smoking-related death and disease among people who do not smoke (Refs. 589 and 590).

To estimate the potential impact of the proposed standard on morbidity and mortality, FDA evaluated the existing scientific literature as well as findings from our population health model, which is described in section VIII.A of this document. Estimation of the mortality benefits of a nicotine product standard for secondhand smoke exposure used a similar approach. This approach relied on scaling the estimate of 437,400 deaths annually attributable to direct cigarette smoking from 2005–2009 (Ref. 1), to the number of deaths attributed to secondhand smoke exposure. That ratio was then applied to the model-derived projected changes in avoided cigarette-attributable deaths under the main product standard scenario to project the number of avoided deaths over time from secondhand smoke exposure. In the population health model, the impacts of a nicotine product standard on mortality from secondhand smoke exposure were estimated by first calculating the ratio of secondhand smoke (41,280 deaths; (Ref. 1)) to primary smoking-attributable deaths. That value, 9.4 percent, was then applied to the projections of cigarette-attributable deaths avoided yielding an estimate of approximately 169,000 cumulative deaths from secondhand smoke exposure avoided by 2060, rising to approximately 415,600 cumulative deaths avoided by the end of the century (see table 9).

TABLE 9—PROJECTED NUMBER OF TOBACCO-ATTRIBUTABLE DEATHS AVOIDED FOR SECONDHAND SMOKE AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027

Year	Scenario	Cumulative secondhand smoking-attributable deaths avoided
2040	Median (5th, 95th)	39,800 (4,900, 49,200)
2060	Median (5th, 95th)	169,000 (38,500, 189,000)
2080	Median (5th, 95th)	297,000 (91,200, 323,200)
2100	Median (5th, 95th)	415,600 (159,700, 444,400)

5. Estimated Mortality Impact of Reduced Smoking-Related Fires, Smoking-Related Perinatal Conditions, and Use of Non-Premium Cigars and Pipe Tobacco as a Result of Implementation of the Proposed Standard

FDA anticipates that the overall public health benefits of this proposed nicotine product standard would be greater than those described above once we account for the impacts of reduced cigarette smoking on smoking-related fires and perinatal conditions, in addition to the impacts of reduced use of other combusted tobacco products. To estimate the potential impact of the proposed standard on mortality, FDA evaluated the existing scientific literature, as well as findings from the population health model—which is described in section VIII.A. of this document. Similar to the approach taken to estimate the mortality benefits of a nicotine product standard for secondhand smoke exposure, estimation of the mortality benefits of a nicotine product standard for smoking-related fires, smoking-related perinatal conditions, and use of non-premium cigars and pipe tobacco used a consistent approach. This approach relied on scaling the estimate of 437,400 deaths annually attributable to direct cigarette smoking from 2005–2009 (Ref. 1), to the number of deaths attributed to each of the following causes: smoking-related fires, smoking-related perinatal conditions, and use of non-premium cigars and pipe tobacco. That ratio was then applied to the model-derived projected changes in avoided cigarette-attributable deaths under the main product standard scenario to project the number of avoided deaths over time from each of these causes (*i.e.,* smoking-related fires, smoking-related perinatal conditions, and use of non-premium cigars and pipe tobacco) (see table 10).

During 2012–2016, an estimated annual average of 18,100 reported home structure fires in the United States were caused by smoking materials, which killed an average of 590 people annually (Ref. 591). Moreover, smoking materials remain a leading cause of fatal home fires in the United States, and people who smoke are not the only victims (Ref. 592). By one estimate, one out of every four fatal victims of smoking-material fires is not the person whose cigarette initiated the fire (Ref. 593). A lower prevalence of cigarette smoking and reduced cigarette consumption is likely to decrease the occurrence of fires caused by smoking materials, including cigarettes and other combusted tobacco products. To estimate the impact of a nicotine product standard on the number of deaths caused by smoking-related fires, we applied the average of 590 deaths annually from 2012–2016 from home structure fires started by smoking materials (Ref. 591). We calculated the ratio of smoking-related fire deaths to cigarette-attributable deaths to be approximately 0.1 percent and applied that value to the projections of avoided cigarette-attributable deaths, yielding an estimate of approximately cumulative 2,400 deaths due to smoking-related fires avoided by 2060, rising to approximately cumulative 5,900 deaths avoided by the end of the century (table 10).

Cigarette smoking is responsible for approximately 1,000 deaths from perinatal conditions annually, including over 600 deaths from prenatal conditions and 400 deaths from SIDS (Ref. 1). Exposure to secondhand smoke can also cause adverse health effects in infants and children. Currently, approximately half of all U.S. children and adolescents ages 3–18 years are exposed to cigarette smoke regularly at home or other locations that still permit smoking (Ref. 1). Exposure to cigarette smoke among children and adolescents can trigger asthma attacks and lead to more frequent respiratory infections compared to those not exposed to smoke (Ref. 1). Prenatal tobacco exposure and postnatal secondhand smoke exposure increase the risks of fetal deaths, fetal growth restriction/low birth weight, respiratory conditions, and SIDS (Ref. 15, Ref. 1). In addition, thirdhand smoke—the chemical residue from combusted tobacco smoke that can become embedded in the environment (*e.g.,* carpet, dust)—results in exposure to harmful constituents, such as tobacco specific nitrosamines (Ref. 138). Exposure to thirdhand smoke is especially concerning for young children, given their size and behaviors, like crawling on the ground and frequently putting their hands in their mouths.

FDA estimated the impacts of a potential nicotine product standard on perinatal mortality by first calculating the ratio of perinatal deaths (1,013 deaths; (Ref. 1)) to primary smoking-attributable deaths. That value, 0.2 percent, was then applied to the projections of cigarette-attributable deaths avoided yielding an estimate of approximately 4,100 cumulative perinatal deaths avoided by 2060, rising to approximately 10,200 cumulative deaths avoided by the end of the century (table 10). Since decreases in cigarette smoking prevalence under the proposed product standard would have immediate, rather than lagged, impacts on fetal health and the health of newborn children, we expect avoided smoking-attributable perinatal deaths to accrue more rapidly than the estimates presented here.

The smoke of other combusted tobacco products, particularly those that could be alternatives to cigarettes, such as cigars and pipes, contains many of the same toxic constituents as cigarette smoke, sometimes at even greater concentrations, and consequently carries significant health risks (Refs. 53 and 594). In fact, NNAL concentrations measured in people who smoke cigars daily were found to be as high as those measured in people who smoke cigarettes daily (Ref. 160). Cigar and/or pipe smoking cause cancers of the lung and upper aerodigestive tract, including the oral cavity, oropharynx, hypopharynx, larynx and esophagus (Ref. 158). Additional evidence suggests that cigar and/or pipe smoking is causally associated with cancers of the pancreas, stomach, and bladder (Ref. 165). People who smoke cigars also have increased risks for coronary heart disease and COPD compared with people who have never used tobacco (Ref. 166). In a 2014 publication, researchers estimated that regular cigar smoking was the cause of approximately 9,000 premature deaths in the year 2010, and more than 140,000 years of potential life lost in the United States in 2010 (Ref. 134). The total number of cigar-attributable deaths may be even larger for several reasons. For example, the analysis included only causes of death found to be statistically significantly higher in two cohorts that studied people who smoke cigars, although there may be additional causes of death that are attributable to cigar smoking. In addition, there may be increases in cigar smoking relative risks over time, due to greater variety of cigar products and differences in inhalation patterns (Ref. 134). Therefore, cessation and reduced initiation of combusted tobacco products other than cigarettes as a result of the proposed product standard could yield even greater public health impacts than those presented.

To estimate the impacts of a potential nicotine product standard on avoided deaths attributable to covered cigar products, we used estimates of premature deaths attributable to regular cigar smoking from a prior publication (Ref. 134). Given that the prior analysis included all cigar types in its estimate of 9,246 premature deaths for the year 2010 and that we did not include premium cigars in our current analysis, we estimated the fraction of deaths attributed to cigar products other than premium cigars. We estimate that

among people who ever smoked cigars fairly regularly and now smoke every day or some days in Wave 4 of the PATH Study, 80 percent reported smoking non-premium cigars and 20 percent reported smoking premium cigars, using a classification methodology described previously (Ref. 290) and subsequently updated (Ref. 595). On that basis, 7,397 (*i.e.,* 9,246 × 0.8) deaths annually are attributed to using non-premium cigar products. By considering a relatively stable trend in adult cigar use [35] and assuming that adult cigar use is the main driver of cigar-attributable deaths in the close future, we assumed that non-premium cigar-attributable mortality would remain constant at 7,397 cigar-attributable deaths per year through 2065 (or roughly the time at which people who use cigars aged 26 and older in 2021 would all have reached age 70 and older). However, as youth and young adult cigar smoking has declined in recent years, we adopt a different trend in baseline cigar-attributable mortality in the further future (after 2065). To obtain baseline non-premium cigar-attributable mortality from 2066 through the end of the modeling period (2100), we assume non-premium cigar-attributable mortality will eventually follow the observed relative decline in cigar use among young adults as they reach older ages. Specifically, we assume that non-premium cigar smoking-attributable deaths among youth who initiate cigar smoking will decrease on average by 37.5 percent [36] over 40 years (from 2078 to 2117).[37] That is, the cigar smoking-attributable deaths will decrease on average to 4,600 ($\approx 7{,}397 \times (1 - 0.375)$) deaths per year over the period from 2078 to 2117.

Assuming a linear decrease in cigar smoking-attributable mortality from 2065 to 2117, and an average of approximately 4,600 deaths per year over the period from 2078 to 2117, implies non-premium cigar smoking-attributable mortality will decline linearly from 7,397 in 2065 to approximately 4,390 deaths in 2100. We assume a linear decrease for simplicity and because trends for cigar use considered in this post-processing strategy come from a short interval (PATH Study data, Waves 1 to 5, and Waves 3 to 5). We then calculate the ratio of non-premium cigar to cigarette-attributable deaths for each year in the projection period and apply those values to the projections of avoided cigarette-attributable deaths to estimate non-premium cigar-attributable deaths under the nicotine policy scenario. Using this approach, by 2060, we estimate approximately 54,800 cumulative deaths due to non-premium cigar products would be avoided, rising to approximately 214,700 cumulative deaths avoided by 2100 (see table 10). Similar methods were used to calculate estimates accounting for the mortality effects of a product standard prohibiting characterizing flavors other than tobacco in cigars. These estimates reduced baseline non-premium cigar-attributable deaths in a phased-in manner reaching a constant reduction of 780 deaths averted per year after 30 years (Ref. 597). These estimates and results are presented in detail in sections VIII.E and VIII.F of this document.

To estimate the impacts of a nicotine product standard on avoided deaths attributable to pipe tobacco smoking, we used the estimate of 1,095 premature deaths per year provided by a prior analysis (Ref. 598). We calculated the ratio of pipe tobacco to cigarette-attributable deaths to be 0.3 percent and applied that value to the projections of avoided cigarette-attributable deaths, yielding an estimate of approximately 4,500 cumulative deaths due to pipe tobacco smoking avoided by 2060, rising to approximately 11,000 cumulative deaths avoided by the end of the century (see table 10).

Based on these collective findings and estimates, FDA anticipates that the proposed product standard will further improve public health due to the impacts of reduced cigarette smoking on smoking-related fires and perinatal conditions, in addition to the impacts of reduced use of other, non-cigarette combusted tobacco products covered by this proposed rule.

TABLE 10—PROJECTED NUMBER OF TOBACCO-ATTRIBUTABLE DEATHS AVOIDED FOR SMOKING RELATED FIRES, SMOKING RELATED PERINATAL CONDITIONS, NON-PREMIUM CIGAR AND PIPE TOBACCO USE AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027

Year	Scenario	Cumulative smoking-related fire deaths avoided	Cumulative perinatal deaths avoided	Cumulative non-premium cigar-attributable deaths avoided	Cumulative pipe tobacco-attributable deaths avoided
2040	Median (5th, 95th)	600 (100, 700)	1,000 (100, 1,200)	8,900 (1,000, 11,000)	1,100 (130, 1,300)
2060	Median (5th, 95th)	2,400 (600, 2,700)	4,100 (900, 4,600)	54,800 (13,200, 60,500)	4,500 (1,000, 5,000)
2080	Median (5th, 95th)	4,200 (1,300, 4,600)	7,300 (2,200, 7,900)	134,700 (46,000, 144,100)	7,900 (2,400, 8,600)
2100	Median (5th, 95th)	5,900 (2,300, 6,400)	10,200 (3,900, 10,900)	214,700 (91,600, 225,800)	11,000 (4,200, 11,800)

6. Public Health Benefits of the Proposed Standard Not Addressed in FDA's Population Health Model

While FDA's population health model's estimates of the potential impact from a nicotine product standard suggest a significant public health benefit to the United States resulting from substantial reductions in smoking prevalence, these analyses do not address other additional benefits. The overall public health benefits of this proposed product standard are likely to be even greater than those quantified, since our analysis does not account for the full range of impacts that smoking has on public health in the United States.

[35] Adult cigar smoking has historically remained stable. Data from the NHIS over 2000–2015 has shown that prevalence of current cigar smoking has remained generally stable at around 2.3 percent among U.S. adults aged 18 years and older (Ref. 596). Adult (ages 26 or older) cigar use also remained relatively stable in NSDUH data for 2011 and 2019 and did not significantly change (4.2 percent in 2011 to 4.0 percent in 2019 for cigars) (Ref. 286).

[36] According to data from the PATH Study, young adult (ages 18–24) past 30-day cigar use declined from 15.7 percent during Wave 1 (2013–2014) to 11 percent during Wave 5 (2018–2019), representing a 30 percent relative decline in prevalence. Additionally, data from the PATH Study Waves 3 (2015–2016) and 5 (2018–2019) indicate that cigar use among 18-year-olds declined from 7.2 percent to 3.9 percent, implying a steeper decline of approximately 45 percent in more recent years within this smaller age cohort. We use these two data points to estimate the decrease in cigar smoking among young people because both provide relevant information from a national survey that is specific to tobacco use and average them to produce an estimate of 37.5 percent (*i.e.,* (30 + 45)/2).

[37] For youth, we assume that initiation occurs by the age of 18, followed by a cigar smoking-attributable death 52 years later. We then assume cigar use initiation occurs during years 2025 to 2064 (40-year period), and cigar smoking-attributable deaths begin to occur a year after the period from 2077 (*i.e.,* 2025 + 52) through 2116 (*i.e.,* 2064 + 52); that is, over the period from 2078 to 2117.

First, although we estimated the impact of self-reported quality of life, this may not capture the full breadth and depth of smoking-attributable morbidity. Tobacco smoke exposure can cause immediate and long-term adverse health effects (Ref. 1). Cigarette smoking ''has been causally linked to diseases of nearly all organs of the body, to diminished health status, and to harm to the fetus'' (Ref. 1). Each year, an estimated 480,000 people in the United States die from smoking; the U.S. Surgeon General has reported that for every person that dies from smoking, about 30 individuals will suffer from at least one smoking-related disease (Ref. 1). One study estimated that individuals in the United States have had 14.0 million major smoking-attributable conditions, including more than 7.4 million cases of COPD, nearly 2.3 million heart attacks, 1.8 million cases of diabetes, nearly 1.2 million stroke events, more than 300,000 cases of lung cancer, and nearly 1 million cases of other smoking-attributable cancers (*i.e.,* bladder, cervix, colon/rectum, kidney, larynx, mouth, tongue, lip, throat, pharynx, stomach) (Ref. 564). Cigarette smoking, in addition to causing disease, can diminish overall health status leading to higher risks for surgical complications, including wound healing and respiratory complications, increased absenteeism from work, and greater use of healthcare services (Ref. 1). In terms of a monetary measure of the impact of cigarette smoking on the public health, in 2018, cigarette smoking cost the United States more than $600 billion, including more than $240 billion in healthcare spending (Ref. 10), nearly $185 billion in lost productivity from smoking-related illnesses and health conditions (Ref. 10), nearly $180 billion in lost productivity from smoking-related premature death (Refs. 1 and 10), and $7 billion in lost productivity from premature death from secondhand smoke exposure (Refs. 1 and 11). Increased smoking cessation, reduced cigarette consumption, and lower progression to regular use will reduce both mortality from smoking and the enormous burden of cigarette-attributable diseases in the United States.

Second, the estimated impacts to public health do not include the reductions in morbidity associated with reduced exposure to secondhand smoke among infants and children. A report of the U.S. Surgeon General (Ref. 1) found that approximately half of all children and adolescents ages 3–18 in the United States are exposed to cigarette smoke regularly at home or other locations that still permit smoking. Also, a recent study using NYTS data reported that, in 2019, 25.3 percent and 23.3 percent of students were exposed to home and vehicle secondhand smoke, respectively (Ref. 145). Exposure to cigarette smoke among children and adolescents can trigger asthma attacks and lead to more frequent respiratory infections compared to those not exposed to smoke (Ref. 1).

Third, a lower prevalence of cigarette smoking and reduced cigarette consumption will decrease the occurrence of fire-related injuries and damages caused by smoking materials, including cigarettes and other combusted tobacco products. From 2012 to 2016, an estimated average of 18,100 home structure fires in the United States annually were caused by smoking materials (Ref. 591). Reductions in smoking as a result of the proposed nicotine product standard are likely to lead to not only fewer fatalities (as described previously) but also reductions in the annual average of 1,130 injuries (Ref. 591).

Fourth, these projections did not include the potential health benefits associated with people who smoke cutting down on the number of cigarettes smoked as a result of the proposed nicotine product standard. Quitting cigarette smoking entirely clearly leads to the greatest reductions in disease risk, and duration of smoking has been shown to be a greater driver of disease risk than frequency of use (Ref. 28). Although some studies have not found evidence of lower disease risk after cutting down on cigarettes (Refs. 28, 266, 599 to 601), others have shown that substantial reductions in cigarette consumption can lead to some reductions in disease risk, especially for lung cancer, for those who would have otherwise continued to smoke (Ref. 602). Such studies have found decreased risk of lung cancer deaths (Ref. 603) and decreased risk of lung cancer among people who smoke who reduce cigarette consumption (Refs. 604 and 605). As described above, studies of VLNC cigarettes have shown that their use results in reductions in cigarettes smoked per day and exposure to toxic constituents among individuals who continue to smoke, which may reduce smoking-related disease risks. Consequently, additional public health benefits may be observed among those who continue to smoke cigarettes (but substantially fewer CPD) after a nicotine product standard is in place.

7. Potential Risks to the Population as a Whole of the Proposed Nicotine Product Standard Versus the Potential Benefits of the Proposed Product Standard

There are possible countervailing effects that could occur from the proposed product standard, if finalized, and potential factors that could limit its population health effect. Potential risks to the population, however, would generally only occur among individuals currently smoking cigarettes and other combusted tobacco products covered by the scope of this proposed rule, as FDA concludes there are little to no risks to those who do not use tobacco. These potential risks do not offset the anticipated benefits of the rule. The countervailing or limiting effects on people who currently use tobacco products could include compensatory smoking. As part of this rulemaking, FDA is required by the Tobacco Control Act to consider information submitted on such possible countervailing effects, including among populations that are disproportionately impacted by tobacco-related morbidity and mortality, such as adolescents who use tobacco and other populations.

With a lower level of nicotine in cigarettes, some people who use cigarettes and certain other combusted tobacco products could alter their smoking behavior in the form of compensatory smoking (*i.e.,* a change in normal smoking behavior that would increase exposure to cigarette smoke to compensate for reduced nicotine intake) when switching from usual brand or NNC cigarettes to VLNC cigarettes. This concern is echoed in qualitative research of people who currently use tobacco who report fears that a potential reduction in nicotine will cause them to engage in compensatory smoking (Refs. 264, 606 to 608). Compensatory smoking—or compensation—occurs when people who smoke seek to obtain the amount of nicotine needed to sustain their addiction by smoking more CPD, taking more and deeper puffs, or puffing with a faster draw rate. In both brief and extended exposure studies with VLNC cigarettes, compensation was measured using CPD, puff topography measures, and biomarkers of CO exposure, such as breath CO or COHb. Some transient compensatory smoking may occur following initial VLNC cigarette exposure. However, after continued use of VLNC cigarettes, people who smoke stop attempting to compensate for the reduced nicotine content, because they are unable to obtain adequate amounts of nicotine through these behaviors. The following

paragraphs discuss data demonstrating this outcome. See also section VII.B of this document discussing compensatory smoking with an immediate nicotine reduction approach versus a gradual reduction approach.

When exposure to VLNC cigarettes is brief (*e.g.,* the first few uses of VLNC cigarettes), transient compensatory smoking may occur. In brief exposure studies, changes in smoking topography (Refs. 393 to 395) and increases in CO (Refs. 393, 411, and 420) have been observed. For example, one study demonstrated the transient nature of compensatory smoking by showing increases in smoking topography and CO exposure during the first and second exposures to VLNC cigarettes, followed by the subsequent dissipation of these effects by the third and fourth exposures ((Ref. 394). Similarly, another study found that during a 5-day study where participants checked into a hotel and were restricted to only study-issued cigarettes, mouth-level nicotine exposure indicated that participants initially puffed VLNC cigarettes with greater intensity than NNC cigarettes, although this effect diminished across sessions (Ref. 609). However, results from the majority of studies show no compensatory smoking as a result of switching from usual brand or NNC cigarettes to VLNC cigarettes. Although not all studies examined every measure of compensatory smoking, most studies found no differences between control and VLNC cigarette conditions regarding CPD (Refs. 5, 32, 34, 40, 41, 265, 331, 374, 387, 386, 390, 396, and 415), CO exposure (Refs. 5, 32, 34, 40, 41, 265, 374, 381, 390, 391, 396, 402, 409, 410, 412 to 414, 467, and 610), smoking topography (Refs. 381, 391, 403, 411, 415, and 611), or all three measures (Refs. 329, 382 to 384).

Notably, compensatory smoking has been observed with some reduced nicotine content cigarettes containing intermediate levels of nicotine (*e.g.,* LNC cigarettes). For example, in a study of 165 people who use cigarettes assigned to switch to LNC cigarettes or VLNC cigarettes, researchers found small but statistically significant differences in CPD between the LNC and VLNC cigarette conditions, such that LNC CPD increased over the course of the 6-week intervention, while VLNC CPD decreased (Ref. 32). However, one of the largest studies involving reduced nicotine content cigarettes found no compensatory smoking behavior for cigarettes containing intermediate levels of nicotine (Ref. 29). Therefore, FDA concludes the nicotine level proposed for this standard would result in limited, if any, compensatory smoking that would likely dissipate over time. These data also support FDA's proposed immediate nicotine reduction approach (see section VII.C of this document).

Studies consistently report that consumers have misperceptions about the harms of nicotine and VLNC cigarettes (see sections IV.F and V.B of this document). A majority of U.S. consumers incorrectly believe that nicotine is the primary cause of cancer and health harms from cigarettes (Refs. 227 to 229, 232, 233, 235 to 245, 264, and 612 to 618), and a proportion of consumers with this misperception also believe that RNC cigarettes are less harmful than NNC cigarettes (Refs. 260 to 262). Additionally, while a majority of consumers understand that nicotine is addictive (Refs. 227 to 229, 232, 233, and 619), they do not necessarily believe that RNC cigarettes would be less addictive than NNC cigarettes (Refs. 260 and 261). There is also evidence from qualitative studies showing that some consumers do not understand the technical feasibility of reducing nicotine in cigarettes to minimally addictive or nonaddictive levels, which may impact consumers' ability to comprehend and accept messages communicating the policy (Refs. 270 and 229). FDA recognizes the importance of addressing consumer misperceptions of the harm and addictiveness of nicotine and VLNC cigarettes to minimize the unintended effects of a proposed product standard that limits the level of nicotine in cigarettes and certain other combusted tobacco products to make those products minimally addictive or nonaddictive. FDA will continue to conduct research on consumer perceptions of tobacco product harms, use communication tools (*e.g.,* consumer outreach, public education initiatives, engagement with interested parties), and consider further regulatory options within our authorities (*e.g.,* potential future labeling and advertising regulations) to ensure that all consumers are informed of the risks of using tobacco products that contain nicotine, including VLNC cigarettes.

Prior work also has explored whether the proposed product standard may have a differential impact on specific populations. Studies that have investigated the effects of VLNC cigarettes in adolescents who smoke cigarettes have done so under conditions of brief exposure (*e.g.,* single exposure to a VLNC cigarette in a laboratory setting). A study comparing VLNC and LNC cigarette smoking topography in adolescents who smoke cigarettes found that participants took statistically significantly more puffs from the VLNC cigarette compared to the LNC cigarette, and a non-significant trend emerged such that increases in breath CO were higher after smoking the VLNC cigarette compared to the LNC cigarette (Refs. 395 and 416). However, the LNC cigarette was rated as statistically significantly more pleasant than the VLNC cigarette (Ref. 395).

Similar to studies in adults who smoke cigarettes, studies in youth and young adults who smoke cigarettes have shown that positive subjective effects ratings (*e.g.,* ''satisfaction,'' ''pleasure,'' ''taste,'' ''strength,'' and ''stimulation'') are lower for VLNC cigarettes compared to LNC and NNC cigarettes. A laboratory study of people ages 15–19 who smoke found no effect of nicotine content on withdrawal, negative affect, or CO boost; however, NNC cigarettes were associated with greater reductions in craving and increased smoking satisfaction relative to VLNC cigarettes (Ref. 442). A similar laboratory study in young adults (age 18–25) found no influence of nicotine content on total nicotine withdrawal score, affect, or smoking topography; however, NNC cigarettes were associated with increased subjective effects ratings compared to LNC and VLNC cigarettes (Ref. 620). Notably, a secondary analysis of data from a clinical trial (Ref. 29) found that, at the end of the 6-week trial, there was no influence of age on subjective effects, TNE levels, or puff volume in participants who smoked LNC or VLNC cigarettes (Ref. 621).

Several studies have examined the effects of nicotine content in cigarettes on adolescents and young adults who smoke. One laboratory study that assessed the effects of nicotine content and menthol preference among adolescents (ages 15–19) who smoke found that VLNC cigarettes were rated statistically significantly lower than NNC cigarettes, and menthol preference did not affect subjective effects ratings of VLNC cigarettes (Ref. 408). One study also found that young adults (ages 18–24) who smoke exhibited lower demand for LNC and VLNC cigarettes than adults, but there were no other differences between the two age groups in smoking topography, breath CO, cigarette puffs, craving, withdrawal, or smoking urge measures (Ref. 622). Another study investigating how nicotine exposure contributes to relief of craving and negative affect among young adults (ages 18–25) who smoke found that smoking reduced craving and negative affect regardless of nicotine content, and smoking topography did not vary as a function of nicotine content (Ref. 611). Finally, a study of youth and young adults who smoke found that two-thirds of participants

believed that study cigarettes had lower health risks than usual brand cigarettes, that they were largely concerned with compensatory smoking following a nicotine reduction policy, and that half stated an intention to quit smoking after the policy is put in place while the other half would continue to smoke or switch to another tobacco product (Ref. 606).

One study assessed longer duration effects (*i.e.,* 3 weeks) of VLNC cigarettes in adolescent daily smokers (ages 15–19) not currently intending to quit. Participants assigned to smoke VLNC cigarettes smoked significantly fewer total CPD than those in the NNC cigarette group. VLNC cigarettes were associated with lower levels of craving reduction than NNC cigarettes; however, there were no differences nicotine dependence or TNE levels among VLNC and NNC cigarette groups at the end of the study (Ref. 623). A secondary analysis of this study showed that participants assigned to smoke VLNC cigarettes had significantly lower demand for study cigarettes than those assigned to smoke NNC cigarettes, suggesting that a nicotine reduction policy may reduce the reinforcing value of combusted cigarettes in adolescents (Ref. 624).

In summary, while existing data suggest that adolescents prefer LNC cigarettes over VLNC cigarettes, and that they may display compensatory smoking behaviors in response to VLNC cigarettes, these data are limited. As discussed in section VII.B of this document, compensation typically dissipates after repeated exposure. Thus, in the absence of extended exposure studies, it is difficult to draw conclusions regarding the effects of VLNC cigarette use on compensatory smoking in adolescents and young adults.

Individuals with symptoms of mental health disorders smoke cigarettes in disproportionately large numbers. People with symptoms of mental health disorders who smoke cigarettes have increased nicotine withdrawal symptoms (Refs. 625 and 626) and are more likely to smoke to ameliorate negative mood (Ref. 627). As a result, this population has increased risk of tobacco-related mortality (Ref. 130).

Researchers have investigated the effects of VLNC cigarettes in people who use cigarettes with symptoms of mental health disorders to determine whether VLNC cigarettes are associated with differential effects on craving, withdrawal, smoking topography, or use behavior among this group compared to the general population. In this group, as in the general population, NNC cigarettes were associated with greater reductions in craving and withdrawal symptoms compared to VLNC cigarettes. In this group, VLNC cigarettes were not associated with increased markers of compensatory smoking (*e.g.,* smoking topography, CO) compared to the general population. Researchers also assessed psychiatric symptomatology as a function of VLNC cigarette use and found that VLNC cigarettes were associated with improvements in mood symptoms, likely due to the anxiety-increasing properties of nicotine.

Several studies investigated the effects of LNC and VLNC cigarettes on mood following mood induction (*i.e.,* an experimental method for inducing a specific mood state) in people who use cigarettes with symptoms of mental health disorders (Refs. 434, 450, and 628). These studies found that, following positive mood induction, LNC cigarettes compared to VLNC cigarettes were associated with an enhancement of positive mood among people who smoke and are prone to depression, but not control participants (Refs. 450 and 628). In addition, LNC cigarettes, but not VLNC cigarettes, were associated with a worsening of negative mood in response to negative mood induction among people who smoke, regardless of baseline mental health status (Ref. 628). Similarly, following an anxiety-eliciting mood induction, participants with post-traumatic stress disorder self-reported greater relief of anxiety after smoking LNC cigarettes compared to VLNC cigarettes; however, LNC cigarettes increased physical autonomic symptoms of anxiety (*e.g.,* skin becomes a better conductor of electricity, heart rate) relative to VLNC cigarettes (Ref. 434).

A secondary analysis of an extended exposure study assessed the effects of cigarettes varying in nicotine content on changes in psychiatric symptomatology among those with and without elevated depression symptoms (Ref. 629). Among participants with elevated depression symptoms, those assigned to smoke LNC or VLNC cigarettes for 6 weeks had lower depressive symptoms at the end of the study compared to those assigned to smoke NNC cigarettes. Another study that assigned participants with serious mental illness to receive either NNC or VLNC cigarettes saw no change in participants' psychiatric symptoms at the end of 6 weeks (Ref. 440).

Several studies assessed the effects of VLNC cigarettes on smoking rates, nicotine craving, dependence, withdrawal, and subjective effects among those with symptoms of mental health disorders (Refs. 391, 409, 434, 467, 468, 629, and 630). While some studies found no statistically significant differences in craving or withdrawal as a function of nicotine content following brief smoking abstinence in those with symptoms of mental health disorders (Refs. 391, 434, and 467), others showed that use of usual brand cigarettes was associated with larger decreases in craving and withdrawal compared to VLNC cigarettes (Ref. 468). An extended exposure study found that, relative to NNC cigarettes, use of LNC and VLNC cigarettes reduced smoking rates, nicotine dependence, and cigarette craving, and these effects were not moderated by baseline depressive symptoms (Ref. 629). In addition, similar to the general population, people who smoke with poor mental health rate NNC cigarettes as more rewarding (*e.g.,* taste, satisfaction) and reinforcing compared to VLNC cigarettes (Refs. 391, 450, 467, and 628). Additionally, a 33-week study that randomized participants to either NNC cigarettes or a gradual nicotine reduction to VLNC levels found that the gradual reduction group exhibited significantly lower cotinine levels, CPD, and exhaled CO compared to the NNC cigarette group. Mental health effects and adverse events did not significantly differ between the two groups, and significantly more participants in the gradual nicotine reduction group were abstinent at the end of the treatment compared to the NNC cigarette group (Ref. 631).

A study that compared the effects of VLNC, LNC, and NNC cigarettes on smoking behavior in people with opioid use disorder who smoke cigarettes, women of childbearing age with a high school education or less who smoke cigarettes, or individuals with affective disorders who smoke cigarettes found no statistically significant differences in smoking topography or breath CO as a function of nicotine content (Ref. 391). Subsequent analyses of this study also found that cannabis use status, presence of chronic health conditions, and sex did not correlate with differences in smoking topography or the reinforcing effects of nicotine among people who smoke (Refs. 459 and 632). A larger 12-week RCT among these same three populations found statistically significantly lower CPD and nicotine dependence levels across study weeks among those assigned to received VLNC or LNC cigarettes compared to those assigned to receive NNC cigarettes (Ref. 633). A secondary analysis of this study found no statistically significant effects of nicotine dose or population on tests of cognitive performance, suggesting that cognitive performance was not

significantly impaired with prolonged exposure to VLNC cigarettes among vulnerable populations (Ref. 634). A study among participants with schizophrenia found that both people with schizophrenia who smoke and control participants smoked fewer puffs and had lower total puff volumes, shorter inter-puff intervals, longer puff durations, and marginally higher individual puff volumes when smoking VLNC cigarettes compared to usual brand cigarettes (Ref. 467). However, a subsequent analysis using data from this same study showed that these differences were not associated with increases in breath CO boost (Ref. 392).

A 33-week randomized clinical study evaluated the effects of gradually reducing the nicotine content in cigarettes to VLNC cigarette levels on ratings of dependence, biomarkers, and cessation in 245 adults of low socioeconomic status. CPD, plasma cotinine, CO, and NNAL levels were significantly lower for the gradual reduction group compared to the NNC cigarette group; however, there were no significant differences in dependence or withdrawal as a function of group. Those who received VLNC cigarettes were statistically significantly more likely to make a quit attempt during the study compared to those in the NNC cigarette group; however, there was no statistically significant difference in quit rates as a function of group among those who chose to make a quit attempt (Ref. 635). A secondary analysis of this study showed that outcomes did not differ as a function of menthol status, except that those participants who smoked menthol cigarettes had less of a cotinine reduction (Ref. 636).

Several studies used laboratory paradigms to assess the effects of alcohol on specific components of smoking behavior for nicotine versus non-nicotine factors in people who consume alcohol heavily. One study found that alcohol increased smoking urge and subjective ratings of smoking for both NNC and VLNC cigarettes (Ref. 637), while another study found that NNC cigarettes were associated with increases in subjective effects and a greater reduction in cigarette craving than VLNC cigarettes, and these effects were enhanced by ethanol self-administration (Ref. 448). In addition, in a sample of people who smoked who also regularly consumed alcohol, NNC cigarettes reduced craving and increased cognitive performance compared to VLNC cigarettes (Ref. 448). Furthermore, several secondary analyses of clinical studies found no evidence that alcohol or marijuana use moderates the effects of VLNC cigarettes, and VLNC cigarette use does not increase compensatory alcohol, marijuana, or other illicit drug use (Refs. 386, 632, and 638). However, one secondary analysis found that although 20-weeks of VLNC cigarette use reduced CPD compared to NNC cigarette use, co-users of marijuana and cigarettes showed increased marijuana use when assigned to VLNC cigarettes (Ref. 639).

In summary, research has shown that VLNC cigarettes reduce the number of cigarettes smoked per day among populations that use tobacco at disproportionately high levels, including those of low socioeconomic status, and those with mental or behavioral health conditions. Importantly, there has been little to no evidence that VLNC cigarettes increase risk of adverse effects (*e.g.,* exacerbations of psychiatric symptomatology, drug use) in these populations. The proposed nicotine product standard is not anticipated to be detrimental to these populations; rather, it is anticipated to benefit these groups, as well as the general population as a whole.

FDA recognizes that actors participating in illicit markets are unlikely to conform their products and sales to Federal, State, and local laws. As discussed elsewhere in this document, the available evidence suggests that the health impacts of counterfeit products should be minimal. As the National Research Council (NRC) and the Institute of Medicine (IOM) (NRC/IOM) Report notes, ''Research on counterfeit cigarettes to date has shown some differences in levels of tar and selected toxicants in comparison with conventional cigarettes . . . but these elevated levels have not been shown to affect overall toxicity and, based on current evidence, are unlikely to significantly increase the health risk of an already dangerous product'' (Ref. 560). Even in studies (Ref. 640) that suggest that counterfeit cigarettes can contain higher levels of harmful substances, the studies cannot make conclusions about the individual or population-wide health risks from such substances, in part because of the variations between them, inconsistent distribution of the products among the population, and inconsistent use among consumers. FDA will continue to monitor the best available science to determine if this changes in the future.

Based on the available evidence, FDA finds that, while there may be potential risks that could diminish the expected population health benefits of the proposed standard, such effects would be significantly outweighed by the potential benefits of the proposed nicotine product standard. FDA requests additional information concerning the potential risks discussed in this section, as well as any other negative effects that could result from this rule, and how they could be minimized.

E. Approach Concerning Adjustments to Inputs to the Model Accounting for Other Tobacco Product Standards

In 2022, FDA issued proposed tobacco product standards to prohibit menthol as a characterizing flavor in cigarettes and to prohibit all characterizing flavors (other than tobacco) in cigars (87 FR 26454, May 4, 2022). If finalized, these rules are anticipated to reduce overall youth initiation and increase cessation among individuals who smoke cigarettes and cigars. In this adjusted model, we utilized estimates of the likely population health impact of these rules, quantified in peer-reviewed publications and discussed in the rules, to adjust the baseline inputs for initiation of combusted and noncombusted products, as well as cessation of combusted products and likelihood of switching to incorporate the impact of the final rules in this proposed nicotine product standard.

We quantified the potential impact of a menthol cigarette product standard on the U.S. population (87 FR 26454), assuming that the implementation of a rule prohibiting menthol affects baseline model input parameters associated with smoking initiation, smoking cessation, noncombusted initiation, and switching from cigarettes to noncombusted products. To avoid confusion with the main analysis baseline scenario, we called this new scenario a ''menthol product standard baseline scenario.'' First, we assumed that a menthol product standard is implemented in 2025, 2 years before the implementation of a potential nicotine product standard in 2027. Changes in tobacco use behaviors due to the implementation of a menthol product standard (primarily for people who would initiate future menthol cigarette use and people who currently use menthol cigarettes) were derived from an expert elicitation that was developed to assess the impact of a menthol product standard on smoking initiation and cessation, and on noncombusted use (Ref. 562). Specifically, 11 experts were asked to estimate anticipated behaviors under a menthol product standard, including transitioning to illicit menthol combusted products, switching to non-menthol combusted products, switching to ENDS products or HTPs, or quitting use of all tobacco products. We used the results of the expert elicitation (finalized in September 2020) to

compute factors that can be used to scale smoking initiation and cessation rates, as well as switching and noncombusted initiation, accounting for a potential reduction/increase in rates. People who currently smoke non-menthol cigarettes were assumed to be unaffected by a menthol product standard. We used the average impact scenario from Levy et al. 2023 (Ref. 562) to be consistent with the approach taken in the proposed menthol product standard rule. Details regarding the calculation of scaling factors, considering the expert elicitation data, can be found in Appendix K of FDA's modeling document (Ref. 42).

In the menthol product standard baseline scenario, baseline smoking initiation and noncombusted initiation rates were adjusted starting in 2025 (*i.e.,* year of a potential menthol prohibition implementation) until the end of the simulation period. Also, baseline smoking cessation and complete switching (from cigarettes to noncombusted products) were adjusted only at the first year of such a potential menthol product standard implementation. After the first year, when a sudden increase in smoking cessation and complete switching was incorporated, the remaining people who smoke initiated use of non-menthol or illicit menthol cigarettes, subject to the cessation and complete switching rates for people who smoke non-menthol cigarettes (Ref. 641). We conducted the analysis considering a mean decrease in cigarette smoking initiation (based on estimates from an expert elicitation), a mean increase in noncombusted product initiation, and a mean increase in smoking cessation and switching, as presented in Levy et al. 2023 (Ref. 562). It is important to note that the menthol-adjusted population health model does not directly estimate the public health impacts of a prohibition on menthol as characterizing flavor in cigarettes. In other words, the difference between the unadjusted baseline scenario and menthol-adjusted baseline scenario of the model should not be expected to approximate the impact of a potential menthol product standard. FDA's determination of the estimated public health impact of the menthol product standard is discussed in detail in the preamble to the proposed menthol product standard. In the nicotine population health model, FDA utilizes results from an expert elicitation (Ref. 562) developed to estimate changes in tobacco use behaviors resulting from a menthol product standard (such as changes in smoking initiation or cessation) to adjust for the effect of a menthol rule over time. One important assumption of the FDA model is that the nicotine product standard would be implemented in 2027, whereas a menthol rule would be implemented in 2025. This is important to keep in mind as public health benefits attributable to a menthol rule (such as mortality and morbidity health impacts) will be accruing for 2 years before implementation of the nicotine product standard (and, therefore, not captured in this model).

A more comprehensive analysis of the public heath impact of the menthol cigarette product standard can therefore be found in the proposed menthol product standard. There are also other important differences between the menthol-adjusted FDA model and the Levy et al. modeling approach that can impact comparability, such as input model parameters, modeling frameworks, assumptions, and source data. For these reasons, it is not appropriate to expect that the difference between public health impact estimates of the nicotine product standard with and without the menthol adjustment would directly approximate the potential public health benefits of the menthol product standard as presented in the proposed menthol product standard.

In 2022, FDA also issued a proposed product standard to prohibit characterizing flavors (other than tobacco) in cigars (87 FR 26396, May 4, 2022). It is estimated that such a standard would prevent 780 deaths due to cigar smoking in the United States each year (Ref. 134). A post-processing analysis of cumulative non-premium cigar-attributable deaths avoided was conducted to account for the effects of such a product standard, considering the adjustments due to the menthol cigarette product standard. For this analysis, we assumed both rules—the menthol cigarette and flavored cigar product standards—to be implemented in 2025. Specifically, we assumed that the avoided cigar-attributable deaths expected to result from the flavored cigar rule begin to occur 2 years after the rule's effective date (2027) and would increase in a phased-in manner over a 30-year period. We then assumed a full annual mortality benefit of 780 avoided deaths would continue after 30 years (from 2026 to 2055), with a constant benefit of 780 deaths avoided until year 2064. We also assumed avoided cigar-attributable deaths will increase from 780 in 2064 to 1,120 in 2100.

Details regarding the calculation of avoided cigar-attributable deaths because of the flavored cigar rule can be found in Appendix L of FDA's modeling document (Ref. 42). The estimated deaths averted by a flavored cigar product standard were subtracted from baseline non-premium cigar deaths in the United States each year to produce yearly estimates for non-premium cigar deaths with a flavored cigar standard. We used these estimates to calculate a ratio of non-premium cigar to cigarette-attributable deaths for each year in the projection period and applied those values to the projections of avoided cigarette-attributable deaths to estimate non-premium cigar-attributable deaths under the nicotine product standard scenario.

F. Benefits and Risks to the Population as a Whole Accounting for Other Tobacco Product Standards

Table 11 presents the impact results of the nicotine product standard using baseline assumptions adjusted for the effect of a menthol cigarette product standard for years 2040, 2060, 2080, and 2100. In general, changes to baseline inputs of initiation and cessation of combusted products as well as switching to noncombusted products as a result of implementation of a menthol cigarette product standard slightly reduced projected smoking prevalence and avoided mortality and morbidity, compared to the main analysis results. Specifically, we estimate that by 2060, the proposed nicotine product standard would avert approximately 1.6 million deaths due to tobacco, rising to approximately 3.4 million by 2100. These estimates are approximately 11 percent and 21 percent less than the corresponding estimates that do not account for the potential impact of a menthol product standard. The reduction in premature deaths as a result of the nicotine product standard, when accounting for a menthol product standard, would result in 17.9 million life years gained by 2060, raising to 60.6 million life years gained by 2100. These estimates represent a 9 percent and 21 percent reduction compared with the corresponding estimates under the main analysis.

TABLE 11—IMPACT OF PROPOSED NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027 ON PROJECTED SMOKING PREVALENCE AND AVOIDED MORTALITY AND MORBIDITY FROM THE MAIN ANALYSIS (UNADJUSTED BASELINE SCENARIO) AND WITH ADJUSTMENT FOR A MENTHOL CIGARETTE PRODUCT STANDARD IMPLEMENTED IN 2025

[Median (5th, 95th percentiles) estimates]

Year/period	Estimates from main analysis	Estimates with adjustment for a menthol cigarette standard
Cigarette Smoking Prevalence (%)		
2040	0.2 (0.07, 4.0)	0.1 (0.06, 2.8)
2060	0.2 (0.07, 2.2)	0.1 (0.05, 1.4)
2080	0.2 (0.06, 2.0)	0.1 (0.05, 1.3)
2100	0.2 (0.06, 1.9)	0.1 (0.05, 1.2)
Cumulative Tobacco-Attributable Deaths Avoided (Millions)		
2040	0.4 (0.1, 0.5)	0.4 (0.1, 0.5)
2060	1.8 (0.4, 2.0)	1.6 (0.4, 1.7)
2080	3.1 (1.0, 3.4)	2.6 (0.7, 2.8)
2100	4.3 (1.6, 4.6)	3.4 (1.1, 3.6)
Cumulative Life Years Gained (Millions)		
2040	2.0 (0.2, 2.7)	2.0 (0.2, 2.6)
2060	19.6 (3.6, 22.7)	17.9 (3.4, 20.4)
2080	47.4 (12.5, 52.5)	40.6 (10.3, 44.5)
2100	76.4 (26.5, 82.5)	60.6 (19.2, 65.3)
Cumulative QALYs Gained from Reduced Smoking Morbidity (Millions)		
2040	9.6 (2.7, 10.0)	7.8 (2.1, 8.1)
2060	24.0 (10.1, 24.7)	17.5 (7.0, 17.9)
2080	38.2 (18.5, 39.2)	26.1 (11.9, 26.6)
2100	53.1 (27.5, 54.4)	34.9 (17.0, 35.7)

Table 12 presents the impact results of the nicotine product standard implemented in 2027, using baseline assumptions adjusted for the effect of a flavored cigar product standard implemented in 2024. We estimate that by 2060, in the United States, approximately 45,600 deaths due to non-premium cigar use will be averted, rising to approximately 164,000 deaths avoided by 2100 (table 12). In general, these estimates are approximately 17 and 30 percent less than the corresponding estimates without the potential impact of a product standard for flavored cigars.

TABLE 12—PROJECTED NUMBER OF TOBACCO-ATTRIBUTABLE DEATHS FROM NON-PREMIUM CIGAR USE AVOIDED FOR AS A RESULT OF A NICOTINE PRODUCT STANDARD IMPLEMENTED IN 2027 FROM THE MAIN ANALYSIS AND WITH ADJUSTMENT FOR FLAVORED CIGAR AND MENTHOL CIGARETTE PRODUCT STANDARDS IMPLEMENTED IN 2025

Year	Percentiles	Cumulative non-premium cigar-attributable deaths avoided from main analysis	Cumulative non-premium cigar-attributable deaths avoided with flavored cigar and menthol cigarette standards
2040	Median (5th, 95th)	8,900 (1,000, 11,000)	8,000 (1,000, 9,500)
2060	Median (5th, 95th)	54,800 (13,200, 60,500)	45,600 (11,100, 49,700)
2080	Median (5th, 95th)	134,7000 (46,000, 144,100)	107,700 (35,000, 114,500)
2100	Median (5th, 95th)	214,700 (91,600, 225,800)	164,000 (65,000, 172,100)

G. Conclusion

FDA has considered scientific evidence related to the likely impact of the proposed rule establishing a maximum nicotine level in cigarettes and certain other combusted tobacco products on people who currently do not use these products, people who currently use these products, and the U.S. population as a whole. The impact of the proposed standard was considered alone, as well as adjusted for the inclusion of other tobacco product standards: prohibition of menthol as a characterizing flavor in cigarettes and prohibition of all characterizing flavors (other than tobacco) in cigars. Based on these considerations, we find that the proposed tobacco product standard is appropriate for the protection of the public health because it would increase the likelihood that many people who currently smoke cigarettes and/or certain other combusted tobacco products would stop smoking altogether, yielding significant health benefits from smoking cessation. Additionally, we find that the proposed standard is appropriate for the protection of the public health because it would decrease the likelihood that people who do not smoke cigarettes and/or use certain other combusted

tobacco products—particularly youth and young adults—who experiment with combusted tobacco products will become addicted to these products, thereby decreasing progression to regular use, resulting in reduced tobacco-related morbidity and mortality associated with combusted tobacco product use. The proposed standard would also yield benefits in terms of reduced mortality as a result of reduced secondhand smoke exposure, smoking-related fires, smoking-related perinatal conditions, and use of alternative tobacco products.

Tobacco use is the leading preventable cause of disease and death in the United States. Cigarettes are responsible for 480,000 premature deaths every year from many diseases, put a substantial burden on the U.S. healthcare system, and cause massive economic losses to society (Ref. 1 at p. 659–666). Even modest reductions in the percentage of people initiating and modest increases in the percentage of people quitting smoking would lead to substantial reductions in the annual smoking-attributable deaths and fewer cases of disease attributed to combustible tobacco products in the United States.

In the United States, approximately 362,000 youth (ages 12–17) smoked their first cigarette in 2021 (Ref. 552). Additionally, nearly 90 percent of adults who currently smoke cigarettes daily in the United States report having smoked their first cigarette by the age of 18 (Ref. 1). Nicotine is a highly addictive substance, and multiple studies have shown that symptoms of nicotine dependence can arise early after youth start smoking cigarettes, even among those who smoke cigarettes infrequently (Refs. 24, 65, and 93).

Reducing the addictive potential of combusted cigarettes and certain other tobacco products via establishing a maximum level of nicotine in these products would help to decrease the likelihood that people who do not smoke cigarettes and/or use certain other combusted tobacco products—particularly youth and young adults—who experiment with them will develop addiction to nicotine and progress to regular use, thereby greatly reducing the chances of suffering from tobacco-related disease and death. FDA anticipates that the proposed standard would produce substantial health benefits. Even small changes in initiation and cessation would result in a significant reduction in the burden of death and disease in the United States caused by smoking, including reductions in smoking-related morbidity and mortality, diminished exposure to secondhand smoke among people who do not smoke cigarettes, decreased potential years of life lost, decreased disability, and improved quality of life for current and future generations to come.

While preventing initiation to regular cigarette smoking and combusted tobacco product use by even modest amounts carries the greatest potential from this proposed standard to improve population health in the long term, FDA anticipates that the proposed standard would produce substantial short- and long-term health benefits resulting from decreased consumption and increased cessation among people who currently smoke cigarettes or other combusted tobacco products and wish to decrease use or quit. In the United States, there are currently approximately 39 million people ages 12 and older who smoke combusted tobacco products (Refs. 275 and 281). As previously described, the health benefits of smoking cessation are substantial. FDA's population health model estimates that approximately 1.8 million deaths in the United States due to tobacco would be avoided by the year 2060, rising to 4.3 million by the end of the century. The reduction in premature deaths attributable to the product standard would result in 19.6 million life years gained by 2060 and 76.4 million life years gained by 2100. Beyond averted deaths, societal benefits would include reduced smoking-related morbidity and health disparities, diminished exposure to secondhand smoke among people who do not smoke cigarettes, decreased potential years of life lost, decreased disability, and improved quality of life among people who formerly smoked cigarettes.

FDA's finding that the proposed product standard would be appropriate for the protection of the public health is reasonable and well-supported by scientific evidence. Cigarettes are the most toxic consumer product when used as intended, and nicotine is the primary constituent in cigarettes and other tobacco products that causes and maintains addiction. Given the existing scientific evidence described in sections VIII.B and VIII.C of this document, FDA finds that the proposed product standard is appropriate for the protection of the public health because it would increase the likelihood that many people who currently smoke cigarettes and/or certain other combusted tobacco products who wish to stop smoking altogether, would be able to do so, yielding significant health benefits from smoking cessation. Additionally, we find that the proposed standard is appropriate for the protection of the public health because it would decrease the likelihood that people who do not smoke cigarettes and/or certain other combusted tobacco products—particularly youth and young adults—who experiment with them and initiate use, develop an addiction to nicotine, and progress to regular use as result of that addiction, thereby greatly reducing the chances of suffering from tobacco-related disease or death. Across the population, these changes in cigarette smoking behavior and combusted tobacco product use would lead to lower disease and death in the United States in both the short-term and in the future, due to diminished exposure to tobacco smoke among both people who smoke cigarettes and people who do not smoke cigarettes.

In addition to the determination that the proposed product is appropriate for the public health, FDA anticipates the proposed product standard also will improve health outcomes among populations that are disproportionately impacted by tobacco use and tobacco-related morbidity and mortality, such as adolescents as well as those with mental health and substance use disorders. As previously described, adolescence is a period of significant vulnerability regarding the onset and progression of tobacco use. Additionally, cigarette smoking is disproportionately prevalent among persons with symptoms of mental health disorders and substance use disorders, resulting in increased risk of tobacco-related morbidity and mortality in these groups. Accordingly, the proposed product standard is anticipated to promote better public health outcomes across these population groups.

IX. Additional Considerations and Requests for Comment

A. Section 907 of the FD&C Act

FDA is required by section 907 of the FD&C Act to consider the following information submitted in connection with a proposed product standard:

- For a proposed product standard to require the reduction or elimination of an additive, constituent (including smoke constituent), or other component of a tobacco product because FDA has found that the additive, constituent (including a smoke constituent), or other component is or may be harmful, scientific evidence submitted by any party objecting to the proposed standard demonstrating that the proposed standard will not reduce or eliminate the risk of illness or injury (section 907(a)(3)(B)(ii) of the FD&C Act).
- Information submitted regarding the technical achievability of compliance with the standard, including with regard

to any differences related to the technical achievability of compliance with such standard for products in the same class containing nicotine not made or derived from tobacco and products containing nicotine made or derived from tobacco (section 907(b)(1) of the FD&C Act).

- All other information submitted, including information concerning the countervailing effects of the tobacco product standard on the health of adolescent tobacco users, adult tobacco users, or nontobacco users, such as the creation of a significant demand for contraband or other tobacco products that do not meet the requirements of chapter IX of the FD&C Act and the significance of such demand (section 907(b)(2) of the FD&C Act).

As required by section 907(c)(2) of the FD&C Act, FDA invites interested persons to submit a draft or proposed tobacco product standard for the Agency's consideration (section 907(c)(2)(B)) and comments on and information regarding structuring the standard so as not to advantage foreign-grown tobacco over domestically grown tobacco (section 907(c)(2)(C)) of the FD&C Act. In addition, FDA invites the Secretary of Agriculture to provide any information or analysis that the Secretary of Agriculture believes is relevant to the proposed tobacco product standard (section 907(c)(2)(D) of the FD&C Act).

With this proposed rule, FDA is requesting all relevant documents and information described in this section. Such documents and information may be submitted in accordance with the ''Instructions'' included in the preliminary information section of this document.

Section 907(d)(5) of the FD&C Act allows FDA to refer a proposed regulation for the establishment of a tobacco product standard to the Tobacco Products Scientific Advisory Committee (TPSAC) at the Agency's own initiative or in response to a request that demonstrates good cause for a referral and is made before the expiration of the comment period. Sections 917(c)(2) and (c)(3) (21 U.S.C. 387q(c)(2) and (c)(3)) also provide that TPSAC shall provide advice, information, and recommendations on the effects of the alteration of the nicotine yields from tobacco products and regarding whether there is a threshold level below which nicotine yields do not produce dependence on the tobacco product involved, respectively.

B. Pathways to Market

To legally market a new tobacco product [38] in the United States, a tobacco product must receive authorization from FDA permitting the marketing of the new tobacco product under one of three premarket review pathways: (1) the applicant obtains an order under section 910(c)(1)(A)(i) of the FD&C Act (order after review of a premarket tobacco product application under section 910(b)); (2) the applicant obtains an order finding the new tobacco product to be substantially equivalent to a predicate tobacco product and in compliance with the requirements of the FD&C Act under section 910(a)(2)(A)(i) (order after review of a Substantial Equivalence (SE) Report submitted under section 905(j) of the FD&C Act (21 U.S.C. 387e(j))); or (3) the applicant makes a request under 21 CFR 1107.1 and obtains an exemption from the requirements related to SE (section 905(j)(3)(A)), and at least 90 days before commercially marketing the product, submits a report under section 905(j) including the information required in section 905(j)(1)(A)(ii) and (B) of the FD&C Act.

Applicants may be able to use the SE pathway for products seeking to comply with this proposed product standard (if finalized) by making modifications to their products in a manner that FDA finds does not cause the new tobacco product to raise different questions of public health. Applicants may be able to submit a streamlined SE Report containing information sufficient to demonstrate that the changes to the subject of that SE Report do not cause the new tobacco product to raise different questions of public health and to certify that no other changes were made to the new tobacco product as compared with the predicate product and that all other characteristics are identical (see relevant provisions of the SE final rule codified at 21 CFR 1107.18(l)(2)). FDA has received numerous successful applications where the manufacturer described all modification(s) between the new and predicate tobacco product and provided a certification statement that all other characteristics are identical. For example, for products modified to comply with this product standard, the applicant could demonstrate how the modification was made to the tobacco filler, provide test data to show that the modification reduced the nicotine content to meet the standard and did not cause the new product to raise any different questions of public health, and provide a certification that no other modifications were made to the new tobacco product other than those made to reduce the level of nicotine.

An applicant may also be able to use the SE Exemption pathway under section 905(j)(3)(A) of the FD&C Act to the extent the applicant is modifying a legally marketed tobacco product by adding or deleting a tobacco additive, or increasing or decreasing the quantity of an existing tobacco additive if such modification would be a minor modification. While the SE Exemption pathway may be a viable option in limited circumstances, FDA notes that the statutory definition of ''additive'' excludes tobacco or a pesticide chemical residue in or on raw tobacco or a pesticide chemical (section 900(1) of the FD&C Act). Therefore, to the extent modifications to a tobacco product involve changes to the tobacco (*e.g.,* changes to the nicotine content of the tobacco used in a tobacco product), such changes would render section 905(j)(3) of the FD&C Act inapplicable.

If a currently legally marketed tobacco product is already in compliance with this proposed product standard, a premarket authorization application would not be needed.

FDA requests comments regarding changes manufacturers may make to their tobacco products to comply with this proposed product standard and what information and evidence they might provide to satisfy the premarket review requirements of the Tobacco Control Act.

C. Considerations and Request for Comments on Scope of Products

As indicated throughout this document, FDA has determined that the proposed standard, which would apply to cigarettes and certain other combusted finished tobacco products, is appropriate for the protection of the public health. It would cover the products that are responsible for the greatest amount of tobacco-related morbidity and mortality. The proposed scope of this rule—applying to cigarettes (other than noncombusted cigarettes, such as HTPs that meet the definition of a cigarette), cigarette tobacco, RYO tobacco, cigars (other than premium cigars), and pipe tobacco—is appropriate to protect the public health and is justified by existing evidence. We request comments, data, and research regarding the proposed scope of this rule.

[38] Products that were commercially marketed in the United States as of February 15, 2007 (referred to as ''pre-existing tobacco products,'' previously referred to as ''grandfathered products''), are not considered new tobacco products and do not require prior authorization to be legally marketed (section 910(a) of the FD&C Act).

FDA is not proposing to include noncombusted cigarettes, such as HTPs that meet the definition of a cigarette in section 900(3) of the FD&C Act (proposed § 1160.3 includes a definition of cigarette), within the scope of this proposed product standard. While noncombusted cigarettes (such as HTPs) that meet the definition of cigarette in the FD&C Act must adhere to existing restrictions for cigarettes under FDA regulations, some of these products may deliver fewer or lower levels of some toxicants than combusted cigarettes (Ref. 642). FDA recognizes that tobacco products exist on a continuum of risk, with combusted cigarettes being the deadliest, and that certain specific products meeting the definition of a cigarette (*e.g.,* some that are not combusted) may pose less risk to individuals who use these products or to population health than other products meeting the definition of a cigarette.

In general, as discussed in this document, nicotine is the primary addictive constituent in tobacco products, and it is the nicotine in such products that both creates and sustains addiction, playing a significant role in creating and perpetuating tobacco-related negative health consequences. While these effects raise concerns in the context of any tobacco product—none of which is without risk—FDA recognizes that certain products that meet the definition of cigarette in the FD&C Act may present different considerations with respect to this proposed product standard. Accordingly, FDA requests comments, data, and research regarding the proposal to exclude noncombusted cigarettes (such as HTPs that are cigarettes) from the scope of this proposed rule, including any data that could justify otherwise.

FDA considered including waterpipe tobacco products within the scope of this proposed product standard; however, the Agency has determined that waterpipe tobacco involves profoundly different use behaviors than combusted cigarettes, which makes it an unlikely substitute for cigarettes. We therefore do not propose including waterpipe tobacco products within the scope of this proposed rule.

Data on frequency of use differentiates waterpipe tobacco from cigarettes. For instance, according to the 2024 NYTS, 0.7 percent of middle and high school students (or approximately 190,000 students) reported using waterpipe tobacco within the previous 30 days, compared with estimates for previous 30-day cigarette use (1.4 percent; 380,000 students) and cigar use (1.2 percent; 330000 students) (Ref. 3). However, waterpipe tobacco is significantly less likely to be smoked daily. In fact, given the relative infrequency of waterpipe use, it is often reported in terms of monthly versus less than monthly use, rather than daily versus non-daily. Data from Waves 1 (2013–2014) and 2 (2014–2015) of the PATH Study indicated that, among adults who used waterpipes in the past year, 77.1 percent reported less than monthly use at Wave 1; by Wave 2, 44.9 percent of these adults continued using waterpipe less than monthly, while 6.4 percent progressed to monthly or more frequent use (Ref. 643). For comparison, 59.1 percent of adults in the 2018 NHIS who smoke cigarettes report daily use (Ref. 644). Wave 3 (2015–2016) PATH Study data also indicate the infrequency of daily waterpipe use: 0.1 percent of youth, 0.3 percent of young adults, and 0 percent of adults 25 and older reported daily waterpipe use (Ref. 645). Comparatively, analysis from Wave 3 of the PATH study found that 0.6 percent of youth, 11.4 percent of young adults, and 15.3 percent of adults older than 25 reported daily cigarette smoking (Ref. 646).

FDA acknowledges that the health consequences of waterpipe usage are far from innocuous. People who use waterpipes are exposed to many of the same toxicants as people who smoke cigarettes, and due to the extended duration of each waterpipe session (*i.e.,* approximately 1 hour), waterpipe use may lead to higher toxicant exposure per session than toxicant exposure from one cigarette (Refs. 647 and 648). Thus, people who use waterpipes are likely subject to many of the same severe negative health effects as people who smoke cigarettes (Ref. 649).

However, FDA does not anticipate significant migration to waterpipe usage under the proposed product standard. Waterpipes as currently marketed are generally large and require time-consuming preparation, leading to an approximate waterpipe smoking session of 1 hour (Ref. 650). The limited accessibility and mobility of waterpipes as generally currently used contribute to their predominant intermittent usage patterns (Ref. 650). FDA assesses that these aspects of waterpipe design would similarly substantially limit their utility as a substitute for cigarettes and other combusted tobacco products that would be subject the proposed product standard, especially as compared to the portability and ease of use of many HTP, ENDS, and other noncombusted tobacco products that are currently legally marketed and not subject to the proposed product standard.

FDA requests information and data regarding the proposal to exclude waterpipe tobacco from the scope of this proposed rule.

FDA is not including noncombusted tobacco products, such as ENDS (which include e-cigarettes) and smokeless tobacco products, in the scope of this proposed product standard. FDA's approach in proposing this product standard for cigarettes and certain other combusted tobacco products seeks to protect public health by reducing combusted tobacco product use (and therefore reducing exposure to harmful toxicants created through combustion) while potentially less harmful, noncombusted tobacco products remain available for people who do not quit all tobacco-product use. As such, at this time, FDA is focusing this proposed rule on nicotine levels in cigarettes and certain other combusted products because combusted tobacco products are responsible for the majority of death and disease due to tobacco use. Importantly, this action would also help to prevent people who experiment with cigarettes and cigars (mainly youth) from moving beyond experimentation, developing an addiction to nicotine, and progressing to regular use of combusted tobacco products as a result of that addiction. We request comments, data, and research regarding the proposed scope of this rule.

D. Considerations and Request for Comments on the Potential for Illicit Trade

The implementation of a maximum nicotine level in cigarettes and certain other combusted tobacco products could result in some people seeking NNC combusted tobacco products through illicit trade markets. FDA is also considering whether illicit trade could occur as a result of a nicotine product standard and whether such activity could significantly undermine the public health benefits of the product standard.

Since the enactment of the Tobacco Control Act, FDA has been committed to studying and understanding the potential effects of a product standard on the illicit tobacco market. As part of FDA's consideration of possible regulations, the Agency asked the NRC and IOM of the National Academy of Sciences (now the National Academies) to assess the international illicit tobacco market, including variations by country; the effects of various policy mechanisms on the market; and the applicability of international experiences to the United States (Ref. 560). In 2015, the NRC/IOM issued its final report entitled ''Understanding the U.S. Illicit Tobacco

Market: Characteristics, Policy Context, and Lessons from International Experiences,'' finding 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 these products, demand for illicit cigarettes would be limited because some people who smoke would quit, and others would use modified products (*e.g.,* VLNC cigarettes) or seek legal alternatives (Ref. 560 2015 at p. 9). In addition, in March 2018, FDA issued a draft concept paper, entitled ''Illicit Trade in Tobacco Products after Implementation of a Food and Drug Administration Product Standard,'' as an initial step in assessing the possible health effects of a tobacco product standard in the form of demand for contraband or nonconforming tobacco products (83 FR 11754). Among other issues, the draft concept paper examined the factors that might support or hinder the establishment of a persistent illicit trade market related to a product standard (Ref. 44). Additionally, in the Nicotine ANPRM, FDA expressed interest in data regarding possible increases in illicit trade and its effect on the marketplace in the event that a nicotine tobacco product standard is finalized. Comments were submitted by members of the tobacco industry, public health organizations, academic researchers, and the public. Comments varied in their conclusions as to how significant illicit trade might be after implementation of an FDA product standard, but no information was submitted in response to the Nicotine ANPRM that caused FDA to revise its overall assessment about the difficulties in establishing sustained, significant illicit trade markets that are able to evade enforcement authorities.

Establishing and maintaining illicit markets in relevant tobacco products will be challenging, and to the extent that they emerge, it is unlikely they will be significant enough to outweigh the benefits of the product standard. Although some people who smoke may seek to purchase illicit products if available and accessible, the NRC/IOM report stated 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'' (Ref. 560 at p. 9). The current illicit cigarette trade in the United States is predominantly based on tax evasion and is facilitated by ease of access to tobacco products close to where the sales to consumers take place (*e.g.,* across State lines). Enforcement against such illicit trade is outside the scope of FDA's authority (as FDA does not enforce tax laws) and is complicated by the inability to distinguish tax-paid from tax-evading cigarette packs in most instances. However, due to the reduction of nicotine in combusted tobacco products nationwide, a lack of supply would likely limit illicit trade of NNC cigarettes and certain other combusted tobacco products once a product standard is in place. Illicit manufacturing of NNC cigarettes at a scale large enough to diminish the public health benefits of this proposed product standard would be difficult to disguise from Federal, State, and local enforcement authorities. Moreover, importation across international borders is substantially more difficult than across State borders, particularly for the volume necessary to sustain nicotine addiction in people who smoke. Additionally, while it would remain legal for domestic cigarette manufacturers to produce NNC cigarettes and certain other combusted tobacco products for export (as previously described in section III.C of this document), it is unclear the extent to which there would be diversion of legally manufactured products for export that are subsequently sold illegally domestically. As noted in multiple FDA reports to Congress regarding U.S. tobacco product exports, after the product standard prohibiting characterizing flavors (other than tobacco or menthol) in cigarettes was implemented, the U.S. Census Bureau surveyed the vast majority of domestic manufacturers and found no evidence that any continued to manufacture flavored cigarettes or their components or parts (Ref. 651). Importantly, and relevant to any continued domestic manufacture for export, section 920(d) of the FD&C Act (21 U.S.C. 387t(d)) requires that manufacturers and distributors notify the Attorney General and the Secretary of the Treasury of illicit trade activities (such as import, export, distribution, or diversion), increasing the overall vigilance on the matter. Finally, as the NRC/IOM Report explains, comprehensive interventions by several countries show it is possible to reduce the size of the illicit tobacco market through enforcement mechanisms and collaborations across jurisdictions (Ref. 560).

Research also has shown that the choice between VLNC and NNC cigarettes can be influenced by factors such as cost (see section VI.B of this document for further discussion). It is well-established that people who smoke are price-sensitive, and there is a direct correlation with the increased price of cigarettes and reductions in consumption (Ref. 652), showing for every ten percent increase in price, there is an overall reduction in consumption of 3–5 percent, and youth smoking decreases by 6–7 percent. This price sensitivity also contributes to the willingness of people who smoke cigarettes to shift consumption toward non-cigarette tobacco products in times of economic or product constraint (Refs. 345, 346, and 349). Additionally, there is an ''inconvenience cost'' to the purchase of illicit tobacco products that rises and falls depending upon the location of illegal sales, reliability of supply, fear of embarrassment and legal penalties, and more (Ref. 560 at p. 67). Although illicit NNC cigarettes and certain other combusted tobacco products will not be subject to taxes, participants in any illicit market will demand profits sufficient to cover both their costs as well as compensate for the risks of enforcement, limiting how low they can price the illicit tobacco products. As a result, when the cost or effort required to obtain illicit products increases, people who smoke may switch their preference from NNC combusted tobacco products to VLNC versions (Ref. 391), to other legal tobacco products, and/or renew their cessation efforts. Each of these alternatives reduces the number of potential buyers of illicit products, lowering the incentives to try, create, and sustain such markets.

Related to concerns about enforcement against individual consumers for possessing or using nonconforming tobacco products acquired through an illicit market, FDA's enforcement will only address manufacturers, distributors, wholesalers, importers, and retailers. This regulation does not include a prohibition on individual consumer possession or use of nonconforming product acquired through an illicit market, and FDA cannot and will not enforce against individual consumers for possession or use of NNC cigarettes or other combusted tobacco products covered by this proposed product standard. In addition, State and local law enforcement agencies do not enforce the FD&C Act. These entities do not and cannot take enforcement actions against any violation of chapter IX of the Act or this regulation on FDA's behalf. FDA recognizes concern about how State and local law enforcement agencies enforce their own laws in a manner that may impact equity and

community safety and seeks comments on how FDA can best make clear the respective roles of FDA and State and local law enforcement.

FDA is not proposing to ban any category of tobacco products with this proposed product standard, and authorized products that are not subject to the proposed product standard will remain legally available. Therefore, this proposed product standard is not expected to lead to a surge in illicit tobacco product use. In reaching this conclusion, FDA has considered several factors that are likely to affect the potential for illicit trade. For example, FDA anticipates that a nationwide standard that prohibits the manufacture (other than for export as previously described in section III.C of this document) and sale of cigarettes and certain other combusted tobacco products that exceed the maximum nicotine level set by this proposed product standard, coupled with FDA's authority to take enforcement actions and other steps regarding the sale and distribution of illicit tobacco products, would limit the manufacture and distribution of these products. FDA also expects that a nationwide product standard would eliminate the use of online retailers to purchase illicit tobacco products as well as any incentive to travel within the United States in search of jurisdictions without a nicotine product standard because no such jurisdictions would exist. FDA thus anticipates that the rule would result in much less illicit trade than observed in the case of a State or local requirement and that any such trade would be significantly outweighed by the benefits of the rule. Even if some amount of illicit trade develops (Refs. 42 and 653 discuss projected impacts of various rates of potential illicit trade), it would have to be of significantly greater magnitude than any previously seen illicit markets in order to outweigh the significant public health benefits of this proposed standard, and it would have to continue to exist at those levels despite the various enforcement agencies and tools involved.

FDA requests comments, including supporting data and research, regarding whether and to what extent this proposed rule would result in an increase in illicit trade in NNC cigarettes and certain other combusted tobacco products covered by the proposed nicotine product standard and how any such increase could impact public health. Data or other reliable information that do not rely on estimates of current, interstate tax-evading illicit trade would be particularly relevant. If an illicit market develops after this proposed product standard is finalized, FDA has the authority to take enforcement actions and other steps regarding the sale and distribution of illicit tobacco products, including those imported or purchased online. FDA conducts routine surveillance of sales, distribution, marketing, and advertising related to tobacco products and takes appropriate actions when violations occur. If this product standard is finalized as proposed and goes into effect, it would be illegal to import cigarettes and certain other combusted tobacco products that exceed 0.70 mg nicotine per gram of total tobacco, and such products would be subject to import examination and refusal of admission under the FD&C Act. Similarly, it would be illegal to sell or distribute cigarettes and certain other combusted tobacco products that do not comply with this product standard, including those sold online, and doing so may result in FDA initiating enforcement or regulatory actions. We note that the Prevent All Cigarette Trafficking Act of 2009 establishes restrictions that make cigarettes generally nonmailable through the U.S. Postal Service, subject to certain exceptions (18 U.S.C. 1716E). Outside of these exceptions, the U.S. Postal Service cannot accept or transmit any package that it knows, or has reasonable cause to believe, contains nonmailable cigarettes, smokeless tobacco, or ENDS.[39]

X. Description of Proposed Regulation

This proposed rule would establish a new part 1160 that would set a maximum level of nicotine in finished cigarettes and certain other finished combusted tobacco products. Part 1160 would describe the scope of the proposed regulation, applicable definitions, the establishment of a maximum nicotine level in products covered by this proposed rule, product testing and related requirements, and recordkeeping requirements.

A. General Provisions (Proposed Subpart A)

1. Scope (Proposed § 1160.1)

Proposed § 1160.1(a) would provide that this part sets out a tobacco product standard under the FD&C Act to limit nicotine yield by setting a maximum nicotine content level for certain finished tobacco products. We are proposing that this product standard would cover the following finished tobacco products: cigarettes (other than noncombusted cigarettes, such as HTPs that meet the definition of a cigarette), cigarette tobacco, RYO tobacco, cigars (other than premium cigars), and pipe tobacco (other than waterpipe tobacco). These products are defined in proposed § 1160.3. As stated throughout this preamble, this proposed product standard focuses on cigarettes and certain other combusted tobacco products given their addictiveness, availability as migration and dual use candidates with cigarettes, and the extent of tobacco-related death and disease associated with such products. As stated in section IX.C of this document, FDA requests comment regarding the scope of products covered by this proposed rule.

Proposed § 1160.1(b) would prohibit the distribution, sale, or offering for distribution or sale within the United States finished tobacco products within the scope of the rule that are not in compliance with the tobacco product standard. For example, FDA would consider such finished tobacco products to be noncompliant if they contain a nicotine level that exceeds the proposed maximum nicotine level set forth in proposed § 1160.10. Additionally, manufacturers and importers would not be allowed to enter or introduce into domestic commerce any finished tobacco product (*i.e.,* cigarettes, cigarette tobacco, RYO tobacco, cigars, and pipe tobacco) that does not comply with the requirements of the final rule, irrespective of the date of manufacture.

Proposed § 1160.1(c) would prohibit the manufacture within the United States of finished tobacco products within the scope of the rule that are not in compliance with the tobacco product standard unless such tobacco products are intended for export and are eligible for export under section 801(e)(1) of the FD&C Act (21 U.S.C. 381(e)(1)). A tobacco product intended for export shall not be deemed to be in violation of section 907 of the FD&C Act or this product standard if it meets the criteria enumerated in section 801(e)(1), including not being sold or offered for sale in domestic commerce.

2. Definitions (Proposed § 1160.3)

Proposed § 1160.3 provides the definitions for the terms used in the proposed product standard. Several of these definitions are included in the FD&C Act or have been used in other regulatory documents.

- *Accessory:* Consistent with 21 CFR 1140.3 and the Consolidated Appropriations Act, 2022 (Pub. L. 117–103), FDA proposes to define ''accessory'' as any product that is intended or reasonably expected to be

[39] These restrictions were updated to include similar prohibitions on the shipment of ENDS in 2021 (86 FR 58399, October 21, 2021).

used with or for the human consumption of a tobacco product; does not contain tobacco or nicotine from any source and is not made or derived from tobacco; and meets either of the following: (1) is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product; or (2) is intended or reasonably expected to affect or maintain the performance, composition, constituents, or characteristics of a tobacco product; but (i) solely controls moisture and/or temperature of a stored product; or (ii) solely provides an external heat source to initiate but not maintain combustion of a tobacco product. Accessories of cigarettes, cigarette tobacco, and RYO tobacco, as three of the originally-regulated products under the FD&C Act, are considered ''tobacco products'' and, therefore, would be subject to this proposed product standard (if finalized). However, accessories of other tobacco products (*e.g.,* cigars) are not regulated as ''tobacco products'' pursuant to FDA's final deeming rule (81 FR 28974 at 29015–29016, May 10, 2016) and, therefore, would not be subject to this proposed product standard. Examples of such accessories would be ashtrays, cigar clips, and pipe pouches, because they do not contain tobacco or nicotine from any source, are not made or derived from tobacco, and do not affect or alter the performance, composition, constituents, or characteristics of a tobacco product. However, if such a product was intended or reasonably expected to affect the performance of a tobacco product (*e.g.,* nicotine impregnated ash tray), it would no longer be considered an accessory and would be subject to the proposed product standard.

• *Batch:* FDA proposes to define ''batch'' as a specific identified amount of a finished tobacco product produced in a unit of time or quantity and that is intended to have the same specifications. FDA proposes to give tobacco product manufacturers flexibility to determine what unit of time or quantity is appropriate for their product, and how batches would be designated. For example, manufacturers likely would have, as part of existing manufacturing processes, defined a ''batch'' for cigarette production, which is almost continuous, differently than a batch for smokeless tobacco, which likely would be defined based on the amount processed in a vat through the fermentation process. Currently, there is no definition of ''batch'' for tobacco products. However, the proposed regulation Requirements for Tobacco Product Manufacturing Practice (TPMP) (see *https://www.federalregister.gov/documents/2023/03/10/2023-04591/requirements-for-tobacco-product-manufacturing-practice*) includes a proposed definition of ''batch,'' and this rulemaking's provision is modeled on the proposed TPMP provision. Pursuant to proposed § 1160.12, manufacturers would be required to conduct batch testing and maintain those records.

• *Cigar:* FDA proposes to define a ''cigar'' as a tobacco product that: (1) is not a cigarette and (2) is a roll of tobacco wrapped in leaf tobacco or any substance containing tobacco. This definition was used in the seven consent orders that the FTC entered into with the largest mass marketers of cigars (see, *e.g., In re Swisher International, Inc.,* Docket No. C–3964 (FTC August 18, 2000)) and also is codified at 21 CFR 1143.1. The cigar wrapper would be considered a ''component or part'' of a cigar (see definition herein) and, therefore, would be covered by this proposed product standard. As discussed elsewhere in this document and in proposed § 1160.1, premium cigars are excluded from the scope of this proposed rule.

• *Cigarette:* As defined in section 900(3) of the FD&C Act, the term ''cigarette'': (1) means a product that: (i) is a tobacco product; and (ii) meets the definition of the term ''cigarette'' in section 3(1) of the Federal Cigarette Labeling and Advertising Act (15 U.S.C. 1332(1)); and (2) includes tobacco, in any form, that is functional in the product, which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette or as RYO tobacco.

• *Cigarette tobacco:* As defined in section 900(4) of the FD&C Act, the term ''cigarette tobacco'' means any product that consists of loose tobacco that is intended for use by consumers in a cigarette. Unless otherwise stated, the requirements applicable to cigarettes under this chapter also apply to cigarette tobacco.

• *Commercial distribution:* Consistent with 21 CFR 1107.12, FDA proposes to define ''commercial distribution'' as any distribution of a finished tobacco product, whether domestic or imported, to consumers or to any person, but does not include interplant transfers of a tobacco product between establishments within the same parent, subsidiary, and/or affiliate company, nor does it include providing a tobacco product for product testing where such product is not made available for consumption or resale. ''Commercial distribution'' does not include the handing or transfer of a tobacco product from one consumer to another for personal consumption.

• *Component or part:* Consistent with 21 CFR 1140.3, FDA proposes to define ''component or part'' as any software or assembly of materials intended or reasonably expected: (1) to alter or affect the tobacco product's performance, composition, constituents, or characteristics or (2) to be used with or for the human consumption of a tobacco product. The term excludes anything that is an accessory of a tobacco product. Components or parts of cigarettes, cigarette tobacco, and RYO tobacco, as three of the originally regulated products under the FD&C Act, are considered ''tobacco products'' and, therefore, would be subject to this proposed product standard (if finalized). Examples of cigarette components or parts that would be subject to this proposed product standard include cigarette paper and filters. In addition, components or parts of other tobacco products (*e.g.,* cigars) are regulated as ''tobacco products'' pursuant to FDA's final deeming rule (81 FR 28974 at 29015–29016) and, therefore, would be subject to this proposed product standard (if finalized). Some examples of such components or parts include cigar blunt wraps, removable tips, mouthpieces, and filters. These examples generally are intended or reasonably expected to alter or affect the performance, composition, constituents, or characteristics of a tobacco product. If a liquid nicotine product or other tobacco product is intended or reasonably expected to alter the nicotine content of any tobacco product covered by this proposed rule, such liquid nicotine or other tobacco product would be considered a component or part of a finished tobacco product covered under the rule's scope and, therefore, would be in violation of the rule if the amount of nicotine in the finished tobacco product exceeds 0.70 mg of nicotine per gram of total tobacco. With respect to these definitions, FDA notes that ''component'' and ''part'' are separate and distinct terms within chapter IX of the FD&C Act. However, for purposes of this rule, FDA is using the terms ''component'' and ''part'' interchangeably and without emphasizing a distinction between the terms. FDA may clarify the distinctions between ''component'' and ''part'' in the future.

• *Finished tobacco product:* Consistent with 21 CFR 1107.12, FDA proposes to define a ''finished tobacco product'' to mean a tobacco product, including all components and parts, sealed in final packaging (*e.g.,* filters or

filter tubes sold to consumers separately or as part of kits) or in the final form in which it is intended to be sold to consumers (*e.g.,* tobacconists selling cigars individually from a box or pipe tobacco filler by weight). Examples of finished tobacco products include a pack of cigarettes or a bag of RYO or pipe tobacco.

- *Manufacturing code:* FDA proposes to define ''manufacturing code'' as any distinctive sequence or combination of letters, numbers, or symbols that begins with the manufacturing date, followed by the batch number, and concludes with ''-NS.'' This information would help determine the product's history (*e.g.,* batch testing records) and assist manufacturers and FDA in the event of a nonconforming tobacco product investigation and any corrective actions that stem from such investigation.
- *Manufacturing date:* FDA proposes to define ''manufacturing date'' as the month, day, and year in 2-digit numerical values in the format (MMDDYY) that a finished tobacco product is packaged for distribution. The manufacturing date is included in the manufacturing code, which can be used by the manufacturer and FDA to help determine the product's history (*e.g.,* batch testing history) in the event of a nonconforming tobacco product investigation. As stated in section X.C of this document, FDA requests comment regarding the manufacturing code requirements in this proposed rule.
- *Nicotine:* FDA proposes to define ''nicotine'' as the chemical substance named 3–1(1-methyl-2-pyrrolidinyl) pyridine or C[10]H[14]N[2], including any salt or complex of nicotine, derived from any source.
- *Nonconforming tobacco product:* FDA proposes to define ''nonconforming tobacco product'' as any tobacco product that does not meet the requirements of § 1160.10 (nicotine level specifications) or § 1160.30 (manufacturing code).
- *Package* or *packaging:* As defined in section 900(13) of the FD&C Act, the term ''package'' means a pack, box, carton, or container of any kind or, if no other container, any wrapping (including cellophane) in which a tobacco product is offered for sale, sold, or otherwise distributed to consumers.
- *Person:* As defined in section 201(e) of the FD&C Act (21 U.S.C. 321(e)), the term ''person'' includes an individual, partnership, corporation, or association.
- *Pipe tobacco:* FDA proposes to define the term ''pipe tobacco'' as any tobacco that, because of its appearance, type, packaging, or labeling, is suitable for use and likely to be offered to, or purchased by, consumers as tobacco to be smoked in a pipe. However, this definition specifically excludes tobacco labeled and sold exclusively for use in a waterpipe (*i.e.,* hookah tobacco). As discussed in section IX.C of this document, FDA is not proposing to include waterpipe tobacco within the scope of this product standard.
- *Rework:* FDA proposes to define ''rework'' as action taken on a nonconforming tobacco product to ensure that the product meets the specifications and other requirements of this part before it is released for commercial distribution.
- *Roll-your-own tobacco:* As modeled after section 900(15) of the FD&C Act, FDA proposes to define the term ''roll-your-own tobacco'' (or RYO) as any tobacco product which, because of its appearance, type, packaging, or labeling, is suitable for use and likely to be offered to, or purchased by, consumers as tobacco for making cigarettes or cigars. This product is frequently used interchangeably with cigarette tobacco and pipe tobacco (as defined in this section).
- *Specification:* We propose to define ''specification'' as any requirement with which a product, process, service, or other activity must conform. A tobacco product specification is a requirement established by the manufacturer, including a requirement established to ensure that the tobacco product meets any applicable product standard under section 907 of the FD&C Act.
- *Tobacco filler:* FDA proposes to define ''tobacco filler'' as cut, ground, powdered, or leaf tobacco or other nicotine-containing substances in a finished tobacco product. For portioned tobacco products, the material enclosing any tobacco or nicotine-containing substances (*e.g.,* cigarette paper) is not considered tobacco filler.
- *Tobacco product:* As defined in section 201(rr) of the FD&C Act, the term ''tobacco product'' means any product made or derived from tobacco, or containing nicotine from any source, that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). The term ''tobacco product'' does not mean an article that is: a drug under section 201(g)(1); a device under section 201(h); a combination product described in section 503(g) (21 U.S.C. 353(g)); or a food under section 201(f) of the FD&C Act if such article contains no nicotine, or no more than trace amounts of naturally occurring nicotine.
- *Tobacco product manufacturer:* As defined in section 900(20) of the FD&C Act, the term ''tobacco product manufacturer'' means any person, including a repacker or relabeler, who: (1) manufactures, fabricates, assembles, processes, or labels a tobacco product or (2) imports a finished tobacco product for sale or distribution in the United States.
- *Total tobacco:* FDA proposes to define the term ''total tobacco'' as the tobacco filler (defined in proposed § 1160.3) and any other tobacco or tobacco-derived material used as part of a tobacco product. For cigars (*i.e.,* those cigars that are covered by this proposed product standard, as defined in proposed § 1160.3), the tobacco included in the wrapper and binder would be part of the ''total tobacco.'' The nicotine content in the total tobacco of the finished tobacco product must not exceed the proposed maximum nicotine level.
- *United States:* As defined in section 900(22) of the FD&C Act, the term ''United States'' means the 50 States of the United States of America and the District of Columbia, the Commonwealth of Puerto Rico, Guam, the Virgin Islands, American Samoa, Wake Island, Midway Islands, Kingman Reef, Johnston Atoll, the Northern Mariana Islands, and any other trust territory or possession of the United States.

B. Product Requirements (Proposed Subpart B)

1. Maximum Nicotine Level (Proposed § 1160.10)

FDA is proposing to regulate nicotine yield by requiring that a finished tobacco product contain no more than 0.70 mg of nicotine per gram of total tobacco. As stated in proposed § 1160.3, the term ''total tobacco'' means both the tobacco filler and any other tobacco or tobacco-derived material used as part of a tobacco product. This level would be based on the nicotine content of the tobacco product, as the means to regulate nicotine yield in the tobacco smoke or emissions. If a liquid nicotine product or other tobacco product (including a tobacco product containing nicotine from any source) is intended or reasonably expected to alter the nicotine content of any tobacco product covered by this proposed rule, such liquid nicotine or other tobacco product would be considered a component or part of a tobacco product covered under the rule's scope and, therefore, would be in violation of the rule if the total amount of nicotine in the finished tobacco

product exceeds 0.70 mg of nicotine per gram of total tobacco.

As stated previously, the term ''finished tobacco product'' refers to those products subject to this regulation, including any components, parts, or accessories that are regulated as tobacco products and sealed in a final package, except for components, parts, or accessories not made or derived from tobacco. For cigarettes, cigarette tobacco, and RYO tobacco, all of which were covered under Congress's original grant of authority (section 901(b) of the FD&C Act), all components, parts, and accessories of such products would be covered under this proposed product standard and subject to the proposed maximum nicotine level. Accessories of deemed tobacco products (*i.e.,* accessories for cigars, pipe tobacco) would not be covered. FDA intends to use its premarket review authority under sections 905 and 910 of the FD&C Act to ensure that manufacturers do not reengineer their products in a way that would circumvent the proposed maximum nicotine level.

2. Product Testing (Proposed § 1160.12)

Proposed § 1160.12 contains provisions for the testing of finished tobacco products that would be subject to this proposed rule. Specifically, proposed § 1160.12(a) would require that tobacco product manufacturers conduct testing on each batch of finished tobacco products to ensure that the batch conforms with proposed § 1160.10. Under this provision, the manufacturer of the finished tobacco product would be required to use an analytical test method that meets the requirements set forth in proposed § 1160.14. FDA recommends manufacturers use one of three analytical test methods described in section VII.D of this document (*i.e.,* FDA's Tobacco Products Laboratory method, CRM No. 62, or CRM No. 87). This section also states that samples for such testing would need to be selected in accordance with proposed § 1160.16.

Proposed § 1160.12(b) would require that a full report of the source data and results of all batch testing be maintained by the tobacco product manufacturer in accordance with proposed § 1160.32. These reports would be generated for test samples from each batch and would not be required for each individual finished tobacco product. This report would have to include the following information:

(1) Full identification of the finished tobacco product that is the subject of the report, including, if applicable, the submission tracking number (STN) associated with marketing authorization (including the static product ID (PD), if applicable), product name(s) (including brand and subbrand and the original name described in the premarket application, if different), product category, subcategory, package type, package quantity, and nicotine source;

(2) Nicotine level of each sample tested from the batch and standard deviation;

(3) The batch manufacturing date and location, including facility name and address, for each sample;

(4) The testing date and location, including the facility name and address;

(5) The manufacturing code of each sample tested (in accordance with proposed § 1160.30(c));

(6) The test method and sampling procedure used;

(7) Names and qualifications of the person(s) conducting the testing and any laboratory accreditation;

(8) The manufacturing and testing equipment used (including documentation to show that the equipment is appropriate for its intended purpose and has been calibrated to ensure accurate and reliable results); and

(9) The criteria used to make a decision to accept or reject each batch and the decision made with respect to each batch (*e.g.,* accept, reject) based on the results of the product testing. This information would constitute the documentation of the source data and actual results of the product testing conducted on each batch.

The main purpose of this report would be to verify that products subject to this proposed product standard do not exceed the maximum nicotine level and to document the company's decision for each batch with respect to acceptance, rejection, and reworking of the products. FDA expects that information collected pursuant to proposed § 1160.16(b) would be integrated into the proposed § 1160.12(b) records (*i.e.,* proposed § 1160.16(b) records would be the basis for documenting background information about the product being tested, including, for example, the product category and subcategory, brand and subbrand, packaging information, nicotine source, manufacturing date, and the manufacturing code). These proposed § 1160.12(b) records also would document the ultimate disposition of the batch based on the testing of the representative samples. Section III.C of this document describes FDA's rulemaking and inspection authorities related to these records.

While the proposed batch testing and sampling requirements would provide FDA with critical information, the Agency also recognizes concerns that it could be costly for certain manufacturers to test each batch. Therefore, FDA requests comment, including supporting data, regarding potential alternatives to batch testing and sampling to ensure finished tobacco product compliance with proposed § 1160.10 that would reduce costs for manufacturers.

3. Analytical Test Method (Proposed § 1160.14)

Proposed § 1160.14 would require that tobacco product manufacturers use an analytical test method and demonstrate that the test method was validated in an analytical test laboratory.

Validation means a process of demonstrating or confirming that the analytical test method is suitable and reliable for its intended purpose. Validation of an analytical method applies to a specific laboratory, for a specific product, and equipment performing the analytical test method for an intended use over a reasonable period. Although there are various approaches to demonstrate that an analytical test method is validated (*e.g.,* ICH Guideline Validation of Analytical Procedures: Text and Methodology Q2), FDA intends to use the approach outlined in the draft guidance entitled ''Validation and Verification of Analytical Testing Methods Used for Tobacco Products'' to determine if a submitted test method is fit-for-purpose. In March 2024, FDA published a final guidance for industry entitled ''Q2(R2) Validation of Analytical Procedures'' and although it is not specific to tobacco products, FDA's approach under that guidance to determine if a method is fit-for-purpose is applicable for use under this tobacco product standard.[40]

As described in section VII.D of this document, FDA recommends manufacturers use one of three publicly available analytical test methods—FDA's Tobacco Products Laboratory method, CRM No. 62, or CRM No. 87—to demonstrate compliance with this proposed product standard. Each of these analytical test methods includes the proposed nicotine level in the range of levels that can be accurately measured.

[40] FDA has announced the availability of a draft guidance for industry entitled ''Validation and Verification of Analytical Testing Methods Used for Tobacco Products'' (86 FR 72603, December 22, 2021; see *https://www.fda.gov/media/155033/download*). The draft guidance, when finalized, would represent FDA's current thinking on method validation for tobacco products. FDA final guidance ''Q2(R2) Validation of Analytical Procedures'' is available at *https://www.fda.gov/media/161201/download.*

It is reasonable to expect some manufacturers may prefer to use other test methods. If they are developed and validated, such methods may have different advantages in ease of use, upper and lower bounds of detection, equipment, and expertise. Thus, under this proposal we would evaluate analytical test methods and data as part of a manufacturer's premarket submission in accordance with section 910 of the FD&C Act.

4. Sampling Plans and Procedures (Proposed § 1160.16)

Proposed § 1160.16 would require each tobacco product manufacturer to design and implement a sampling plan that covers each finished tobacco product that it manufactures. This sampling plan must be based on a valid statistical rationale to ensure that the finished tobacco product complies with proposed § 1160.10. This sampling plan would be used in conjunction with the analytical test method in proposed § 1160.14 and would provide procedures for the manufacturer to select samples to demonstrate conformance to the proposed maximum nicotine level requirement.

The required procedures are intended to help ensure that tobacco products containing more than the maximum nicotine level are not sold or distributed to consumers. Manufacturers would be required to ensure that all finished tobacco products comply with the requirements of this proposed product standard. Products that do not conform to this standard would be deemed adulterated under section 902(5) of the FD&C Act and subject to enforcement action.

Proposed § 1160.16(a) provides the general requirements for sampling plans. The proposed provision would require manufacturers to design and implement a sampling plan or plans for each finished tobacco product based on a valid scientific rationale to ensure that the product consistently conforms to the requirements set forth in § 1160.10. This provision also explains that the sampling plan must ensure that samples taken are representative of an entire batch (*i.e.,* randomized or systematically selected across the entire batch) and collected from each batch for testing. To account for the variability of nicotine in finished tobacco products, the following factors must be based on adequate statistical criteria: the confidence intervals, the level of necessary precision, and the number of finished products sampled. The sampling plan must take into account the manufacturing quality history of the manufacturer (*e.g.,* batch testing records, nonconforming tobacco product investigations). For example, a manufacturer that has a high number of nonconforming tobacco product investigations or a high number of batch rejections may decide to create a more robust sampling plan because of its history of producing nonconforming tobacco products.

The basic principles of an adequate sampling plan include the following: the samples are representative of the batch or quantity being sampled; the number of samples is based on a valid scientific rationale; and the number of samples is sufficient for the intended purpose. ''Valid scientific rationale'' refers to scientific techniques or methods used to establish the number of representative samples and should take into account tolerance for variability, confidence levels, and the degree of precision required (Refs. 654 to 656). FDA believes that requiring the number of samples to be based on a ''valid scientific rationale'' would provide manufacturers with the flexibility to determine the appropriate number of representative samples for any sampling plan. While FDA is proposing this flexibility, this provision would require that manufacturers have support for the scientific technique or methods used to establish the number of representative samples used and to show that the sampling size is representative of the material being sampled. FDA requests comment, including supporting data, regarding whether a final rule should provide a more detailed definition of or criteria for what constitutes ''valid scientific rationale'' (such as representative sampling) with regard to an adequate sampling plan.

Proposed § 1160.16(a) also would require that the sampling plan describe the sampling methodology (including scientific rationale), incorporate all sources of variability (including variability of the analytic method and nicotine levels), and describe the sample size needed (including a full description of how the sample size is calculated) consistent with the sampling plan to achieve the sampling objective. The sampling plan must also describe the criteria the manufacturer would use to make a decision to accept or reject each batch. FDA proposes to give tobacco product manufacturers flexibility to determine what unit of time or quantity is appropriate for their product and how batches would be designated. For example, manufacturers likely would define a batch for cigarette production, which is almost continuous, differently than a batch for machine or hand-rolled cigars.

With regard to the variability of the tobacco product, confidence intervals, level of necessary precision, and number of finished tobacco products sampled must be based on adequate statistical criteria. This provides manufacturers flexibility to determine the appropriate number of representative samples for any sampling plan. While FDA is proposing this flexibility, this provision would require that manufacturers have the support for the scientific technique or methods used to establish the representative samples used and to show that the sampling size is representative of the material being sampled. The manufacturer must maintain a nicotine content level no greater than 0.70 mg nicotine per gram of total tobacco for any products within the batch.

Proposed § 1160.16(b) would require that test samples from each batch be collected and examined in accordance with certain procedures. These procedures are consistent with ISO 8243, an international standard that specifies two methods of providing representative samples of a population of cigarettes manufactured for sale.

Under proposed § 1160.16(b)(1), test samples would have to consist of the finished tobacco product as it is intended to be sold or distributed to consumers and not of a separate production sample.

Proposed § 1160.16(b)(2) would require that all test samples be stored according to the intended storage conditions for the finished tobacco product. In addition, the manufacturer would have to include all of its factories, stock rooms, warehouses, and other locations containing finished tobacco products among the population to be sampled. Because a batch may include product that is in the warehouse and product that is in the factory, or in a place between the warehouse and factory, this requirement would ensure that the sample is representative of the entire population (batch) of finished tobacco products packaged for consumer use. This practice is consistent with the ISO 8243 standard (for sampling nicotine) and ensures that the samples are representative of the population of finished tobacco products packaged for consumer use.

Under proposed § 1160.16(b)(3), the manufacturer would have to take test samples from each batch within 30 calendar days of the date the product is manufactured. Based on FDA's experience, any protracted time between manufacturing and testing will add uncertainty in the accuracy of reported results. Thus, we are proposing a 30 calendar day timeframe from the

manufacture date for the manufacturer to take test samples from each batch. The amount of material acquired during sampling must be sufficient to complete all testing required by proposed § 1160.14, including any repeat testing that may be necessary. The sample materials would have to be selected from each batch in accordance with the applicable sampling plan. This would ensure that there has not been any degradation or change in part of the samples.

Proposed § 1160.16(b)(4) would require that sampling be performed by persons who have sufficient education, training, and experience to accomplish their assigned functions.

Under proposed § 1160.16(b)(5), each test sample would need to be identified so that the following information can be determined:

- Full identification of the finished tobacco product sampled, including, if applicable, the STN associated with marketing authorization (including the PD, if applicable), product name(s) (including brand and subbrand and the original name described in the premarket application, if different), product category, subcategory, package type, package quantity, and nicotine source;
- The manufacturing code;
- The date on which the sample was taken;
- The sampling location (including the address of the facility and specific location within the facility where the sample was taken);
- The name of the person(s) who collected the sample; and
- The location where the sample will be tested (including the facility name and address).

This information would be generated at the time the samples are pulled for testing and for each sample pulled, rather than reflecting aggregate information for all the samples in a particular batch. The purpose of this information is to fully identify each sample, including what the product is, when and where it was taken, and the batch from which it was taken. These records would serve dual purposes. First, they could be used to verify that a company is following its sampling plan and the required procedures in the codified including number of samples pulled, when they are pulled, and locations from where they are pulled. Second, these records would be used to generate some of the information for the records required under proposed § 1160.16(b)(8). They also would document the start of the chain of custody for the samples.

Proposed § 1160.16(b)(6) provides packaging requirements for when samples are sent for testing. Test samples would have to be packed securely with adequate protection against damage that might occur, including mechanical damage or adverse changes in humidity or temperature. The manufacturer also would have to send, under separate cover, a list of the samples included in each shipment to the testing facility. These samples should be identified by the relevant information required by proposed § 1160.16(b)(5).

Proposed § 1160.16(b)(7) would require that all samples from a single batch be tested at the same testing facility. This requirement is designed to ensure consistency in the procedures used and to protect against sample degradation.

Proposed § 1160.16(b)(8) provides sampling requirements for the testing facility. If samples will be transported to a different facility from the manufacturing facility for testing, once test samples arrive at the testing facility, samples must be inspected, accounted for, and properly stored under the finished tobacco product's intended storage conditions. The facility also would be responsible for generating a report for the batch test, maintained by the manufacturer in accordance with § 1160.32, which includes the information in proposed § 1160.16(b)(8)(i) through (vi):

- Full identification of the finished tobacco product sampled, including, if applicable, the STN associated with marketing authorization (including the PD, if applicable), product name(s) (including brand and subbrand and the original name described in the premarket application, if different), product category, subcategory, package type, package quantity; and nicotine source;
- The manufacturing code;
- The date on which the samples were taken, if available;
- The sampling location (including the address and specific locations within any facilities where the samples were taken);
- The number of test samples drawn from the batch; and
- Complete records of the samples received and tested, including the date of receipt, the identifier of all persons who tested the samples, and the test results.

This information would be generated once the test samples arrive at the testing facility. Unlike the information required under proposed § 1160.16(b)(5), this report would be an aggregate report for all the samples taken from a batch. The primary purpose of this information, along with the information required by proposed § 1160.16(b)(5), would be to establish the chain of custody for the samples from the time they were taken through their transfer to the testing facility where they will be tested. FDA expects that this information would be integrated into the records required by proposed § 1160.12(b) to provide information across the batch.

Proposed § 1160.16(b)(9) explains that each batch must be withheld from commercial distribution until it has been sampled and tested, and a decision has been made by the tobacco product manufacturer that the batch conforms to the requirements of this part and may be released for commercial distribution. As discussed in proposed § 1160.18, the manufacturer would be required to reject any nonconforming tobacco products unless a disposition decision and justification to release the batch is made after an investigation determines that the batch meets the requirements of this part.

As noted in the discussion of proposed §§ 1160.12 and 1160.16, the reporting requirements in proposed §§ 1160.12(b), 1160.16(b)(5), and 1160.16(b)(8) are interrelated but intended for different purposes.

Because this tobacco product standard defines the amount of nicotine relative to the amount of total tobacco, manufacturers may be able to base sampling plans on batch sizes based on the tobacco filler. For example, cigarettes of two different lengths made from the same tobacco filler blend may be able to be considered a single batch for the purposes of calculating the sampling plan under proposed § 1160.16. Testing for nonconforming tobacco product under proposed § 1160.16 would require the manufacturer to adequately sample from the entire batch in proportion to production. For example, if two-thirds of the batch is produced as cigarette length A and one-third as cigarette length B, then two-thirds of the samples for testing for conformance would have to be sampled from cigarette length A and one-third from cigarette length B.

Manufacturers that purchase bulk tobacco filler can utilize results of filler testing by the seller in designing and implementing their sampling plan. Reliance on the seller's filler testing would not relieve the manufacturer of the finished tobacco product from its responsibility to test finished tobacco products or from responsibility for complying with this proposed product standard.

5. Nonconforming Tobacco Product (Proposed § 1160.18)

Proposed § 1160.18 would require finished tobacco product manufacturers to establish procedures for the control and disposition of nonconforming tobacco products. A ''nonconforming tobacco product'' is proposed to be defined as any tobacco product that does not meet the requirements of § 1160.10 (nicotine level specifications) or § 1160.30 (manufacturing code). These procedures are necessary to help prevent the distribution of nonconforming tobacco products by ensuring that all potential nonconforming products are identified, investigated, and segregated, and that appropriate disposition and followup are taken for products determined to be nonconforming. These provisions are also intended to help manufacturers determine the extent of any nonconformity and, in cases in which nonconforming product has already been released for distribution, determine where it was distributed.

Proposed § 1160.18 would require tobacco product manufacturers to establish and maintain procedures to identify, investigate, segregate, and make disposition decisions (*i.e.,* acceptance, rejection, rework) about nonconforming tobacco products to prevent their release for commercial distribution. ''Establish and maintain'' for purposes of proposed § 1160.18 means define, document (in writing or electronically), implement, follow, and, when necessary, update. This section allows manufacturers the flexibility to determine how they would perform these activities.

Proposed § 1160.18(a) would require tobacco product manufacturers to identify and segregate potential nonconforming tobacco product to prevent the commercial distribution of such products prior to investigation and disposition. Identification of potential nonconforming product can be accomplished in many ways (*e.g.,* applying a label with the relevant information directly to the product container; if an electronic system is utilized, associating the nonconforming product information with the relevant barcode). Identification is a critical first step to preventing further processing, production, or distribution of potential nonconforming tobacco products.

Proposed § 1160.18(a) also would require potential nonconforming tobacco product to remain segregated pending an investigation until it is determined to be conforming. If a potential nonconforming product is determined to be nonconforming, it would need to remain segregated throughout investigation and disposition, including any rework. For purposes of proposed part 1160, ''segregation'' means setting the identified potential nonconforming product apart from other product (*i.e.,* placing it away from conforming finished product). This segregation could be accomplished by placing it in a quarantined or specifically marked-off area. Manufacturers should use prudence and segregate potential nonconforming tobacco product in a manner that is appropriate, given the nature of the potential nonconformity. The requirements to identify and segregate would be triggered upon discovery of a potential nonconforming product. For example, if a tobacco product manufacturer tests samples of finished tobacco product and determines that the representative samples from that batch do not conform to the requirement set forth in proposed § 1160.10, the manufacturer would determine that the batch and related products must be identified and segregated as they may be nonconforming products.

Proposed § 1160.18(b) would require tobacco product manufacturers to investigate all potential nonconforming tobacco products. This may include, for example if:

- The nicotine level of a test sample from any batch of finished tobacco products is determined to be out of conformance with the requirements of proposed § 1160.10;
- FDA notifies the manufacturer that a finished tobacco product in commercial distribution does not conform to the requirements of part 1160; or
- The manufacturer has come to know through any other means that a product is nonconforming.

In this context, a test sample would consist of a number of individual test units that are drawn based on a valid scientific rationale (such as representative sampling) and intended to ensure that the sample accurately reflects the material being sampled. The purpose of a nonconforming product investigation would be to determine the extent and the cause, if possible, of the nonconformity so that additional nonconforming products are not produced or released for commercial distribution. In addition, it would help to prevent recurrence of the nonconformity.

Under proposed § 1160.18(b), the manufacturer would be required to conduct an investigation to determine the extent of the nonconformity upon identification of a nonconforming product and, as applicable, the locations where the nonconforming products have been distributed. We expect the manufacturer would be able to determine the locations of initial consignees (*e.g.,* wholesalers, distributors, retailers) where the affected products were shipped in the event a corrective action needs to be taken. The investigation would have to include an examination of all relevant processes and controls, laboratory testing, complaints, and any other relevant records and sources of information concerning the nonconforming product. For example, a manufacturer could determine the extent of the nonconformity by examining records and in-process control records for any batches, or portions of batches, that have been rejected during either in-process or finished inspection for failing to meet any or all of the product's specifications. Furthermore, in the event that a similar nonconforming product is identified in a different batch, a manufacturer's investigation could include any applicable information and records from the previous nonconforming product investigation that are relevant to determining the extent of the nonconformity of the affected batch.

Proposed § 1160.18(b) would also require that, for products determined to be nonconforming, the investigation must also determine the scope and cause of nonconformance. Examination of relevant production processes and controls and any other relevant records and sources of information could help a manufacturer determine if any other batches are affected or if nonconforming product has been distributed. For example, if a manufacturer's sampling plan and subsequent repeat testing under proposed § 1160.18 determines that a batch of finished cigarettes fail to meet the established nicotine level specification and acceptance criteria, the manufacturer will have to investigate the scope and cause of the nonconformance under this proposed section. If the investigation determines that the cause of the nonconformance is attributed to cut filler received from its supplier that contain nicotine levels that exceed the maximum nicotine level established by the proposed product standard, the manufacturer must also determine the scope of the nonconformance, such as all batches of finished cigarettes that used the affected cut filler.

The manufacturer would have to document any investigation, including any material review, name of the person(s) making the disposition decisions, justification for the

disposition decisions, results of retesting, decisions with respect to reworking, and followup results from the investigation (*e.g.,* corrective actions). FDA may inspect these records to verify that the manufacturer has performed an adequate investigation.

For example, if a manufacturer uses a laboratory to perform product testing under proposed § 1160.12, and there is an out-of-specification (OOS) laboratory test result, the manufacturer would need to investigate the OOS test result under proposed § 1160.18(b) to determine whether the product is nonconforming or the OOS result is due to another cause, such as laboratory error. Under proposed § 1160.18(b), the investigation would be required to include an examination of relevant processes, operations, and any other relevant sources of information such as the laboratory method and review of initial testing and calibration of the laboratory equipment. Such an investigation could determine that the OOS test results came from an aberration of the measurement process (*e.g.,* laboratory error, defective testing equipment, deviation from an established laboratory test method) and that the potential nonconforming tobacco product is not nonconforming. Alternatively, an investigation could conclude that the OOS test result was valid, and that the product was nonconforming as a result of, for example, the manufacturing process. If the manufacturer's nonconforming product investigation determines that the OOS result is due to a legitimate reason such as a testing aberration, *e.g.,* instrument malfunction, and the re-test or rework establishes that the finished tobacco product conforms to the nicotine level of the product standard, such product could be released for commercial distribution.

Proposed § 1160.18(c) would require tobacco product manufacturers to reject a batch of a finished tobacco product if the nicotine level of the test sample does not meet the requirements of § 1160.10, unless a disposition decision and justification to release the batch is made after an investigation shows the batch meets the requirements of part 1160. This might occur in the event of a laboratory or sampling error. Manufacturers would not be able to simply resample a batch until the batch conforms with the proposed maximum nicotine level in § 1160.10 if previous test samples did not the meet the requirements of part 1160. If the initial test samples of the batch were not in conformance, the manufacturer must conduct a nonconforming tobacco product investigation. If the manufacturer, for instance, determines that the nicotine levels were erroneously high due to a malfunction of the testing equipment, the manufacturer could determine that the batch is acceptable for release for commercial distribution.

Proposed § 1160.18(d) would require manufacturers to determine the disposition of all nonconforming tobacco products and any necessary followup. Under proposed § 1160.18(d), nonconforming product cannot be released for distribution without rework or an adequate justification (developed and maintained in accordance with § 1160.32). Thus, nonconforming product could be reworked, distributed with an adequate justification, or discarded. Additionally, nonconforming product could be exported if it meets the requirements of section 801(e)(1) of the FD&C Act. Proposed § 1160.18(d) also would require the manufacturer to develop an adequate written justification before releasing such product for commercial distribution. An adequate written justification would be required to address how the nonconforming product meets all requirements under this part. Nonconforming product cannot be released for commercial distribution without rework or an adequate written justification supporting its release. An example of reworking a nonconforming product would be a manufacturer reblending the cut filler and retesting to ensure that it conforms to the established product standard.

Proposed § 1160.18(e) would require each tobacco product manufacturer to maintain records of all activities required under § 1160.18. Records must include the date and time of the activity, the individual performing the activity, the type of activity performed, any information that demonstrates the requirement was met, and any data or calculations necessary to reconstruct the results.

C. Manufacturing Code and Recordkeeping Requirements (Proposed Subpart C)

1. Manufacturing Code Requirements (Proposed § 1160.30)

Proposed § 1160.30 would require that the packaging of all finished tobacco products include a manufacturing code. The manufacturing code would allow manufacturers and FDA to identify the production batch of a particular finished product that has been released for distribution. This information is intended to help determine the product's history (*e.g.,* batch production records) and assist manufacturers and FDA in the event of a nonconforming tobacco product investigation and any corrective actions to be taken by a manufacturer as a result of the investigation. The ''-NS'' designation will enable retailers to readily identify that a finished tobacco product conforms with this standard. Finished tobacco products that do not have this designation do not conform to this standard. The manufacturing code information also would aid FDA in ensuring compliance with this proposed product standard by clearly identifying those products that conform to the standard and linking those products to records that substantiate their conformance.

As stated in proposed § 1160.30(a), the manufacturing code would be required to be permanently affixed to the packaging or label of all finished tobacco products. The manufacturing code must be affixed in a manner that ensures it will remain on the packaging or label through the expected duration of use of the product by the consumer. In addition, proposed § 1160.30(b) would require that the manufacturing code be permanently affixed, legible, conspicuous, prominent, and appear in the English language.

As stated in proposed § 1160.30(c), the manufacturing code must contain the following information listed in the following order:

- The manufacturing date in 2-digit numerical values in the month-day-year format (MMDDYY);
- The finished tobacco product batch number; and
- The designation ''-NS'' at the end [41] (to signify that the product was manufactured in accordance with this nicotine product standard).

FDA requests comment on the manufacturing code requirements in this proposed rule.

2. Recordkeeping Requirements (Proposed § 1160.32)

Proposed § 1160.32 contains recordkeeping requirements. This information is necessary for FDA to ascertain and confirm that finished tobacco products are in compliance with the proposed product standard.

First, proposed § 1160.32(a) would require that each facility that manufactures tobacco products subject to this part (*i.e.,* cigarettes and certain other finished tobacco products) establish and maintain records related to compliance with this part, including the following:

[41] The ''-NS'' designation will enable retailers to readily identify that a finished tobacco product conforms with this standard. Finished tobacco products that do not have this designation do not conform to this standard.

(1) The source data and results of analyses conducted to determine conformance with § 1160.10, including all information identified in § 1160.12(b);

(2) All source data used to validate an analytical test method;

(3) All sampling plans and sampling reports under § 1160.16;

(4) Documentation that the persons performing sampling under § 1160.16 have sufficient education, training, and experience to accomplish the assigned functions; and

(5) All nonconforming tobacco product identification, segregation, investigation, rework, and disposition decision procedures, including justifications under § 1160.18.

This information is necessary for FDA to ascertain and confirm that the products are in compliance with the proposed product standard.

Second, proposed § 1160.32(b) provides certain specifications for these records. All records required under this part, regardless of storage medium, would need to be attributable (*i.e.,* traceable to its source), legible (*i.e.,* in a readable format), contemporaneously recorded (*i.e.,* recorded at the time of performance), original (*i.e.,* first capture of the data), and accurate (*i.e.,* correct, truthful, complete, valid, and reliable). In addition, these records would be required to be written in English; alternatively, an accurate English translation must be made available upon request. Documents that have been translated from a foreign language into English would have to be accompanied by the foreign language version of the document and a certification by the manufacturer's authorized representative (which could be a U.S. agent for the manufacturer) that the English language translation is complete and accurate, and a brief statement of the qualifications of the person who made the translation (*e.g.,* education, experience). These records would need to be maintained at the manufacturing establishment or another location that is readily accessible to responsible officials of the manufacturer and to FDA. These records, including those not stored at the establishment, would need to be readily accessible to FDA during the retention period (as discussed in § 1160.32(c)) for inspection and photocopying or other means of reproduction. Original or true copies of these records that can be immediately retrieved from another location, including by computer or other electronic means, would satisfy the requirements of this section.

FDA expects that requested records that are maintained offsite would be made available within 24 hours or, if that is not feasible, as soon as possible before the close of the inspection. While the Agency expects that most records can be made available to FDA within 24 hours, FDA recognizes that, in some cases, additional time may be needed to retrieve records from a third party or archival storage. Records that can be immediately retrieved from another location, including by computer or other electronic means, would meet the requirement that the records be readily available.

Proposed § 1160.32(c) would require that the records kept under this part be retained for at least 4 years from the date of commercial distribution of the finished tobacco product that is the subject of the record. FDA has selected 4 years to help ensure that the records would be available for at least one biennial FDA inspection under sections 704 and 905(g) of the FD&C Act.

FDA believes that detailed recordkeeping requirements are necessary to confirm that finished tobacco products are in compliance with the proposed product standard. For example, requiring manufacturers to document their test results would enable FDA to confirm that the manufacturer's analytical test method is adequate to meet the requirements of part 1160. In addition, requiring nonconforming tobacco product records would help the manufacturer and FDA determine the extent of the nonconformity with the product standard and, as applicable, the locations where the nonconforming products have been distributed, for example, in the event of a recall.

XI. Proposed Effective Date

In accordance with section 907(d)(2) of the FD&C Act,[42] FDA proposes that any final rule that may issue based on this proposal become effective 2 years after the date of publication of the final rule. Therefore, after the effective date, no manufacturer or importer would be allowed to distribute, sell, or offer for distribution or sale within the United States any finished tobacco product that does not comply with proposed part 1160. After the effective date of the final rule, manufacturers and importers would not be allowed to enter or introduce into domestic commerce any finished tobacco product (*i.e.,* cigarettes, cigarette tobacco, RYO tobacco, cigars, and pipe tobacco) that does not comply with the requirements of the final rule, irrespective of the date of manufacture. Prior to the effective date of any final rule that may issue based on this proposed rule, wholesalers, retailers, and related entities would be able to sell available stock of finished tobacco products that are not in compliance with part 1160 while transitioning inventory in anticipation of the effective date of the final rule; however, they would not be permitted to sell off such stock after the effective date. FDA notes that keeping products subject to this proposed rule with higher nicotine levels on the market for an extended period of time is not in the interest of public health.

The Nicotine ANPRM requested comment on a proposed effective date for a nicotine tobacco product standard. Several comments recommended that FDA establish a 1-year timeframe for implementation. Other comments urged FDA to set a 2-year timeframe for implementation, which they stated would be the minimum required by section 907 of the FD&C Act due to the impact on farmers. A few comments argued that an implementation period should be required for all manufacturers, regardless of the number of employees and/or annual revenues, because the long time to develop the regulation plus the implementation period would be sufficient warning for all companies. However, many comments argued that the implementation period should be significantly longer than a 1- or 2-year period to allow farmers, tobacco intermediaries, and manufacturers to develop and implement the methods of reduction.

The comments differed as to whether FDA should allow manufacturers any time to sell off nonconforming tobacco product. Several comments urged FDA to allow manufacturer sell-off of existing nonconforming inventory, with some stating that a 6-month or 12-month selloff period should be sufficient for nonconforming product to move through the supply chain. Nevertheless, several comments opposed provisions that would allow sell-off of existing inventory, arguing that the extensive period of the development of the standard combined with a 2-year phase-in period would give the companies more than enough time to sell-off or recall existing inventory. Some comments stated that a 60-day selloff period would be a sufficient selloff period while still maintaining the public health goals of the standard. FDA requests comments, including

[42] Section 907(d)(2) of the FD&C Act states that a regulation establishing a tobacco product standard shall set forth the date or dates upon which the standard shall take effect, but no such regulation may take effect before 1 year after the date of its publication unless the Secretary determines that an earlier effective date is necessary for the protection of the public health.

supportive data and research, regarding a selloff period (*e.g.,* 60 days after the effective date of the final rule) for retailers to sell through their current inventory of nonconforming product.

FDA considered many factors in determining an appropriate proposed effective date. Pursuant to section 907(d)(2) of the FD&C Act, FDA considered the technical achievability of compliance with the proposed product standard and the existence of patents that would make it impossible to comply in the proposed 2-year timeframe. For example, for manufacturers that may not want to use chemical extraction, FDA considered how long it would likely take for a tobacco product manufacturer to acquire sufficient VLNC tobacco to meet the proposed product standard. Industry documents indicate that the timing of availability of leaf once commercial seed is provided is one growing season (Ref. 657). Seed production and germination testing can be conducted in multiple seasons within a single year with small-scale trial to commercial availability taking place over the course of 1 year (Ref. 658). For example, industry documents indicate that a request for purchase of low alkaloid nicotine in March 1990 would be expected to result in leaf delivery during August and September (Ref. 657).

Once purchased, FDA considered how long tobacco must be stored prior to use in cigarettes and other combusted tobacco products. Industry documents suggest a minimum storage age (particularly for burley and flue-cured tobaccos) of around 12 months (Refs. 659 to 663). Other tobacco manufacturers suggest that tobaccos should be stored for 22 months, although other studies suggest that aging beyond 12 months has minimal effects (Refs. 662 and 664). Industry documents also indicate that processed tobaccos do not appear to require long-term inventory or aging in the same manner as whole-leaf tobaccos (Ref. 659). FDA requests comments, including supportive data and research, on the technical achievability of compliance with the proposed product standard and the existence of patents that would make it impossible to comply in the proposed 2-year timeframe.

FDA also finds that a 2-year effective date will ''minimize, consistent with the public health, economic loss to, and disruption or dislocation of, domestic and international trade'' pursuant to section 907(d)(2) of the FD&C Act. As discussed extensively throughout this document, tobacco use is the leading cause of preventable disease and death in the United States, and nearly all of the adverse health effects are ultimately the result of addiction to the nicotine in cigarettes and certain other combusted tobacco products, which leads to repeated exposure to toxicants from these products. Given the tremendous public health risks presented—particularly to youth who experiment with these products, develop an addiction to nicotine, and progress to regular use—by combusted tobacco products, FDA finds that any balancing of impacts to domestic and international trade is far outweighed by the significant public health benefits of this proposed product standard for all age groups. FDA also believes that a 2-year effective date would allow adequate time for implementing any necessary changes in technology to achieve the proposed nicotine level, for making any changes to tobacco purchasing choices and curing methods, and for preparation or changes needed in facilities, which can be accomplished simultaneously. In addition, this timeframe should provide adequate time for manufacturers to seek and obtain marketing authorization from FDA for their new tobacco products. FDA believes that this 2-year period would provide sufficient time for a tobacco product manufacturer to submit, and FDA to review, applications for new tobacco products that comply with this provision. This is particularly true given our expectation that most manufacturers that reduce the nicotine levels of their products to comply with the proposed standard would be submitting SE Reports, which may decrease the amount of data required for authorization. See section IX.B of this document regarding pathways to market tobacco products that have been modified to meet the proposed standard. FDA requests comments, including supportive data and research, on the timeframe for manufacturers to prepare applications and obtain marketing authorization from FDA for their new tobacco products.

FDA finds this proposed effective date to be appropriate for the protection of the public health, given that current nicotine levels in the finished tobacco products cause addiction and repeated exposure to toxicants, which ultimately result in the majority of tobacco-related disease and death in the United States. Additional delay, past 2 years, would only increase the number of youth and young adults who transition to regular use of cigarettes and certain other combusted tobacco products and would delay switching to potentially less harmful tobacco products or cessation by people who currently smoke cigarettes.

Pursuant to section 907(d)(2), FDA requests comments by interested parties, including manufacturers and tobacco growers, regarding the technical achievability of compliance with this proposed product standard, including information concerning the existence of patents that make it impossible to comply in the proposed 2-year timeframe. FDA also requests comment on the timeframe for manufacturers to prepare applications and obtain marketing authorization from FDA for their new tobacco products. Further, FDA requests comments and data regarding whether 2 years is sufficient to comply with this standard or whether this effective date should be later to provide additional time for manufacturers to develop any necessary changes in technology, facilities, farming methods, or other factors or business practices affecting compliance. FDA also requests comments and supporting data as to whether a shorter effective date would be necessary for the protection of the public health.

XII. Preliminary Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Rules are ''significant'' under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they ''have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of [the Office of Information and Regulatory Affairs (OIRA)] for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities.'' OIRA has determined that this proposed rule is a significant regulatory action under Executive Order 12866 Section 3(f)(1).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because businesses, including small businesses, would incur costs to comply with the proposed product standard, we find that the proposed rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The 2023 threshold after adjustment for inflation is $183 million, using the 2023 Implicit Price Deflator for the Gross Domestic Product. This proposed rule would result in an expenditure in at least 1 year that meets or exceeds this amount.

B. Summary of Costs and Benefits

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 653) and at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.* The summary of costs, benefits, and transfers is presented in table 13. Benefits occur because the proposed rule would discourage people who do not use tobacco products from initiating combusted tobacco products and progressing to regular use and increase cessation or switching to potentially lower risk tobacco products among people who currently use covered combusted tobacco products and wish to quit. Lower prevalence of combusted tobacco product use would lead to reduced health consequences for people who formerly used combusted tobacco products and those who were previously exposed to secondhand smoke. The main quantified benefits come from averted mortality and morbidity as a result of reduced prevalence for people who currently use combusted tobacco products, and reduced mortality from reduced exposure to secondhand smoke among people. As described in section VIII.A above, to assess the potential public health impacts of a nicotine product standard, FDA developed a population health model using inputs derived from available empirical evidence and expert opinion to estimate the impact of changes in tobacco product initiation, cessation, switching, and dual use on tobacco use prevalence, morbidity, and mortality in the United States. We use output from this population health model to estimate averted mortality and preliminarily apply the value of a statistical life while requesting feedback about how to follow HHS guidance (see PRIA Section II.M.6). The morbidity estimates come from population health model output that evaluates the health difference for being in the state of smoking verse not smoking. Unquantified benefits include medical cost savings, productivity loss savings, reduced exposure to thirdhand smoke, and environmental impacts. We estimate that the present value of the quantified benefits over a 40-year time horizon ranges between $7.6 trillion and $33.2 trillion with a primary estimate of $30.6 trillion at a 2 percent discount rate. The primary annualized quantifiable benefits equal $1.1 trillion at a 2 percent discount rate.

As most of the benefits from avoided initiation among youth and young adults due to this proposed product standard are expected to fall outside of the 40-year time horizon of the main analysis, we present an extended analysis over a period beyond the 40-year time horizon to capture the impact on youth and young adults. The present value of quantified benefits, mostly attributable to youth and young adults, over this extended period range between $8.4 trillion and $19.7 trillion with a primary estimate of $19.1 trillion at a 2 percent discount rate. Additionally, we present the incidence of benefits for specific populations in the Distributional Effects section.

We expect this proposed rule, if finalized, to impose costs on industry to follow the product standard, on the broader economy to repurpose land, labor, and capital, on consumers impacted by the product standard, and on FDA to enforce this product standard. The tobacco market faces a one-time primary cost with a present value of $374 million at a 2 percent discount rate (low-impact scenario estimate of $112 million to a high-impact scenario estimate of $700 million) to read and understand the rule.[43] We also use population health model output on prevalence to estimate the baseline and policy market size. These estimates feed into cost estimates, such as lost producer surplus. Producers of combusted tobacco products incur a primary annualized producer surplus loss of $1.7 billion (low-impact scenario of $0.2 billion and a high-impact scenario of $2 billion) at a 2 percent discount rate. We expect that some manufacturers would reformulate their products to comply with this standard. We estimate a one-time reformulation cost with present value of $0.6 billion (low-impact scenario estimate of $8.8 billion to a high-impact scenario estimate of $0.04 billion). Manufacturers that reformulate would collectively incur a one-time cost to submit their new tobacco product for FDA review, estimated at a present value $1 million at a 2 percent discount rate (low-impact scenario estimate of $15 million to a high-impact scenario estimate of $0.1 million). In addition, these manufacturers would also incur recurring costs to test the nicotine level of their products with a primary annualized estimate of $0.3 million (low-impact scenario estimate of $1.9 million to a high-impact scenario estimate of $0.1 million) at a 2 percent discount rate. We estimate a one-time cost for FDA to review submissions for new tobacco products at a present value of $1.0 million at a 2 percent discount rate (low-impact scenario estimate of $15.3 million to a high-impact scenario estimate of $0.1 million). The economy faces a one-time economic transition cost with a present value of $7.2 billion at a 2 percent discount rate (low-impact scenario estimate of $4.3 billion to a high-impact scenario estimate of $9.1 billion) to reallocate productive resources (such as labor and capital) currently devoted to the manufacture of NNC covered combusted tobacco products to other tobacco products or to non-tobacco products. We estimate transition cost based on average industry capital expenditures and literature on the cost of labor transition. Consumers of NNC covered combusted tobacco products would face a one-time search cost with a present value of $1.4 billion at a 2 percent discount rate (low-impact scenario estimate of $0.46 billion to a high-impact scenario estimate of $2.8 billion) to find other tobacco products or NRT as a replacement for the prohibited NNC products. We estimate one-time withdrawal costs for

[43] For the purposes of our analysis, we use the population health model described in section VIII.A of this document to estimate impacts for a range of averted mortality and tobacco prevalence. The ''high impact scenario'', generally referred to as the upper bound, corresponds to the scenario where the policy has 95th percentile averted mortality projected by the population health model, which also corresponds with the lowest (5th percentile) post-policy combusted tobacco prevalence. For some costs (product reformulation, premarket submission, and review, and testing costs), the ''upper bound'' corresponds to the scenario with the fewest products and, thus, would reflect the lowest estimate of costs.

consumers who quit tobacco products, with a primary estimate of $1.4 billion at a 2 percent discount rate (low-impact scenario estimate of $0.02 billion to a high-impact scenario estimate of $8.99 billion), at a 2 percent discount rate. We estimate additional costs associated with FDA enforcement of the product standard to range from an annualized value of $3.3 million to $7 million at a 2 percent discount rate. Unquantified costs may include changes in consumer surplus for some people who smoke NNC products, including potential utility changes for consumers who switch from NNC to VLNC combusted tobacco products. The present value of the costs over a 40-year time horizon has a primary estimate of $58 billion (low-impact scenario estimate of $19.3 billion to a high-impact scenario of $76.2 billion) at a 2 percent discount rate. The primary estimates for the annualized costs are $2.1 billion at a 2 percent discount rate.

In addition to benefits and costs, this rule would cause transfers from the Federal Government, State governments, and firms to consumers, who in turn would spend this money in other sectors of the economy (including savings), in the form of reduced revenue and tax revenue. We also estimate transfers between or within firms to cover shifts in user fee obligation. The primary estimate for the annualized transfers from the Federal Government, in the form of reduced excise tax, ranges from $1.4 billion to $4.3 billion, with a primary estimate of $4.1 billion at a 2 percent discount rate. The primary estimate for the annualized transfers from State governments, in the form of reduced excise tax, ranges from $2.8 billion to $8.9 billion, with a primary estimate of $8.4 billion at a 2 percent discount rate. The primary estimate for the annualized transfers from the firms, in the form of reduced revenue, is $20.0 billion at a 2 percent discount rate (low-impact scenario of $6.2 billion; high-impact scenario of $17.6 billion). The primary estimate for the annualized user fee obligation shifted from combusted tobacco products to noncombusted tobacco products has a range from $26.3 million to $461.1 million with a primary estimate of $332.6 million at a 2 percent discount rate. Transfers are summarized in table 13.

TABLE 13—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE

[Millions of 2023 dollars over a 40-year time horizon]

Category	Primary estimate	Low estimate	High estimate	Dollar year	Discount rate (%)	Time horizon	Notes
Benefits							
Annualized monetized benefits	$1,097,053	$273,521	$1,190,582	2023	2	2025–2064 (40 years)	See footnote.[44]
Annualized quantified, but non-monetized, benefits.							
Unquantified benefits	Medical cost savings, productivity loss savings, reductions in smoking-related fires (excluding mortality), reduced litter, and other associated harms to the environment						
Costs							
Annualized monetized costs	2,077	690	2,729	2023	2	2025–2064 (40 years).	
Annualized quantified, but non-monetized, costs.							
Unquantified costs	Changes in consumer surplus for some people who smoke normal nicotine content combusted tobacco products, including potential utility changes for consumers who switch from NNC to VLNC combusted tobacco products.						
Transfers							
Annualized monetized Federal budgetary transfers.	4,092	1,386	4,313	2023	2	2025–2064 (40 years).	
Bearers of transfer gain and loss?	Transfers of Excise Tax Revenues from Federal Governments to Consumers						
Annualized monetized State budgetary transfers.	8,414	2,848	8,877	2023	2	2025–2064 (40 years).	
Bearers of transfer gain and loss?	Transfers of Excise Tax Revenues from State Governments to Consumers						
Other annualized monetized transfers	19,964	6,235	17,603	2023	2	2025–2064 (40 years).	
Bearers of transfer gain and loss?	Transfers of Revenues from Tobacco Firms to Consumers						
Other annualized monetized transfers	333	26	461	2023	2	2025–2064 (40 years).	
Bearers of transfer gain and loss?	Transfers from User Fees Owed by Combusted Tobacco Firms to s Owed by Noncombusted Tobacco Firms						
Net benefits							
Annualized monetized net benefits	1,094,976	272,831	1,187,853	2023	2	2025–2064 (40 years).	
Category	*Effects*						*Notes*
Effects on State, local, or Tribal governments.	Significant transfer of tax revenues for State governments. Potential transfer of tax revenue for local and Tribal governments.						
Effects on small businesses	Significant revenue reductions and compliance costs for small, combusted tobacco product manufacturers. We expect most small, combusted manufacturers would shut down or switch industries.						
Effects on wages	No significant wage impacts.						

TABLE 13—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE—Continued
[Millions of 2023 dollars over a 40-year time horizon]

Category	Primary estimate	Low estimate	High estimate	Dollar year	Discount rate (%)	Time horizon	Notes
Category	*Effects*						*Notes*
Effects on growth	Anticipated growth in the noncombusted tobacco sector.						

We request comment on our estimates of benefits, costs, and transfers of this proposed rule.

XIII. Analysis of Environmental Impact

The Agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The Agency's finding of no significant impact and the evidence supporting that finding is available in the docket for this proposed rule (Refs. 665 and 666) and may be seen in Dockets Management Staff (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at *https://www.regulations.gov.* Under FDA's regulations implementing the National Environmental Policy Act (21 CFR part 25), an action of this type would require an environmental assessment under 21 CFR 25.20.

XIV. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). A description of these provisions is given in the *Description* section of this document with an estimate of the annual reporting, recordkeeping, and third-party disclosure burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information. If finalized, this proposed rule will seek approval of a new information collection.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology; and (5) the standard and customary business practices of tobacco manufacturers as it relates to capital, operating, and maintenance costs associated with this collection of information.

Title: Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products (0910–NEW).

Description: The FD&C Act authorizes FDA to adopt tobacco product standards, including product standards that include provisions for nicotine yields and for the reduction or elimination of other constituents (including smoke constituents) or harmful components (section 907(a)(3)(A) and (4) of the FD&C Act). FDA is proposing to limit nicotine yield by setting a maximum nicotine content level for finished cigarettes and certain other finished combusted tobacco products not to exceed 0.70 mg of nicotine per gram of total tobacco.

Subpart A contains the general provisions of this proposed product standard including scope, prohibited activities, and definitions.

Subpart B contains the proposed product standard requirements pertaining to finished tobacco products that cover product testing (§ 1160.12), sampling plans (§ 1160.16), analytical test methods (§ 1160.14), nonconforming tobacco products (§ 1160.18), package label requirements (§ 1160.30) and recordkeeping requirements (§ 1160.32).

Subpart C contains manufacturing code (§ 1160.14) and recordkeeping (§ 1160.32) requirements.

Proposed § 1160.12 contains provisions for the testing of finished tobacco products that would be subject to this proposed rule. Specifically, proposed § 1160.12(a) would require that tobacco product manufacturers conduct testing on each batch of finished tobacco products.

Proposed § 1160.12(b) would require that a full report of the source data and results of all batch testing be maintained by the tobacco product manufacturer. Based on FDA subject matter expertise and experience from tobacco inspections, we expect that manufacturers would discuss in these reports how their product is batched. These reports would be generated for test samples from each batch and would not be required for each individual finished tobacco product. This report would have to include the following information:

(1) Full identification of the finished tobacco product that is the subject of the report, including the product category, subcategory, product name (brand and subbrand), package type, package quantity, and nicotine source;

(2) Nicotine level of each sample tested from the batch and standard deviation;

(3) The batch manufacturing date and location, including facility name and address, for each sample;

(4) The testing date and location, including the facility name and address;

(5) The manufacturing code of each sample tested (in accordance with proposed § 1160.30(c));

(6) The test method and sampling procedure used;

(7) Names and qualifications of the person(s) conducting the testing and any laboratory accreditation;

[44] FDA notes that these results hinge on an expert elicitation in which the experts were provided peer reviewed literature on VLNC and NNC cigarette use in experiments. The expert elicitation and much of the literature specifically referenced the nicotine level of 0.4 mg nicotine per gram total tobacco. However, in 22nd Century Group, Inc.'s modified risk tobacco product applications, the company reported that after 9 years of sampling by the company, the average nicotine content of its genetically engineered VLNC tobacco is 0.6 mg nicotine per gram of total tobacco, with a range of 0.4 to 0.7 mg nicotine per gram of total tobacco. It is likely that the Quest and SPECTRUM Nicotine Research Cigarettes, used throughout the scientific literature, also contained between 0.4 to 0.7 mg nicotine per gram of total tobacco (Ref. 257). This suggests the literature the experts reviewed studied cigarettes in the range of 0.4–0.7 mg nicotine per gram total tobacco as opposed to only 0.4 mg nicotine per gram total tobacco. Therefore, the results of the expert elicitation are still applicable to a nicotine level of 0.7 mg nicotine per gram total tobacco. For reference, nicotine content in the top 100 cigarette brands (2017) is 17.2 mg nicotine per gram total tobacco (Ref. 9).

(8) The equipment used (including documentation to show that the equipment is appropriate for its intended purpose and has been calibrated to ensure accurate and reliable results); and

(9) The criteria used to make a decision to accept or reject each batch and the decision made with respect to each batch (*e.g.,* accept, reject) based on the results of the product testing. This information would constitute the documentation of the source data and actual results of the product testing conducted on each batch.

The main purpose of this report would be to verify that products subject to this proposed product standard do not exceed the maximum nicotine level and to document the company's decision for each batch with respect to acceptance, rejection, and reworking of the products. FDA expects that information collected pursuant to proposed § 1160.12(b) would be integrated with the proposed § 1160.18(b) records (*i.e.,* proposed § 1160.12(b) records regarding the product being tested, including, for example, the product category and subcategory, brand and subbrand, packaging information, nicotine source, manufacturing date, and the manufacturing code would inform the 1160.18(b) investigation). These proposed § 1160.12(b) records also would document the ultimate disposition of the batch based on the testing of the representative samples.

Proposed § 1160.14 would require that manufacturers analyze the nicotine levels of cigarettes and certain other finished combusted tobacco products covered by the rule using a validated analytical test method. Manufacturers would be required to demonstrate that the test method used was validated in an analytical test laboratory. Proposed § 1160.16 would require each tobacco product manufacturer to design and implement a sampling plan that covers each finished tobacco product that it manufactures. This sampling plan would provide procedures for the manufacturer to select samples to demonstrate conformance to the proposed maximum nicotine level requirement. The required procedures would help ensure that products that exceed the maximum level of nicotine are not sold or distributed to consumers. This provision also explains that the sampling plan must ensure samples taken are representative of an entire batch and are randomly selected and collected from each batch for testing.

This section would also require test samples from each batch be collected and examined in accordance with certain procedures (proposed § 1160.16(b)). Each test sample would need to be identified so that the following information can be determined:

- Full identification of the finished tobacco product sampled, including product category, subcategory, product name (brand and subbrand), package type, package quantity, and nicotine source;
- The manufacturing code;
- The date on which the sample was taken;
- The sampling location (including the address of the facility and specific location within the facility where the sample was taken);
- The name of the person(s) who collected the sample; and
- The location where the sample will be tested (including the facility name and address).

Proposed § 1160.18 would require finished tobacco product manufacturers to establish procedures for the control and disposition of nonconforming tobacco products. The proposed procedures would require tobacco product manufacturers to establish and maintain procedures to identify, investigate, segregate, and make disposition decisions (*i.e.,* acceptance, rejection, rework) about nonconforming finished tobacco products to prevent their release for commercial distribution. FDA interprets ''establish and maintain'' for purposes of proposed § 1160.18 to mean define, document (in writing or electronically), implement, follow, and, when necessary, update.

Identification of potential nonconforming product (*i.e.,* a tobacco product that does not conform to the proposed maximum nicotine level requirement) can be accomplished in many ways (*e.g.,* applying a label with the relevant information directly to the product container; if an electronic system is utilized, associating the nonconforming product information with the relevant barcode). If a potential nonconforming product is determined to be nonconforming, it would need to remain segregated throughout investigation and disposition, including any rework. For purposes of proposed part 1160, ''segregation'' means setting the identified potential nonconforming product apart from other product (*i.e.,* placing it away from conforming finished product). This segregation could be accomplished by placing it in a quarantined or specifically marked-off area.

The manufacturer would be required to conduct an investigation to determine the extent of the nonconformity upon identification of a nonconforming product and, as applicable, the locations where the nonconforming products have been distributed. We expect the manufacturer would be able to determine the locations of initial consignees (*e.g.,* wholesalers, distributors, retailers) where the affected products were shipped in the event a corrective action needs to be taken. The investigation would have to include an examination of all relevant processes and controls, laboratory testing, complaints, and any other relevant records and sources of information concerning the nonconforming product. Tobacco product manufacturers would be required to reject a batch of a finished tobacco product if the nicotine level of the test sample does not meet the requirements unless a disposition decision and justification to release the batch is made after an investigation shows the batch meets the requirements.

Tobacco product manufacturers would be required to determine the disposition of all nonconforming tobacco products and any necessary followup. Nonconforming product cannot be released for commercial distribution without rework or an adequate justification (developed and maintained in accordance with § 1160.32). Thus, nonconforming product could be reworked, distributed with an adequate justification, or discarded. An adequate written justification would be required to address how the nonconforming product meets all requirements under this part.

Proposed § 1160.18(e) would require each tobacco product manufacturer to maintain records of all activities required under § 1160.18. Records must include the date and time of the activity, the individual performing the activity, the type of activity performed, any information that demonstrates the requirement was met, and any data or calculations necessary to reconstruct the results.

FDA expects that information collected pursuant to proposed § 1160.12(b) would be integrated with the proposed § 1160.18(b) records (*i.e.,* proposed § 1160.12(b) records regarding the product being tested, including, for example, the product category and subcategory, brand and subbrand, packaging information, nicotine source, manufacturing date, and the manufacturing code would inform the 1160.18(b) investigation). These proposed § 1160.12(b) records also would document the ultimate disposition of the batch based on the testing of the representative samples.

Proposed § 1160.30 would require the use of a manufacturing code to serve as

a common identifier for production and distribution records. The purpose of the manufacturing code is to allow manufacturers and FDA to identify the production batch of a particular finished product that has been released for distribution. This information is intended to help determine the product's history (*e.g.,* batch production records) and assist manufacturers and FDA in the event of a nonconforming product investigation and any corrective actions to be taken as a result of the investigation.

The manufacturing code would be required to be permanently affixed to the packaging or labeling of all finished tobacco products. The manufacturing code must be affixed in a manner that ensures it will remain on the packaging or label through the expected duration of use of the product by the consumer. In addition, proposed § 1160.30(b) would require that the manufacturing code be permanently affixed, legible, conspicuous, prominent, and appear in the English language.

As stated in proposed § 1160.30(c), the manufacturing code must contain the following information listed in the following order:

- The manufacturing date in 2-digit numerical values in the month-day-year format (MMDDYY);
- The finished tobacco product batch number; and
- The designation ''-NS'' at the end.

The manufacturing code would allow manufacturers and FDA to identify the production batch of a particular finished product that has been released for distribution. This information is intended to help determine the product's history (*e.g.,* batch production records) and assist manufacturers and FDA in the event of a nonconforming product investigation and any corrective actions to be taken as a result of the investigation.

Proposed § 1160.32 contains recordkeeping requirements that are necessary for FDA to ascertain and confirm that finished tobacco products are in compliance with the proposed product standard. The proposed product standard would require that manufacturers establish and maintain records regarding the results of testing conducted on each batch to determine conformance with the proposed standard. In addition, this proposed product standard would require that manufacturers maintain records of batch testing, source data for analytical test method validation, sampling plans and sampling procedures, and nonconforming tobacco products.

First, proposed § 1160.32(a) would require that each facility that manufactures tobacco products subject to this part (*i.e.,* finished tobacco products) establish and maintain records related to compliance with this part, including the following:

(1) The source data and results of analyses conducted to determine conformance with § 1160.10, including all information identified in § 1160.12(b);

(2) All source data used for analytical test method validation;

(3) All sampling plans and sampling reports under § 1160.16;

(4) Documentation that the persons performing sampling under § 1160.16 have sufficient education, training, and experience to accomplish the assigned functions; and

(5) All nonconforming tobacco product identification, segregation, investigation, rework, and disposition decision procedures, including justifications, under § 1160.18. This information is necessary for FDA to ascertain and confirm that the products are in compliance with the proposed product standard.

Second, proposed § 1160.32(b) provides certain specifications for these records. All records required under this part, regardless of storage medium, would need to be attributable, legible, contemporaneously recorded, original, and accurate. In addition, these records would be required to be written in English; alternatively, an accurate English translation must be made available upon request. Documents that have been translated from a foreign language into English would have to be accompanied by the foreign language version of the document and a certification by the manufacturer's authorized representative (which could be a U.S. agent for the manufacturer) that the English language translation is complete and accurate, and a brief statement of the qualifications of the person who made the translation (*e.g.,* education, experience). These records would need to be maintained at the manufacturing establishment or another location that is readily accessible to responsible officials of the manufacturer and to FDA.

Proposed § 1160.32(c) would require that the records kept under this part be retained for at least 4 years from the date of commercial distribution of the finished tobacco product that is the subject of the record. FDA has selected 4 years as a means to help ensure that the records would be available for at least one biennial FDA inspection under sections 704 and 905(g) of the FD&C Act.

FDA believes that detailed recordkeeping requirements are necessary to confirm that finished tobacco products are in compliance with the proposed product standard. For example, requiring manufacturers to document their test results would enable FDA to confirm the manufacturer's test method is adequate to meet the requirements of part 1160. In addition, requiring nonconforming product records would help the manufacturer and FDA determine the extent of the nonconformity with the product standard and, as applicable, the locations where the nonconforming products have been distributed; for example, in the event of a recall.

Description of Respondents: The information collection requirements in the proposed standard would apply to tobacco product manufacturers, which means any person, including a repacker or relabeler, who (1) manufactures, fabricates, assembles, processes, or labels a tobacco product; or (2) imports a finished tobacco product for sale or distribution in the United States. Specifically, the information collection would apply to manufacturers of cigarettes (other than noncombusted cigarettes, such as heated tobacco products that meet the definition of a cigarette), cigarette tobacco, roll-your-own (RYO) tobacco, cigars (including little cigars, cigarillos, and large cigars, but excluding ''premium cigars''), and pipe tobacco (other than waterpipe tobacco). FDA recognizes that many of the proposed provisions of the proposed rule are in accordance with the quality control and manufacturing practices that manufacturers have already adopted on a voluntary basis. Application requirements are set by the final Substantial Equivalence (0910–0673) and Premarket Tobacco Product Application (0910–0879) rules. For products covered by this proposed standard, we expect most manufacturers will seek authorization using the substantial equivalence premarket pathway, which may decrease the amount of data required for authorization. See section IX.B of this document regarding pathways to market tobacco products that have been modified to meet the proposed standard. Based on FDA's subject matter expertise and industry data, we recognize that between 85 and 90 percent of all cigarette production is conducted by large manufacturers. We also find that the other tobacco product categories, such as non-premium cigars, pipe, and RYO tobacco, have similar levels of market concentration. We assume that large tobacco product manufacturers represent the bulk of tobacco product

production capacity and so represent the majority of recordkeeping burden.

The proposed provision § 1160.12 (batch testing), is part of standard and customary business practices of tobacco manufacturers. As such, there are no capital costs or operating and maintenance costs associated with this collection of information. Batch testing is conducted either by the manufacturer in-house or by a 3rd-party accredited laboratory. If sent to a 3rd-party laboratory, we do not expect any capital, operating, or maintenance costs associated with batch testing to be incurred by the manufacturer. We expect a manufacturer would only test their products in-house if they already possess an in-house laboratory accredited to conduct scientific tests. We would not anticipate capital, operating, or maintenance costs for these in-house laboratories as capital and maintenance are components of maintaining accreditation. We do not expect any manufacturers currently without an in-house laboratory to newly establish an in-house accredited laboratory as a result of this product standard.

The proposed provision § 1160.14 (analytical test method), is also part of standard and customary business practices of tobacco manufacturers. As such, there are no capital costs or operating and maintenance costs associated with this collection of information. Manufacturers are already required to submit test results of analytical testing for nicotine and other relevant harmful and potentially harmful constituents (HPHCs) as part of premarket submissions. As the establishment and use of analytical testing is already generally required for premarket submissions, we do not anticipate capital, operating, or maintenance cost from these provisions.

The proposed provision § 1160.16 (sampling plans), is part of standard and customary business practices of tobacco manufacturers. As such, there are no capital costs or operating and maintenance costs associated with this collection of information. Manufacturers already routinely conduct analytical testing to check for consistency in their finished products. To conduct such testing, manufacturers would have needed to establish a sampling plan to generate a representative sample of their product for testing. As such, we do not anticipate capital, operating, or maintenance cost from these provisions.

The proposed provision § 1160.18 (nonconforming tobacco products), is part of standard and customary business practices of tobacco manufacturers. As such, there are no capital costs or operating and maintenance costs associated with this collection of information. Based on FDA subject matter expertise and inspections, we find that almost all manufacturers already check for consistency and conformance of their products and rework product as necessary to supply information for internal quality checks and distribution purposes, we do not anticipate capital, operating, or maintenance cost from these provisions.

The proposed provision § 1160.30 (manufacturing code labeling), is part of standard and customary business practices of tobacco manufacturers. As such, there are no capital costs or operating and maintenance costs associated with this collection of information. Based on FDA subject matter expertise and industry information, we find that almost all manufacturers already apply a manufacturing code to their products. Because a manufacturing code also supplies information that the manufacturer needs for internal quality and distribution purposes (standard and customary practices), we do not anticipate additional capital, operating, or maintenance cost from these provisions.

FDA specifically invites comments on our discussion of the standard and customary business practices of tobacco manufacturers as it relates to capital, operating, and maintenance costs associated with this collection of information.

FDA estimates the burden of this collection of information as follows:

TABLE 14—ESTIMATED ANNUAL RECORDKEEPING BURDEN[45]

21 CFR section or activity	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
§ 1160.12 Product Testing	143	50.84	7,270	9	65,430
§ 1160.14 Analytical Test Method	143	4	572	1	572
§ 1160.16 Sampling Plan	143	4	572	1	572
§ 1160.18 Procedures for Nonconforming Tobacco Products and Related Investigations; Procedures for Control and Disposition of Nonconforming Tobacco Products	143	1	143	14	2,002
§ 1160.30 Package Label Requirements (Manufacturing Code)	143	4	572	7	4,004
§ 1160.32 Recordkeeping Requirements (Batch Testing Records)	143	50.84	7,270	6	43,620
Total Annual Burden	.....	.....	.....	.....	116,200

Table 14 displays the recordkeeping burden associated with this proposed rule. Included in this estimate is the recordkeeping burden for establishing and maintaining records regarding the results of testing conducted on each batch to determine conformance with the proposed standard, sampling plans and sampling procedures, and records related to manufacturing controls. FDA's burden estimates are based on CTP's Tobacco Registration and Listing Module Next Generation (TRLM NG) data and Dun & Bradstreet firm data (D&B). The requirements in the Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products proposed rule would apply to both domestic and foreign manufacturers of finished tobacco products that are distributed or sold in the United States. We estimate the number of affected entities, by tobacco product category and size of operation group. We estimate that there are a total of 143 entities potentially affected by the proposed rule (domestic manufacturers and importers of impacted tobacco products, including 133 manufacturers and importers of

[45] There are no capital costs or operating and maintenance costs associated with this collection of information.

cigarettes, cigars, pipe tobacco, and RYO tobacco and 10 dual operation facilities that manufacture both combusted and noncombusted products). For purposes of the PRA estimates, FDA used the entities affected and a weighted average of the median hours to calculate the respondents and total burden hours.

We estimate a total of 7,270 batches per year are required to be tested under § 1160.12 (product testing). Based on information from inspections and other FDA subject matter expertise, including typical batch sizes and projected combusted tobacco production by year, FDA estimates that there will be 50.84 records per recordkeeper with 9 hours of average burden per recordkeeping. FDA assumes respondents will establish a total of 7,270 annual records for a total of annual 65,430 hours.

Based on information from inspections and other FDA subject matter expertise, we expect that core blends are the products that manufacturers will choose to reformulate to meet the product standard. Manufacturers would incur a burden to establish an analytical test method and sampling plan for each reformulated core blend. FDA experts assume that each manufacturer, on average, utilizes four different core blends per tobacco category that they manufacture. Under § 1160.14 (analytical test method), respondents would determine an analytical test method to use for complying with the product standard. During validation of the analytical test method within the laboratory to be used, the respondent would record and collect the data generated and maintain these records. FDA estimates there will be 4 records per recordkeeper with 1 hour of average burden per recordkeeping and respondents will establish a total of 572 annual records for a total of annual 572 hours. Under § 1160.16 (sampling plan), FDA estimates there will be 4 records per recordkeeper with 1 hour of average burden per recordkeeping. FDA assumes respondents will establish a total of 572 annual records for a total of annual records for a total of annual 572 hours.

Under § 1160.18 (procedures for nonconforming products), FDA assumes there will be 1 record per recordkeeper with 14 hours of average burden per recordkeeping for a total of 143 annual records and a total of annual 2,002 hours. This estimate is based on information from tobacco inspections and FDA experience in developing good manufacturing practices in non-tobacco industries. Further, as stated above, based on FDA subject matter expertise and inspections, we find that almost all manufacturers already check for consistency and conformance of their products and rework product as necessary to supply information for internal quality checks and distribution purposes.

Proposed § 1160.30 would require manufacturers to apply a manufacturing code to the packaging and label of tobacco products. Based on FDA subject matter expertise and market tracking information, we find that almost all manufacturers already apply a manufacturing code to their products. FDA assumes 4 records per recordkeeper with 7 hours of average burden per recordkeeping, and a total of 572 annual records for a total of annual 4,004 hours.

Under § 1160.32 (batch testing records), FDA assumes 50.84 records per recordkeeper with 6 hours of average burden per recordkeeping. This estimate is based on establishing the format and maintaining batch test records for detailed recordkeeping requirements, including English translation and accessibility, that are necessary to confirm that finished tobacco products are in compliance with the proposed product standard. FDA assumes that respondents will maintain a total of 7,270 annual records for a total of annual 43,620 hours.

FDA expects the additional one-time (*i.e.,* occurring only in the first year) reporting burden for the information collection that will result from this rule, to be as follows:

TABLE 15—ESTIMATED ONE-TIME REPORTING BURDEN

Activity	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Review and familiarization with the rule	1,465	1	1,465	10	14,650
Total One-Time Burden					14,650

Based on FDA subject matter expertise, we assume that all entities affected by this proposed rule would spend time to read and understand the rule, resulting in a one-time reporting burden. FDA estimates that there will be 293 entities and 5 individuals at each entity that will read the final rule. It is estimated that each respondent will spend up to 10 hours reading and understanding the rule for a total of 14,650 one-time burden hours. Per the requirements of this proposed rule, FDA estimates the total burden will be 130,850 hours (116,200 + 14,650).

FDA invites comments on the estimates in this section and specifically any burden specific to small manufacturers to whom this proposed standard would apply. To ensure that comments on information collection are received, OMB recommends that written comments be submitted through *reginfo.gov* (see **ADDRESSES**). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the **Federal Register**.

XV. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires Agencies to ''construe . . . a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.'' We have determined that the proposed rule, if finalized, would not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the rule does not contain policies that have

federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

This rule is being issued under section 907 of the FD&C Act, which enables FDA to prescribe regulations relating to tobacco product standards, and the sale and distribution restriction in this rule is also being issued under section 906(d) of the FD&C Act, which enables FDA to prescribe regulations restricting the sale and distribution of a tobacco product. If this proposed rule is made final, the final rule would create requirements whose preemptive effect would be governed by section 916 of the FD&C Act (21 U.S.C. 387p) entitled ''Preservation of State and local authority.''

Section 916 of the FD&C Act broadly preserves the authority of States and localities to protect the public against the harms of tobacco use. Specifically, section 916(a)(1) of the FD&C Act establishes a general presumption that FDA requirements do not preempt or otherwise limit the authority of States, localities, or tribes to, among other things, enact and enforce laws regarding tobacco products that relate to certain activities (*e.g.,* sale, distribution) and that are in addition to or more stringent than requirements established under chapter IX of the FD&C Act.

Section 916(a)(2)(A) of the FD&C Act is an express preemption provision that establishes an exception to the preservation of State and local governmental authority over tobacco products established in section 916(a)(1). Specifically, section 916(a)(2)(A) of the FD&C Act provides that ''[n]o State or political subdivision of a State may establish or continue in effect with respect to a tobacco product any requirement which is different from, or in addition to, any requirement under the provisions of this chapter relating to tobacco product standards . . . .''

However, section 916(a)(2)(B) limits the applicability of section 916(a)(2)(A) of the FD&C Act, narrowing the scope of State and local requirements that are subject to express preemption. Paragraph (a)(2)(B) provides that preemption under paragraph (a)(2)(A) does not apply to State or local ''requirements relating to the sale, distribution, possession, information reporting to the State, exposure to, access to, the advertising and promotion of, or use of, tobacco products by individuals of any age, or relating to fire safety standards for tobacco products.''

If this proposed rule is finalized as proposed, the final rule would create requirements that fall within the scope of section 916(a)(2)(A) of the FD&C Act because they are ''requirements under the provisions of the chapter relating to tobacco product standards.'' Accordingly, the preemptive effect of those requirements on any State or local requirement would be determined by the nature of the State or local requirement at issue—specifically, whether the State or local requirement is preserved under section 916(a)(1) of the FD&C Act, and/or excepted under section 916(a)(2)(B) of the FD&C Act (such as if it relates to the ''sale, distribution, possession, information reporting to the State, exposure to, access to, the advertising and promotion of, or use of, tobacco products''). State and local prohibitions on the sale and distribution of tobacco products would not be preempted by this rule, if finalized, because such prohibitions would be preserved by section 916(a)(1) of the FD&C Act or, as applicable, excepted from express preemption by section 916(a)(2)(B) of the FD&C Act. FDA invites comments on how State or local laws may be implicated if this proposed rule is finalized.

XVI. Severability

In accordance with section 5 of the Tobacco Control Act, which provides for the severability of, *inter alia,* all ''regulations promulgated under'' the authorities provided by that Act, FDA would consider the various requirements and prohibitions established by this rule, if finalized, to be severable. It is FDA's interpretation and position that the invalidity of any provision of a final rule would not affect the validity of any other part of the rule. In the event any court or other lawful authority were to temporarily or permanently invalidate, restrain, enjoin, or suspend any provision of a final rule, FDA intends for the remaining parts to continue to be valid. Additionally, as further stated in section 5 of the Tobacco Control Act, if certain applications of a final rule to persons or circumstances (discussed in the preamble or otherwise) are held to be invalid, application of such provisions to any other person or circumstance will not be affected and will continue to be enforced to the fullest extent possible. Each provision of the rule is independently supported by data and analysis as described or referenced in this preamble and, if issued separately, would remain a proper exercise of FDA authority.

XVII. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule contains policies that may have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. We expect some tribal governments to be impacted given that some are manufacturers and retailers of cigarettes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XVIII. References

The following references marked with an asterisk (*) are on display at 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 also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

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List of Subjects in 21 CFR Part 1160

Administrative practice and procedure, Labeling, Smoke, Smoking, Tobacco, Tobacco products.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that chapter I of title 21 of the Code of Federal Regulations be amended by adding part 1160 to subchapter K to read as follows:

PART 1160—TOBACCO PRODUCT STANDARD FOR NICOTINE YIELD OF CIGARETTES AND CERTAIN OTHER COMBUSTED TOBACCO PRODUCTS

Subpart A—General Provisions

Sec.

Subpart B—Product Requirements

Subpart C—Manufacturing Code and Recordkeeping Requirements

Authority: 21 U.S.C. 331, 371(a), 374, 381(e), 381(p)(2), 387b, 387c, 387f(d), 387f(e), 387g, 387i, 387j.

Subpart A—General Provisions

§ 1160.1 Scope.

(a) This part sets forth the product standard to limit nicotine yield by setting a maximum nicotine content level for certain finished tobacco products. The provisions of this part are applicable to cigarettes (other than noncombusted cigarettes, such as heated tobacco products that meet the definition of a cigarette), cigarette tobacco, roll-your-own tobacco, cigars (other than premium cigars), and pipe tobacco (other than waterpipe tobacco).

(b) No person may distribute, sell, or offer for sale or distribution within the United States finished tobacco products, as described in paragraph (a) of this section, that are not in compliance with this part.

(c) No person may manufacture within the United States finished tobacco products, as described in paragraph (a) of this section, that are not in compliance with this part, unless such tobacco products are intended for export and are eligible for export under section 801(e)(1) of the Federal Food, Drug, and Cosmetic Act.

§ 1160.3 Definitions.

For purposes of this part:

Accessory means any product that is intended or reasonably expected to be used with or for the human consumption of a tobacco product; does not contain tobacco or nicotine from any source and is not made or derived from tobacco; and meets either of the following:

(1) Is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product; or

(2) Is intended or reasonably expected to affect or maintain the performance, composition, constituents, or characteristics of a tobacco product; but

(i) Solely controls moisture and/or temperature of a stored tobacco product; or

(ii) Solely provides an external heat source to initiate but not maintain combustion of a tobacco product.

Batch means a specific identified amount of a finished tobacco product produced in a unit of time or quantity and that is intended to have the same specifications.

Cigar means a tobacco product that:

(1) Is not a cigarette; and

(2) Is a roll of tobacco wrapped in leaf tobacco or any substance containing tobacco.

Cigarette, as used in this part:

(1) Means a product that:

(i) Is a tobacco product; and

(ii) Meets the definition of the term ''cigarette'' in section 3(1) of the Federal Cigarette Labeling and Advertising Act; and

(2) Includes tobacco, in any form, that is functional in the product, which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette or as roll-your-own tobacco.

Cigarette tobacco means any tobacco product that consists of loose tobacco that is intended for use by consumers in a cigarette. Unless otherwise stated, the requirements applicable to cigarettes under this chapter also apply to cigarette tobacco.

Commercial distribution means any distribution of a finished tobacco product, whether domestic or imported, to consumers or to any person, but does not include interplant transfers of a tobacco product between establishments within the same parent, subsidiary, and/or affiliate company, nor does it include providing a tobacco product for product testing where such product is not made available for personal consumption or resale. ''Commercial distribution'' does not include the handing or transfer of a tobacco product from one consumer to another for personal consumption.

Component or *part* means any software or assembly of materials intended or reasonably expected:

(1) To alter or affect the tobacco product's performance, composition, constituents, or characteristics; or

(2) To be used with or for the human consumption of a tobacco product. The term excludes anything that is an accessory of a tobacco product.

Finished tobacco product means a tobacco product, including all components and parts, sealed in final packaging (*e.g.,* filters or filter tubes sold to consumers separately or as part of kits) or in the final form in which it is intended to be sold to consumers.

Manufacturing code means any distinctive sequence or combination of letters, numbers, or symbols that begins with the manufacturing date, followed by the batch number, and concludes with ''-NS.''

Manufacturing date means the month, day, and year in 2-digit numerical values in the format (MMDDYY) that a finished tobacco product is packaged for distribution.

Nicotine means the chemical substance named 3-(1-methyl-2-pyrrolidinyl) pyridine or C[10]H[14]N[2], including any salt or complex of nicotine, derived from any source.

Nonconforming tobacco product means any tobacco product that does not meet the requirements of § 1160.10 or § 1160.30.

Package or *packaging* means a pack, box, carton, or container of any kind or, if no other container, any wrapping (including cellophane) in which a tobacco product is offered for sale, sold, or otherwise distributed to consumers.

Person includes an individual, partnership, corporation, or association.

Pipe tobacco means any tobacco product that, because of its appearance, type, packaging, or labeling, is suitable for use and likely to be offered to, or purchased by, consumers as tobacco to be smoked in a pipe.

Rework means action taken on a nonconforming tobacco product to ensure the product meets the specifications and other requirements of this part before it is released for commercial distribution.

Roll-your-own tobacco means any tobacco product which, because of its appearance, type, packaging, or labeling, is suitable for use and likely to be offered to, or purchased by, consumers as tobacco for making cigarettes or cigars.

Specification means any requirement with which a product, process, service, or other activity must conform.

Tobacco filler means cut, ground, powdered, or leaf tobacco or other nicotine-containing substances in a finished tobacco product.

Tobacco product means any product made or derived from tobacco, or containing nicotine from any source, that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). The term ''tobacco product'' does not mean an article that under the Federal Food, Drug, and Cosmetic Act is: a drug (section 201(g)(1)); a device (section 201(h)); a combination product (section 503(g)); or a food under section 201(f) if such article contains no nicotine, or no more than trace amounts of naturally occurring nicotine.

Tobacco product manufacturer means any person, including a repacker or relabeler, who:

(1) Manufactures, fabricates, assembles, processes, or labels a tobacco product; or

(2) Imports a finished tobacco product for sale or distribution in the United States.

Total tobacco means tobacco filler and any other tobacco or tobacco-derived material used as part of a tobacco product.

United States means the 50 States of the United States of America and the District of Columbia, the Commonwealth of Puerto Rico, Guam, the Virgin Islands, American Samoa, Wake Island, Midway Islands, Kingman Reef, Johnston Atoll, the Northern Mariana Islands, and any other trust territory or possession of the United States.

Subpart B—Product Requirements

§ 1160.10 Nicotine level.

A finished tobacco product must not exceed a nicotine content of 0.70 milligrams of nicotine per gram of total tobacco.

§ 1160.12 Product testing.

(a) *Batch testing.* Tobacco product manufacturers must conduct testing on finished tobacco products to ensure that the batch conforms with § 1160.10. The manufacturer must use an analytical test method that meets the requirements set forth in § 1160.14. Samples for testing each batch to determine if it conforms with § 1160.10 must be selected in accordance with the requirements set forth in § 1160.16.

(b) *Documentation of test results.* A full report of the source data and results of all batch testing must be maintained by the tobacco product manufacturer in accordance with § 1160.32, including the following:

(1) Full identification of the finished tobacco product that is the subject of the report, including, if applicable, the submission tracking number (STN) associated with marketing authorization (including the static product ID (PD), if applicable), product name(s) (including brand and subbrand and the original name described in the premarket application, if different), product category, subcategory, package type, package quantity, and nicotine source;

(2) Nicotine level of each sample tested and standard deviation;

(3) The batch manufacturing date and location, including facility name and address, for each sample;

(4) The testing date and location, including the facility name and address;

(5) The manufacturing code of each sample tested;

(6) The test method and sampling procedure used;

(7) The names and qualifications of the person(s) conducting the testing and any laboratory accreditation;

(8) The equipment used (including documentation to show that the

equipment is appropriate for its intended purpose and has been calibrated to ensure accurate and reliable results); and

(9) The criteria used to make a decision to accept or reject each batch and the decision made with respect to each batch (*e.g.,* accept, reject) based on the results of the product testing.

§ 1160.14 Analytical test method.

Tobacco product manufacturers must use an analytical test method and must demonstrate that the test method used was validated in an analytical test laboratory.

§ 1160.16 Sampling plans and procedures.

(a) *Sampling plans.* Each tobacco product manufacturer must design and implement a sampling plan or plans that cover each finished tobacco product based on a valid scientific rationale to ensure that the product consistently conforms to the requirement set forth in § 1160.10. The sampling plan must ensure that samples taken are representative of an entire batch (*i.e.,* randomized or systematically selected across the entire batch) and collected from each batch for testing. To account for the variability of nicotine in finished tobacco products, the following factors must be based on adequate statistical criteria: the confidence intervals, the level of necessary precision, and the number of finished products sampled. The sampling plan must take into account the manufacturing quality history of the manufacturer (*e.g.,* batch testing records, nonconforming tobacco product investigations). Each sampling plan must describe the sampling methodology, with scientific rationale, incorporate all sources of variability (including variability of the analytic method and nicotine levels), and describe the sample size needed (including a full description of how the sample size is calculated) consistent with the sampling plan to achieve the sampling objective. The sampling plan must also describe the criteria the tobacco product manufacturer will use to make a decision to accept or reject each batch.

(b) *Sampling procedures.* Test samples must be collected from each batch and examined in accordance with the following procedures:

(1) Test samples are to consist of the finished tobacco product as it is intended to be sold or distributed to consumers and not of a separate production sample.

(2) All test samples must be stored according to the intended storage conditions for the finished tobacco product. A tobacco product manufacturer must include all of its factories, stock rooms, warehouses, and other locations containing finished tobacco products in the population to be sampled.

(3) Test samples must be taken from each batch and tested within 30 calendar days of the manufacturing date. The amount of material acquired during sampling must be sufficient for all testing required by § 1160.14, including any repeat testing that may be necessary. Samples must be selected from each batch in accordance with the applicable sampling plan.

(4) Sampling must be performed by persons who have sufficient education, training, and experience to accomplish the assigned functions.

(5) Each test sample must be identified so that the following information can be determined:

(i) Full identification of the finished tobacco product sampled, including, if applicable, the STN associated with marketing authorization (including the PD, if applicable), product name(s) (including brand and subbrand and the original name described in the premarket application, if different), product category, subcategory, package type, package quantity, and nicotine source;

(ii) The manufacturing code;

(iii) The date on which the sample was taken;

(iv) The sampling location (including the address of the facility and specific location within the facility where the sample was taken);

(v) The name of the person(s) who collected the sample; and

(vi) The location where the sample will be tested (including the facility name and address).

(6) Samples sent for testing must be packed securely with adequate protection against damage (*e.g.,* mechanical damage, adverse changes in humidity or temperature). A list of the samples in each shipment must be sent to the testing facility under separate cover.

(7) All samples for a batch test must be tested at the same facility.

(8) If samples will be transported to a different facility from the manufacturing facility for testing, once test samples arrive at the testing facility, they must be inspected, accounted for, and properly stored under the finished tobacco product's intended storage conditions, and a report that includes the following information must be generated for the batch test and be maintained by the tobacco product manufacturer in accordance with § 1160.32:

(i) Full identification of the finished tobacco product sampled, including, if applicable, the STN associated with marketing authorization (including the PD, if applicable), product name(s) (including brand and subbrand and the original name described in the premarket application, if different), product category, subcategory, package type, package quantity, and nicotine source;

(ii) The manufacturing code;

(iii) The date on which samples were taken, if available;

(iv) The sampling location (including the address and specific locations within any facilities where samples were taken);

(v) The number of test samples drawn; and

(vi) Complete records of the samples received and tested, including the date of receipt, the identifier of all persons who tested the samples, and the test results.

(9) Each batch must be withheld from commercial distribution until it has been sampled and tested and a decision has been made by the tobacco product manufacturer that it conforms to the requirements of this part and may be released for commercial distribution.

§ 1160.18 Nonconforming tobacco product.

Each tobacco product manufacturer must establish and maintain procedures for the control and disposition of nonconforming tobacco product. The procedures must include the following requirements:

(a) *Identification and segregation.* Each tobacco product manufacturer must identify and segregate potential nonconforming product in a manner that prevents commercial distribution of potential nonconforming product prior to investigation and disposition.

(b) *Investigation.* Each tobacco product manufacturer must investigate all potential nonconforming tobacco products to determine if the product is nonconforming. The investigation must include an examination of relevant production processes and controls, laboratory testing, complaints, and any other relevant records and sources of information. For products determined to be nonconforming, the investigation must also determine the scope and cause of nonconformance.

(c) *Rejection of nonconforming product.* Tobacco product manufacturers must reject a batch of a finished tobacco product if the nicotine level of a test sample from the batch does not conform to the requirements of this part unless a disposition decision and justification to release the batch is

made after an investigation determines that the batch meets the requirements of this part.

(d) *Disposition and followup.* Each tobacco product manufacturer must determine the disposition of all nonconforming tobacco products and any necessary followup. If the disposition decision is that the tobacco product can be released for distribution without rework, an adequate written justification must be developed and maintained in accordance with § 1160.32. An adequate written justification must address why releasing the nonconforming product would not result in the tobacco product being adulterated or misbranded. Nonconforming product cannot be released for distribution without rework or an adequate justification.

(e) *Records.* Each tobacco product manufacturer must maintain records of all activities required under this section. Records must include the date and time of the activity, the individual performing the activity, the type of activity performed, any information that demonstrates that the requirement was met, and any data or calculations necessary to reconstruct the results.

Subpart C—Manufacturing Code and Recordkeeping Requirements

§ 1160.30 Manufacturing code requirements.

(a) Each tobacco product manufacturer must permanently affix a manufacturing code to the packaging or labeling of all finished tobacco products. For a finished tobacco product, the manufacturing code must be affixed in a manner that assures it will remain on the packaging or labeling through the expected duration of use of the tobacco product by the consumer.

(b) The manufacturing code for each finished tobacco product must be permanently affixed, legible, conspicuous, prominent, and appear in the English language.

(c) The manufacturing code must contain the following information listed in the following order:

(1) The manufacturing date in 2-digit numerical values in the month-day-year format (MMDDYY);

(2) The finished tobacco product batch number; and

(3) The designation ''–NS'' at the end.

§ 1160.32 Recordkeeping requirements.

(a) Each facility that manufactures tobacco products subject to this part must establish and maintain records related to compliance with this part, including the following:

(1) The source data and results of batch testing conducted to determine conformance with § 1160.10, including all information specified in § 1160.12(b);

(2) All source data for analytical test method validation;

(3) All sampling plans and reports under § 1160.16;

(4) Documentation that the persons performing sampling under § 1160.16 have sufficient education, training, and experience to accomplish the assigned functions; and

(5) All nonconforming tobacco product identification, segregation, investigation, rework, and disposition decision procedures, including justifications, under § 1160.18.

(b) All records required under this part, regardless of storage medium, must be attributable, legible, contemporaneously recorded, original, and accurate. These records must be written in English, or an accurate English translation must be made available upon request. Documents that have been translated from another language into English must be accompanied by the original language version of the document, a signed statement by the authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation. These records must be maintained at the manufacturing establishment or another location that is readily accessible to responsible officials of the tobacco product manufacturer and to FDA. These records, including those not stored at the establishment, must be made readily accessible to FDA during the retention period for inspection and photocopying or other means of reproduction. Original or true copies of these records that can be immediately retrieved from another location, including by computer or other electronic means, meet the requirements of this paragraph.

(c) All records required under this part must be retained for a period of at least 4 years from the date of commercial distribution of the finished tobacco product that is the subject of the record.

Dated: January 6, 2025.

Robert M. Califf,

Commissioner of Food and Drugs.

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