Embracing the Continuum of Risk: CTP Builds Policy on Product Standards and Tobacco Flavoring, and Reassesses Regulatory Priorities in Aftermath of the Deeming Rule

Moderator
Brian J. Malkin, Esq.
Arent Fox LLP | Washington, DC

Speakers:
Anne Pierson Allen, Esq.
King & Spalding, Esq. | New York, NY

Christina Young, Ph.D.
King & Spalding | New York, NY

Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule

Guidance for Industry (Revised)*

Comments may be submitted at any time for Agency consideration. Electronic comments may be submitted to http://www.regulations.gov. Alternatively, submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD, 20852. All comments should be identified with FDA-2017- D-2834.

For questions regarding this guidance, contact the Center for Tobacco Products at (Tel) 1-877- CTP-1373 (1-877-287-1373) Monday-Friday, 9 a.m. – 4 p.m. EDT.

Additional copies are available online at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/default.htm. You may send an e-mail request to SmallBiz.Tobacco@fda.hhs.gov to receive an electronic copy of this guidance. You may send a request for hard copies to U.S. Food and Drug Administration, Center for Tobacco Products, Attn: Office of Small Business Assistance, Document Control Center, Bldg. 71, Rm. G335, 10903 New Hampshire Ave., Silver Spring, MD 20993-2000.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products

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* This is the fourth edition of this guidance, which originally issued in May 2017. Revisions are noted by date at the end of the guidance.

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Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance document is intended to assist any person who manufactures, packages, sells, offers to sell, distributes, or imports for sale and distribution within the United States newly regulated tobacco products, roll-your-own tobacco, and cigarette tobacco. This guidance document discusses:

- FDA's extension of future compliance deadlines for certain provisions under the May 2016 final Deeming rule.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance was prepared by the Office of Regulations and the Office of Compliance and Enforcement in the Center for Tobacco Products at FDA.

[2] Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products, 81 Fed. Reg. 28,974 (May 10, 2016).

II. BACKGROUND

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31) granted FDA the authority to regulate the manufacture, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own tobacco (RYO), and smokeless tobacco products to protect the public health and to reduce tobacco use by minors. The Tobacco Control Act also gave FDA the authority to issue regulations deeming other products that meet the statutory definition of a tobacco product to be subject to Chapter IX of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (section 901(b) of the FD&C Act).

In accordance with that authority, on May 10, 2016, FDA issued a final rule deeming all products that meet the statutory definition of a tobacco product, except accessories of newly deemed tobacco products, to be subject to FDA's tobacco product authority. This included electronic nicotine delivery systems (ENDS), cigars, hookah, pipe tobacco, nicotine gels, dissolvables that were not already subject to the FD&C Act, and other tobacco products that may be developed in the future (81 FR 28976).

Chapter IX of the FD&C Act now applies to newly regulated products, including sections 904(a)(1) and (4) (ingredient listing and health document submissions), 903(a)(4) and 903(a)(8) (labeling requirements), 904(c)(1) (timing of submissions), 905(b), (c), (d), and (h) (establishment registration), 905(i)(1) (product listing), 907(a)(1)(B) (additional special rules), 911 (modified risk claims), 904(a)(3) and 915 (harmful and potentially harmful constituent reporting), 920 (labeling, recordkeeping, and records inspection), and 905 and 910 (premarket review requirements). The final rule also included several requirements that apply to a subgroup of products referred to "covered tobacco products."[3]

In May 2017, FDA published the first edition of this guidance document, under which it provided a three-month extension of all future compliance deadlines for requirements under the final deeming rule. The May 2017 guidance applied to all categories of newly regulated products, including ENDS (e.g., e-cigarettes and e-cigars), hookah, pipe tobacco, and cigars, as well as the addictiveness warning requirement for RYO and cigarette tobacco. The guidance noted that the three-month extension did not apply to requirements under the final deeming rule where compliance deadlines already had passed, such as mandatory age and photo-ID checks to prevent illegal sales to minors. It explained that FDA would continue to enforce such requirements.

[3] The final deeming rule defines covered tobacco product to include any tobacco product deemed to be subject to Chapter IX of the FD&C Act under 21 C.F.R. 1100.2, but "excludes any component or part that is not made or derived from tobacco" (21 C.F.R. § 1140.3).

III. DISCUSSION

A. FDA's Extension of Certain Future Compliance Deadlines Related to the Final Deeming Rule

FDA is providing a further extension of certain future compliance deadlines for requirements under the final deeming rule. This further extension applies only to compliance deadlines relating to premarket review requirements, specifically for substantial equivalence exemption requests (SE EX requests), substantial equivalence reports (SE reports), and premarket tobacco product applications (PMTAs). No compliance deadlines relating to other provisions in the final deeming rule are being further extended, either those that have already passed and are being enforced, or those scheduled for a future date that were extended in the May 2017 guidance.

The further extension of premarket review compliance deadlines covered by this guidance applies to all categories of newly regulated products that were on the market on August 8, 2016, including ENDS (e.g. e-cigarettes and e-cigars), hookah, pipe tobacco, and cigars. The compliance dates are being extended from November 8, 2017 (SE EX requests), May 8, 2018 (SE reports), and November 8, 2018 (PMTAs) to August 8, 2021 (SE EX requests, SE reports, and PMTAs for newly regulated combustible tobacco products, such as most cigars, pipe tobacco and hookah tobacco) and August 8, 2022 (SE EX requests, SE reports, and PMTAs for newly regulated noncombustible tobacco products, such as most ENDS or e-cigarettes). These new compliance dates are reflected in the chart in Section III.B., along with the compliance dates from the May 2017 guidance that are not being further extended.

The preamble to the May 10, 2016, final deeming rule explained that FDA was providing two compliance periods: One for submission and FDA receipt of applications and one for obtaining premarket authorization. It explained that under the latter compliance period:

> Unless FDA has issued an order denying or refusing to accept the submission, products for which timely premarket submissions have been submitted will be subject to a continued compliance period for 12 months after the initial compliance period described previously. For such products, FDA does not intend to initiate enforcement for failure to have premarket authorization during this continued compliance period.

81 Fed. Reg. 29,011 (May 10, 2016). The preamble further explained that this compliance policy did not apply to any new tobacco product that was not on the market on August 8, 2016. *Id*. FDA is revising the compliance policy relating to the period after FDA receipt of SE EX requests, SE reports, and PMTAs for newly regulated products that were on the market on August 8, 2016. Under this new compliance policy, there will be a continued compliance period pending review of those applications (SE EX requests, SE reports, and PMTAs). This compliance period will continue until the agency renders a decision on an application (i.e., issuance of: a Marketing Order; a No Marketing Order; a Refuse to File; or Refuse to Accept) or the application is withdrawn. The chart in Section III.B has been revised from the first edition of this guidance, issued in May 2017, to reflect this revised compliance policy.

For purposes of this guidance, FDA is using "future compliance deadlines" to refer to dates in the future on which it intends to begin enforcement of certain requirements under the deeming rule. Such dates include both (1) the effective date a particular requirement will become effective as a matter of law (e.g., the effective date for the health warning requirements in 21 C.F.R. part 1143) or (2) a compliance date that FDA has set as a matter of enforcement discretion, stating that it does not intend to enforce a particular requirement that is already in effect for a period of time in order to give industry more time to comply (e.g., compliance dates for various provisions of the FD&C Act set forth in the preamble to the final deeming rule, see 81 FR 29006).

This guidance revises and updates the first edition of this guidance, issued in May 2017. As with the May 2017 guidance, the compliance dates announced in this guidance supersede the compliance dates included in any other guidance issued prior to this guidance.

B. Compliance Dates

The compliance dates for requirements under the final deeming rule are detailed in the following chart. Requirements under the final deeming rule where compliance deadlines have already passed are not affected by this guidance and are not listed on the chart.

Required Warning Statements

Provision	Products Affected	Requirement and Compliance Date Under This Guidance
Product packages and ads must contain the addictiveness warning statement (21 C.F.R. § 1143.3(a) and (b)) • "WARNING: This product contains nicotine. Nicotine is an addictive chemical." • The warning must follow size and format requirements	Cigarette tobacco, roll-your-own tobacco, and covered tobacco products (other than cigars and those covered tobacco products that do not contain nicotine)	Manufacturers, importers, distributors, and retailers who direct their own advertising: Advertisements must bear the addictiveness warning August 10, 2018 Manufacturers cannot manufacture products with non-compliant packages August 10, 2018 Manufacturers cannot distribute such products irrespective of the date of manufacture September 11, 2018 Retailers cannot offer for sale, sell, distribute, or import products with non-compliant packages unless the retailer falls within the retailer safe harbor[4] August 10, 2018
Product packages and ads of covered tobacco products <u>that do not contain nicotine</u> may bear an alternative warning statement: • "This product is made from tobacco." • Manufacturers must submit to FDA a self-certification • For more information, visit FDA.gov and search for "extending authorities"	Covered tobacco products that do not contain nicotine	Manufacturers, importers, distributors, and retailers who direct their own advertising: Advertisements must bear the alternative warning August 10, 2018 Manufacturers cannot manufacture products with non-compliant packages August 10, 2018 Manufacturers cannot distribute such products irrespective of the date of manufacture September 11, 2018

[4] A retailer of any cigarette tobacco, roll-your-own tobacco, or covered tobacco products (other than cigars) will not be in violation of this section for packaging that: (i) Contains a health warning; (ii) Is supplied to the retailer by the tobacco product manufacturer, importer, or distributor who has the required state, local, or Alcohol and Tobacco Tax and Trade Bureau (TTB)-issued license or permit, if applicable; and (iii) Is not altered by the retailer in a way that is material to the requirements of this section. 21 C.F.R §1143(a)(3)(ii).

		Retailers cannot offer for sale, sell, distribute, or import products with non- compliant packages unless the retailer falls within the safe harbor[5] August 10, 2018
Rotational cigar warning statements on product packages and ads (21 C.F.R. § 1143.5) • Cigar product packages and ads must contain warnings that follow size format, rotational, and distribution requirements • For more information, visit FDA.gov and search for "extending authorities"	Cigars	Manufacturers, importers, distributors, and retailers who direct their own advertising: Advertisements must bear one of the required warnings August 10, 2018 Manufacturers cannot manufacture products with non-compliant packages August 10, 2018 Manufacturers cannot distribute such products beginning irrespective of the date of manufacture September 11, 2018 Retailers cannot offer for sale, sell, distribute, or import products with non-compliant packages unless the retailer falls within the safe harbor[6] August 10, 2018

[5] A retailer of any covered tobacco products that do not contain nicotine and may bear the alternative warning statement will not be in violation of this section for packaging that: (i) Contains a health warning; (ii) Is supplied to the retailer by the tobacco product manufacturer, importer, or distributor who has the required state, local, or Alcohol and Tobacco Tax and Trade Bureau (TTB)-issued license or permit, if applicable; and (iii) Is not altered by the retailer in a way that is material to the requirements of this section.

[6] A cigar retailer will not be in violation of this section for packaging that: (i) Contains a health warning; (ii) Is supplied to the retailer by the tobacco product manufacturer, importer, or distributor who has the required state, local, or Alcohol and Tobacco Tax and Trade Bureau (TTB)-issued license or permit, if applicable; and (iii) Is not altered by the retailer in a way that is material to the requirements of this section.

Point-of-sale warning statement requirement for cigars sold individually without packaging (21 C.F.R. § 1143.5(a)(3)) • Specific placement and formatting requirements • Sign must bear all six required warnings • For more information, visit FDA.gov and search for "extending authorities"	Cigars sold individually without packaging	August 10, 2018
Cigar warning plans on how warnings will be randomly displayed and distributed on packages and rotated on advertisements must be submitted to and approved by FDA (21 C.F.R. § 1143.5(c)(1)) For more information, visit FDA.gov and search for "extending authorities"	Cigars	August 10, 2017

Premarket Review Requirements

Compliance Period	Products Affected	Compliance Date Under this Guidance
Compliance period for manufacturers to submit a substantial equivalence exemption request (§910 of the FD&C Act) For more information, visit FDA.gov and search for "substantial equivalence"	New,[7] newly deemed finished tobacco products[8 9] that were on the market as of August 8, 2016	August 8, 2021 (combustible tobacco products) August 8, 2022 (noncombustible tobacco products)
Compliance period for manufacturers to submit a substantial equivalence report (§910 of the FD&C Act) For more information, visit FDA.gov and search for "substantial equivalence"	New, newly deemed finished tobacco products[10] that were on the market as of August 8, 2016	August 8, 2021 (combustible tobacco products) August 8, 2022 (noncombustible tobacco products)
Compliance period for manufacturers to submit a premarket tobacco product application (PMTA) (§905 of the FD&C Act) For more information, visit FDA.gov and search for "premarket tobacco product applications"	New, newly deemed finished tobacco products[11] that were on the market as of August 8, 2016	August 8, 2021 (combustible tobacco products) August 8, 2022 (noncombustible tobacco products)

7 A "new tobacco product" is any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007, or any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007. §910(a)(1) of the FD&C Act.

8 FDA has defined "finished tobacco product" as a tobacco product, including all components and parts, sealed in final packaging intended for consumer use (e.g., filters or filter tubes sold separately to consumers or as part of kits).

9 Note that while the deeming rule extends FDA's tobacco product authority to all tobacco products (except for accessories of newly deemed tobacco products), FDA intends to limit enforcement of the premarket authorization requirements to newly regulated finished tobacco products at this time.

10 Note that while the deeming rule extends FDA's tobacco product authority to all tobacco products (except for accessories of newly deemed tobacco products), FDA intends to limit enforcement of the premarket authorization requirements to newly regulated finished tobacco products at this time.

11 Note that while the deeming rule extends FDA's tobacco product authority to all tobacco products (except for accessories of newly deemed tobacco products), FDA intends to limit enforcement of the premarket authorization requirements to newly regulated finished tobacco products at this time.

Other Provisions

Provision	Products Affected	Compliance Date Under this Guidance
Registration of establishments engaged in the manufacture, preparation, compounding, or processing of a tobacco product and product listings (§905(b), (c), (d), (h), and (i)(1) of the FD&C Act)	Newly deemed finished tobacco products[12]	For entities engaged in the manufacture, preparation, compounding, or processing of tobacco products in the United States prior to August 8, 2016, and continuing operations after August 8, 2016: October 12, 2017 For entities first engaging in the manufacture, preparation, compounding, or processing of tobacco products in the United States on or after August 8, 2016: **Immediately upon first engaging in the manufacturing of a tobacco product**
Ingredient listing (§904(a)(1) of the FD&C Act) For more information, visit FDA.gov and search for "tobacco ingredients"	Newly deemed finished tobacco products[13]	For products on the market on August 8, 2016: **May 8, 2018,** or **November 8, 2018** for small-scale tobacco product manufacturers[14] For products entering the market after **August 8, 2016:** 90 days prior to marketing

[12] Note that while the deeming rule extends FDA's tobacco product authority to all tobacco products (except for accessories of newly deemed tobacco products), FDA intends to limit enforcement of the registration and product listing requirements to newly regulated finished tobacco products at this time.

[13] Note that while the deeming rule extends FDA's tobacco product authority to all tobacco products (except for accessories of newly deemed tobacco products), FDA intends to limit enforcement of the ingredient listing requirements to newly regulated finished tobacco products at this time.

[14] FDA considers "small-scale tobacco product manufacturers" to be a manufacturer of any regulated tobacco product with 150 employees or fewer and annual total revenues of $5,000,000 or less.

[15] These compliance dates apply to all firms regardless of whether the manufacturer or importer is in an area impacted by recent natural disasters, as described in the October 2017 edition of this guidance.

Other Provisions (Continued)

Provision	Products Affected	Compliance Date Under this Guidance
Harmful and potentially harmful constituents (HPHCs) (§904 and 915 of the FD&C Act) For more information, visit FDA.gov and search for "HPHC"	Newly deemed finished tobacco products[16]	November 8, 2019 or For products entering the market after November 8, 2019: 90 days prior to marketing
Tobacco health documents (§904(a)(1) and (4) of the FD&C Act) For more information, visit FDA.gov and search for "tobacco health documents"	Newly deemed finished tobacco products[17]	November 8, 2017, for small-scale tobacco product manufacturers[18] or May 8, 2018, for small-scale tobacco product manufacturers in areas impacted by recent natural disasters[19]
Prohibition on the introduction into interstate commerce of products that contain "light," "low," "mild," or other similar descriptors in the label, labeling, or advertising of such products without a modified risk tobacco product order in effect (§911 of the FD&C Act) For more information, visit FDA.gov and search for "modified risk"	All newly deemed tobacco products	Stop manufacturing: November 8, 2017 Stop distribution into interstate commerce: December 8, 2017

[16] Note that while the deeming rule extends FDA's tobacco product authority to all tobacco products (except for accessories of newly deemed tobacco products), FDA intends to limit enforcement of the HPHC reporting requirements to newly regulated finished tobacco products at this time.

[17] Note that while the deeming rule extends FDA's tobacco product authority to all tobacco products (except for accessories of newly deemed tobacco products), FDA intends to limit enforcement of the tobacco health document submission requirements to newly regulated finished tobacco products at this time.

[18] FDA considers "small-scale tobacco product manufacturers" to be a manufacturer of any regulated tobacco product with 150 employees or fewer and annual total revenues of $5,000,000 or less. The compliance deadline for submission of tobacco health documents for entities other than small-scale tobacco product manufacturers has already passed (February 8, 2017) and is not affected by the extension announced in this guidance.

[19] For a complete list complete list of the areas that have been impacted by recent natural disasters, please visit https://www.fda.gov/TobaccoProducts/NewsEvents/ucm579265.htm.

Tobacco products will be considered foreign-grown tobacco[20]	All newly deemed tobacco	August 10, 2018
All required label and labeling statements must be prominent and in such terms that render it likely to be read and understood (§903(a)(3) of the FD&C Act)	All newly deemed tobacco products	November 8, 2017

[20] FDA issued a Draft Guidance titled "Interpretation of and Compliance Policy for Certain Label Requirement; Applicability of Certain Food, Drug, and Cosmetic Act Requirements to Vape Shops," which included a proposed compliance policy relating this requirement (pp. 5-6). This compliance policy would apply to all tobacco products.

DOCUMENT HISTORY

May 2017 – First edition of guidance issued.

August 2017 – *Three-Month Extension of Certain Compliance Deadlines Related to the Final Deeming Rule* is revised to reflect changes to premarket review compliance policy related to "deemed" tobacco products. Specific revisions include the following:

- Title – Removal of "Three-Month" to reflect the inclusion of extended compliance deadlines for premarket review policy.
- Section II – Added explanation of extension of compliance policies included in May 2017 first edition of guidance.
- Section III.A – Added explanation of previous premarket review compliance policy and summary of revised premarket review compliance policy for deemed tobacco products.
- Section III.B – Updated chart to include revised premarket review compliance policy, and third column revised from "new compliance date" to "compliance date under this guidance" to provide additional clarity.

October 2017 — (1) Revised compliance date for "Registration of establishments engaged in the manufacture, preparation, compounding, or processing of a tobacco product and product listings" to reflect the date extension found in the "Registration and Product Listing for Owners and Operators of Domestic Tobacco Product Establishments" guidance issued in September 2017; (2) Revised compliance date for "Ingredient listing" to provide a six-month extension for tobacco product manufacturers and importers impacted by recent natural disasters; and (3) Revised compliance date for "Tobacco health documents" to provide a six-month extension for tobacco product manufacturers and importers in areas impacted by recent natural disasters.

November 2017 --- Revised compliance date for "Ingredient listing" to provide a six-month extension for all tobacco product manufacturers and importers, regardless of whether the manufacturer or importer is in an area impacted by recent natural disasters, as described in the October 2017 edition of this guidance.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 1132

[Docket No. FDA–2016–N–2527]

Tobacco Product Standard for N-Nitrosonornicotine Level in Finished Smokeless Tobacco Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing a tobacco product standard that would establish a limit of N-nitrosonornicotine (NNN) in finished smokeless tobacco products. FDA is taking this action because NNN is a potent carcinogenic agent found in smokeless tobacco products and is a major contributor to the elevated cancer risks associated with smokeless tobacco use. Because products with higher NNN levels pose higher risks of cancer, FDA finds that establishing a NNN limit in finished smokeless tobacco products is appropriate for the protection of the public health.

DATES: Submit either electronic or written comments on the proposed rule by April 10, 2017. In accordance with 21 CFR 10.40(c), in finalizing this rulemaking FDA will review and consider all comments submitted before the time for comment on this proposed regulation has expired. If your comment is submitted after the expiration of the comment period, it will not be reviewed and considered by FDA unless you apply for, and receive, an extension of the comment period pursuant to 21 CFR 10.40(b)(3). Submit comments on information collection issues under the Paperwork Reduction Act of 1995 (the PRA) by February 22, 2017, (see the ''Paperwork Reduction Act of 1995'' section). See section VII of this document for the proposed effective date of a final ruled based on this document.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

• *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *http://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 *http://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):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

• For written/paper comments submitted to the Division of Dockets Management, 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–2016–N–2527 for ''Tobacco Product Standard for N-nitrosonornicotine Level in Finished Smokeless Tobacco Products.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *http://www.regulations.gov* or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *http://www.regulations.gov.* Submit both copies to the Division of Dockets Management. 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: *http://www.fda.gov/regulatoryinformation/dockets/default.htm.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *http://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 Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Submit comments on information collection issues to the Office of Management and Budget in the following ways:

• Fax to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–7285, or email to *oira_submission@omb.eop.gov.* All comments should be identified with the title, Tobacco Product Standard: NNN Level in Finished Smokeless Tobacco Products.

FOR FURTHER INFORMATION CONTACT: Beth Buckler or Colleen Lee, Office of Regulations, Center for Tobacco Products (CTP), Food and Drug Administration, Document Control Center, Bldg. 71, Rm. G335, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002, 877–287–1373, *CTPRegulations@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing a tobacco product standard that would establish a limit of NNN in finished smokeless tobacco products sold in the United States. NNN is a potent carcinogenic agent found in smokeless tobacco products and is a major contributor to the elevated cancer risks associated with smokeless tobacco use. By FDA's estimates, in the 20 years following implementation of the proposed product standard, approximately 12,700 new cases of oral cancer and approximately 2,200 oral cancer deaths would be prevented in the United States because of this rule. Moreover, during that 20-year period, FDA estimates that approximately 15,200 life years would be gained as a result of the proposed standard. Because oral cancer is associated with significant health and economic impacts, we expect positive public health benefits due to prevention of new and fatal cancer cases. For the reasons discussed in the preamble of this rule, FDA finds that the proposed standard would be appropriate for the protection of the public health.

B. Summary of the Major Provisions of the Proposed Rule

This proposed rule would establish a limit of NNN in finished smokeless tobacco products. Under the proposed rule, no person may manufacture, distribute, sell, or offer for distribution or sale within the United States a finished smokeless tobacco product that is not in compliance with the product standard. However, the proposed rule would provide an exception for tobacco retailers and distributors; we would not consider tobacco retailers and distributors to be in violation of part 1132 as it relates to the sale or distribution of finished smokeless tobacco products that exceed the allowed NNN level if they meet certain criteria set forth in the rule.

The proposed rule would require that the mean level of NNN in any batch of finished smokeless tobacco products not exceed 1.0 microgram per gram (µg/g) of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by specified product testing. The rule would require that all finished smokeless tobacco products have an expiration date and provide that the expiration date be no later than the final date the manufacturer can demonstrate that the NNN level in the finished smokeless tobacco product conforms to the limit when the product is stored under its intended conditions (*e.g.,* room temperature or refrigeration).

To ensure that products conform to the product standard, the proposed rule would establish requirements for testing the products. Two types of testing would be required for smokeless tobacco products—stability testing and batch testing. Stability testing would be required to assess the stability of the NNN level in the finished smokeless tobacco products and to establish and verify the product's expiration date and storage conditions. In addition, each batch of finished smokeless tobacco product would be required to be tested to determine whether the products conform to the proposed NNN level. The proposed rule would also establish the standard test method (to be incorporated by reference) and requirements for using an alternative test method as well as the sampling requirements for all testing.

The proposed rule would require that the labels of finished smokeless tobacco products contain a manufacturing code, expiration date, and, if applicable, storage conditions for the finished smokeless tobacco product (such as refrigeration). In addition, the proposed rule would require manufacturers of finished smokeless tobacco products to establish and maintain certain records.

C. Legal Authority

This proposed rule is being issued upon FDA's authority to establish a tobacco product standard under section 907 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387g) including authority related to the reduction of constituents or harmful components in tobacco products under section 907(a)(4)(A)(ii) and to the testing of tobacco products under section 907(a)(4)(B)(ii) through (iv); FDA's authorities related to the sale and distribution of tobacco products under sections 907(a)(4)(B)(v) and 906(d); FDA's authority to require tobacco product manufacturers to establish and maintain records under section 909 of the FD&C Act (21 U.S.C. 387i); FDA's authorities related to adulterated and misbranded tobacco products under sections 902 and 903 (21 U.S.C. 387b and 387c); FDA's authorities related to prohibited acts under section 301 of the FD&C Act (21 U.S.C. 331); and FDA's rulemaking and inspection authorities under sections 701 and 704 of the FD&C Act (21 U.S.C. 371 and 374).

D. Costs and Benefits

The costs of the proposed rule, when finalized, will be due to affected entities ensuring that the smokeless tobacco products comply with the proposed product standard. We have estimated the annualized costs associated with the proposed rule over 20 years to be between $17.91 million and $42.72 million using a 3 percent discount rate, with a primary value of $30.31 million, and between $20.11 million and $50.57 million, with a primary value of $35.34 million using a 7 percent discount rate. The primary estimate for the present value of total quantified costs over 20 years is approximately $450.97 million at a 3 percent discount rate and $374.36 million at a 7 percent discount rate.

NNN is a carcinogenic agent found in smokeless tobacco products. As described in the preamble of the proposed rule, on the basis of the available scientific evidence, FDA has determined that NNN is the predominant driver of excess oral cancer risk among smokeless tobacco users. We quantify benefits associated with the proposed rule in the form of reduced oral cancer morbidity and mortality attributable to smokeless tobacco. As described in section V.A.3 of the preamble of the proposed rule, we also expect the standard to reduce the risk of esophageal cancer, and it may reduce the risks of other cancers such as pancreatic, laryngeal, prostate, and lung cancer. However, there is more limited information to directly quantify these health benefits. As such, we only consider estimated reductions in oral cancer as the quantified benefit of the proposed product standard.

Most of the estimated benefits arise from quality life-years gains gained from reduced oral cancer mortality. The

annualized value over 20 years of quality adjusted life-years gained from reduced oral cancer mortality ranges from $228.66 million to $2.46 billion at a 3 percent discount rate, with a primary value of $858.46 million. Using a 7 percent discount rate, the annualized value of quality life-years gained from averted deaths ranges from $182.01 million to $1.96 billion, with a primary value of $683.34 million. The primary estimate of the present value of mortality reductions quantified over 20 years is $12.77 billion at a 3 percent discount rate and $7.24 billion at a 7 percent discount rate. The annualized value over 20 years of quality adjusted life-years gained from reduced oral cancer mortality and morbidity ranges from approximately $283.95 million to $3.05 billion at a 3 percent discount rate, with a primary value of $1.06 billion, and approximately $246.40 million to $2.65 billion, with a primary value of $0.92 billion at a 7 percent discount rate. The primary estimate of the present value of total quantified benefits over 20 years is approximately $15.86 billion at a 3 percent discount rate and $9.80 billion at a 7 percent discount rate for reductions in oral cancer alone. These values are likely an underestimate of the benefits associated with the proposed rule, as we do not quantify reductions in mortality and morbidity from cancers other than oral cancer. Costs and benefits are summarized in table 8 of the preamble of the proposed rule.

II. Background Information

A. Purpose

FDA is issuing this proposed rule to address the harm caused by the toxicant NNN in smokeless tobacco products. When Congress enacted the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) in 2009, it included the finding that ''the Food and Drug Administration is a regulatory agency with the scientific expertise to identify harmful substances in products to which consumers are exposed, [and] to design standards to limit exposure to those substances'' (section 2(44) of the Tobacco Control Act).

Smokeless tobacco products, including those currently marketed in the United States, have been demonstrated to cause certain types of cancer. Several authoritative reviews have been conducted on the relationship between smokeless tobacco use and cancer risk and have reached similar conclusions (Refs. 1, 2, 3, 4). The International Agency for Research on Cancer (IARC) concluded in its 2007 monograph ''Smokeless Tobacco and Some Tobacco-Specific Nitrosamines'' that there is sufficient evidence in humans to indicate that smokeless tobacco is carcinogenic and that it causes oral and pancreatic cancer (Ref. 1). IARC confirmed these findings of the carcinogenicity of smokeless tobacco in a 2012 review, concluding that there is sufficient evidence in both humans and experimental animal studies that smokeless tobacco causes oral, esophageal, and pancreatic cancer (Ref. 2). In addition, a 2014 report on smokeless tobacco by the National Cancer Institute (NCI) and Centers for Disease Control and Prevention (CDC) estimated that smokeless tobacco use is responsible for approximately 1,600 new cases of oral cancer, 200 cases of esophageal cancer, and 500 cases of pancreatic cancer in the United States each year (Ref. 4).

NNN [1] is a potent carcinogenic agent found in smokeless tobacco products and is a major contributor to the elevated cancer risks associated with smokeless tobacco use (see section IV, Rationale for Developing a Standard for NNN, of this document). NNN levels vary substantially across subcategories of smokeless tobacco products (*e.g.,* moist snuff, chewing tobacco, dry snuff) and within product subcategories (*e.g.,* moist snuff) (Ref. 5, 10). International comparisons of oral cancer rates and smokeless tobacco products suggest that products with higher NNN levels may pose higher risks of cancer (Refs. 6, 100). FDA is using its authority to propose a standard that would reduce tobacco-related harms by establishing a limit of NNN in smokeless tobacco products sold in the United States (see section V of this document).

FDA is proposing that the standard would apply to finished smokeless tobacco products. Although NNN is also found in other tobacco products, this rule focuses solely on NNN levels in smokeless tobacco products, and not on additional products. Different measures are required to evaluate the contribution to cancer of NNN among users of other tobacco products, such as combustible products like cigarettes and dissolvable tobacco products that do not meet the statutory definition of ''smokeless tobacco product.'' For example, additional factors, such as polycyclic aromatic hydrocarbons (PAH), aldehydes and other chemicals (Refs. 147, 106), contribute to the cancer burden associated with combustible products, which make the relationship between NNN and cancer in these products different from that in smokeless tobacco products. With regard to dissolvable tobacco products that do not meet the statutory definition of smokeless tobacco, different product testing methods than the ones developed and available for smokeless tobacco, as described in this proposal, may be necessary to evaluate NNN in these products because they do not consist of cut, ground, powdered or leaf tobacco. Therefore, at this stage, FDA has chosen to focus on smokeless tobacco and has evaluated data relevant to establishing an NNN limit in smokeless tobacco products.

This proposed product standard would require that the mean level of NNN in any batch of finished smokeless tobacco products not exceed 1.0 µg/g of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by testing in compliance with § 1132.12 (proposed § 1132.10). FDA expects that, in the 20 years following implementation of the proposed product standard, approximately 12,700 new cases of oral cancer and approximately 2,200 oral cancer deaths would be prevented in the United States because of this rule. Moreover, during that 20-year period, approximately 15,200 life years would be gained in the United States as a result of the proposed standard. We believe that the main source of variability in the estimated impacts would be different assumptions about oral cancer relative risks due to smokeless tobacco use. Using alternate relative risk estimates that are somewhat lower and higher than our main estimate results in approximately 7,300 to 24,000 new cases of oral cancer prevented and 1,300 to 4,200 oral cancer deaths prevented over the 20-year period. Because oral cancer is associated with significant health and economic impacts, we expect positive public health benefits due to prevention of new and fatal cancer cases. These benefits are discussed in detail in section V of this proposed rule. Accordingly, based on the information discussed in the following sections of the preamble to this proposed rule, FDA finds that the proposed standard would be appropriate for the protection of the public health.

B. Legal Authority

1. Product Standard

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 (Pub. L. 111–31; 123 Stat. 1776). Among

[1] Since 2012, manufacturers have been required to test and report to FDA the levels of harmful and potentially harmful constituents (HPHCs), including NNN, in each tobacco product (section 904(A)(3) of the FD&C Act).

the authorities provided to FDA is the authority to establish tobacco product standards. To establish a tobacco product standard, section 907(a)(3)(A) and (B) of the FD&C Act (21 U.S.C. 387g(a)(3)(A) and (B)) requires that we find that the standard is appropriate for the protection of the public health, taking into consideration scientific evidence concerning:

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

Section 907 of the FD&C Act authorizes FDA to promulgate tobacco product standards that are appropriate for the protection of the public health, including provisions, where appropriate, for the reduction or elimination of constituents or harmful components of tobacco products (section 907(a)(4)(A)(ii) of the FD&C Act). This proposed rule would limit the level of NNN in finished smokeless tobacco products. To ensure that finished smokeless tobacco products comply with the proposed NNN level, FDA also is including provisions to require that tobacco product manufacturers test their products on a sample basis (*i.e.,* batch testing) using a specified testing procedure for conformance with the limit 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) states that product standards must, where appropriate for the protection of public health, include provisions requiring that the sale and distribution of the 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). 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 sales and distribution 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 along with section 701, which provides FDA with the authority to ''promulgate regulations for the efficient enforcement of this Act,'' FDA is including provisions to restrict the manufacture, sale, and distribution of finished smokeless tobacco products that are not in compliance with this standard. Specifically, FDA is proposing to require that no person may manufacture, distribute, sell, or offer for distribution or sale within the United States a finished smokeless tobacco product that is not in compliance with part 1132 (proposed § 1132.1(b)). However, tobacco retailers and distributors would not be considered in violation of part 1132 as it relates to the sale or distribution or offer for sale or distribution of finished smokeless tobacco products that exceed the NNN level required in proposed § 1132.10 if they: (1) Store and transport the finished smokeless tobacco products according to the package label, (2) do not sell or distribute or offer for sale or distribution finished smokeless tobacco products past their expiration date, except to return expired products to the manufacturer, (3) do not conceal, alter or remove the expiration date or storage conditions on the package label, and (4) do not sell or distribute or offer for sale or distribution finished smokeless tobacco products that are open or have broken seals (proposed § 1132.1(c)). FDA is proposing this exception for tobacco retailers and distributors because they are not in a position to know or to confirm by testing whether the smokeless tobacco products they are selling or distributing or offering for sale or distribution comply with the proposed NNN level.

FDA is also proposing, under these authorities, to require that the labels of finished smokeless tobacco products contain a manufacturing code, expiration date, and, if applicable, storage conditions for the finished smokeless tobacco product (proposed § 1132.30). The labeling requirement for storage conditions is also consistent with FDA's authority under section 907(a)(4)(C), which provides that a product standard shall, where appropriate, require the use and prescribe the format and content of labeling for the proper use of the tobacco product. These label requirements would enable FDA to determine whether a product on store shelves purports to comply with the standard, link the product to its manufacturing history so that compliance with the standard can be verified, provide traceability of the product in the event of a nonconforming product investigation and corrective action, and ensure that the product is handled and stored under appropriate conditions, in accordance with the standard. In addition, the proposed manufacturing code would serve as a common identifier that will provide a history of the manufacturing, processing, packaging, labeling, holding, and initial distribution of the tobacco product from records maintained by the smokeless tobacco product manufacturer. The expiration date would also inform retailers that the manufacturer has not demonstrated compliance with the standard beyond the date after which the product should not be sold to consumers.

Manufacturers would be responsible for ensuring that finished smokeless tobacco products contain labels with a manufacturing code, expiration date, and, if applicable, storage conditions prior to sale and commercial distribution. In addition, retailers and distributors would be responsible for not selling or distributing or offering for sale or distribution finished smokeless tobacco products that lack the required labels, not concealing, altering, or removing the expiration date or storage conditions on the package label, not selling or distributing or offering for sale or distribution finished smokeless tobacco products after their expiration date (except to return expired product to the manufacturer), not selling or distributing or offering for sale or distribution finished tobacco products that are open or have broken seals, and, if applicable, storing finished smokeless tobacco product in accordance with the package label.

Because these requirements would assist FDA in enforcing the standard and would ensure that manufacturers and retailers are selling product that complies with the standard, the Agency has found all of these requirements to be appropriate for the protection of the public health consistent with sections 907(a)(4)(B)(v) and 906(d).

4. Testing Requirements

FDA's proposed rule contains provisions regarding testing requirements under sections

907(a)(4)(B) and 907(a)(4)(A)(iii) of the FD&C Act to ensure that finished smokeless tobacco products conform to the requirements of the product standard before they are distributed to consumers and remain in conformance until their expiration date. Section 907(a)(4)(B)(ii) provides that a product standard must, where appropriate for the protection of public health, include ''provisions for the testing (on a sample basis or, if necessary, on an individual basis) of the tobacco product.'' In addition, section 907(a)(4)(B)(iv) provides that, where appropriate for the protection of public health, a product standard must include provisions requiring that the results of the tests of the tobacco product required under section 907(a)(4)(B)(ii) show that the product is in conformity with the portions of the standard for which the tests were required.

Consistent with these statutory provisions, proposed §§ 1132.12, 1132.14, 1132.16, and 1132.18 would establish product testing and sampling plan requirements. Proposed § 1132.12 would require two types of testing for smokeless tobacco products—stability testing and batch testing. Proposed § 1132.12(a) would require testing to assess the stability of the NNN level in finished smokeless tobacco products and to establish and verify the product's expiration date and storage conditions (either room temperature or refrigeration). Proposed § 1132.12(b) would require manufacturers to conduct testing on each batch of finished smokeless tobacco product to determine whether the products conform to the proposed NNN level. Proposed § 1132.12(c) would require the tobacco product manufacturer to document all testing. Proposed §§ 1132.14 and 1132.16 would establish the standard and alternative test methods, while § 1132.18 would establish the sampling requirements for all testing.

Section 907(a)(4)(A)(iii) states that product standards must include provisions that are appropriate for the protection of the public health, including provisions, where appropriate, relating to any requirement under subparagraph 907(a)(4)(B). As discussed, FDA is proposing specific testing requirements in §§ 1132.12, 1132.14, 1132.16, and 1132.18. To support these proposed requirements, proposed § 1132.22(b) would require that if the mean of the representative samples from any batch of a finished smokeless tobacco product is determined to be out of conformance with the requirements of § 1132.10, or a finished smokeless tobacco product's expiration date must be shortened due to the results of annual real-time stability testing, or if FDA notifies a tobacco product manufacturer that a distributed finished smokeless tobacco product does not conform to the requirements of part 1132, the manufacturer would have to conduct an investigation to determine the scope of the nonconformity and locations to which nonconforming 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 additional nonconforming product batches are not distributed to consumers and to prevent future nonconformity.

FDA finds that such provisions are appropriate for the protection of the public health and relate to requirements under section 907(a)(4)(B) because they will help to ensure that the finished smokeless tobacco products are properly tested and conform to the requirements of the proposed product standard.

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. In addition, section 701(a) of the FD&C Act authorizes FDA to promulgate regulations for the efficient enforcement of the FD&C Act. The recordkeeping requirements would help FDA with the efficient enforcement of the product standard issued under the FD&C Act.

FDA is proposing to require that manufacturers of smokeless tobacco products maintain records regarding the product testing (*i.e.,* stability and batch testing), including a full report of the source data and results; all notifications of an alternative test method and source data for alternative test method validation; all sampling plans and reports; documentation that the persons performing sampling have sufficient education, training, and experience to accomplish the assigned functions; all identification, investigation, segregation, and disposition procedures; and all nonconforming product investigations and rework (*i.e.,* the processing of nonconforming finished smokeless tobacco products to meet the requirements of part 1132).

FDA is also proposing to require copies of all records be retained for a period of not less than 4 years from the date of distribution of the finished smokeless tobacco product that is the subject of the record, except that certain records relating to alternative test methods would be required to be retained for a period of not less than 4 years after the last date the method is used. Retention of these records would help ensure that finished smokeless tobacco products are in conformance with the proposed standard and are not adulterated or misbranded.

C. Additional Considerations and Requests for Comment

1. 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, or other component of a tobacco product because FDA has found that the additive, constituent, or other component is or may be harmful, scientific evidence submitted that demonstrates 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 (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 information regarding structuring the standard so as not to advantage foreign-grown tobacco over domestically grown tobacco (section 907(c)(2)(C)). In addition, FDA invites the Secretary of Agriculture to provide any information or analysis which the Secretary of Agriculture believes is relevant to the proposed tobacco product standard (section 907(c)(2)(D) of the FD&C Act).

FDA is requesting the documents and information described in this section with this proposed rule. 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 the Agency 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 for good cause made before the expiration of the comment period. If FDA opts to refer this proposed regulation to TPSAC, the Agency will publish a notice in the **Federal Register** announcing the TPSAC meeting to discuss this proposal.

2. Pathways to Market

To legally market a new tobacco product in the United States, a tobacco product manufacturer must receive authorization from FDA permitting the marketing of the new tobacco product under one of three pathways for legally marketing a new tobacco product: (1) The manufacturer obtains an order under section 910(c)(1)(A)(i) of the FD&C Act (order after review of a premarket tobacco application under section 910(b)); (2) the manufacturer obtains an order finding the new product 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); or (3) the manufacturer makes a request under 21 CFR 1107.1, obtains an exemption from the requirements related to substantial equivalence (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 (j)(1)(B).

A smokeless tobacco product that has been modified to comply with the product standard would be a ''new tobacco product'' and subject to premarket review. FDA believes that changes made solely to bring a smokeless tobacco product in compliance with the proposed rule would be appropriate for an SE submission. We believe it is possible for manufacturers to modify their product so that it is both in compliance with the proposed product standard and substantially equivalent to an appropriate predicate product (*i.e.,* products that are grandfathered or SE).

FDA believes that manufacturers would likely choose to comply with the proposed standard in a manner that makes the modified products eligible for the SE pathway. For products that are eligible for an SE report, FDA is considering whether a change to the level of NNN in smokeless tobacco products could be reviewed with the submission of an SE report containing a reduced, specific set of information that focuses on the changes to the smokeless tobacco where the SE report demonstrates that the only modifications made to the new product were made to comply with the NNN product standard and do not present different questions of public health (*e.g.,* significant increase in another harmful or potentially harmful constituent (HPHC)). As there may be multiple modifications needed to comply with the product standard, FDA requests comments as to the type of modifications that may allow a reduced amount of information to proceed through the SE pathway, and what types of brief, specific supporting information submitted as part of a substantial equivalence application could demonstrate that modifications made to comply with this product standard do not cause the new product to raise different questions of public health.

III. Scope of Proposed Standard

Scientific evidence documents that smokeless tobacco products cause certain types of cancer (Refs. 1, 2, 3, 4). As discussed in section IV of this document, NNN is a potent carcinogenic agent found in smokeless tobacco products and is a major contributor to the elevated cancer risks associated with smokeless tobacco use (Refs. 7, 8, 1, 2).

FDA is issuing this proposed standard to address the harm to smokeless tobacco users caused by NNN by establishing a limit for NNN in finished smokeless tobacco products (see proposed § 1132.10), thereby reducing exposure to this harmful toxicant. NNN levels vary substantially across subcategories of smokeless tobacco products (*e.g.,* moist snuff, chewing tobacco, dry snuff) and within product subcategories (*e.g.,* moist snuff) (Ref. 5). Geographical comparisons show that oral cancer rates among smokeless tobacco users are higher in areas where smokeless tobacco products have higher NNN levels (Refs. 6, 100). Given this geographic variation and the toxicological evidence described in the preamble of this rule, we expect that lowering the level of NNN in smokeless tobacco products in the United States will lower the rate of oral cancers among smokeless tobacco users. FDA concludes that establishing a limit for NNN in finished smokeless tobacco products is appropriate for the protection of the public health (see section V of this document).

A. Smokeless Tobacco Products

The term ''smokeless tobacco'' covers a wide range of tobacco products that are used orally or nasally without combustion (Ref. 1). Smokeless tobacco is defined in section 900(18) of the FD&C Act as ''any tobacco product that consists of cut, ground, powdered, or leaf tobacco and that is intended to be placed in the oral or nasal cavity.'' This includes moist snuff, snus, dry snuff, chewing tobacco, and some dissolvables. Some dissolvable tobacco products do not meet the statutory definition of ''smokeless tobacco product'' because they do not contain cut, ground, powdered, or leaf tobacco; instead, these products contain nicotine extracted from tobacco. Dissolvable products that do not meet the statutory definition of ''smokeless tobacco product'' are not covered by this proposed rule.

Moist snuff is the most popular type of smokeless tobacco in the United States (Refs. 4, 131). It is typically made of fire-cured or air-cured tobacco that has been finely ground or shredded and fermented (Ref. 4). Moist snuff may contain up to 60 percent moisture and it is often flavored (*e.g.,* wintergreen) (Refs. 4, 10). It is sold as loose tobacco or in sachets or small pouches (Ref. 1). When loose moist snuff is used, a small amount (*e.g.,* a pinch or dip) is placed and held between the lip or cheek and gum and typically is held in the mouth for at least 30 minutes (Refs. 1, 5). Excess saliva may be spit out or swallowed (Ref. 1). When pouched moist snuff is used, a sachet or small pouch containing the tobacco is placed and held between the lip or cheek and gum but it does not require spitting (Ref. 9).

Snus is a type of moist snuff and it can have different characteristics depending on where it is manufactured. Swedish snus products generally have much lower levels of tobacco-specific nitrosamines (TSNAs) than smokeless tobacco products found in the United States (Refs. 5, 6, 10), and, therefore, they were of particular interest in the development of this proposed rule.

Swedish snus is commonly used in Sweden but it is relatively new to the U.S. market (Refs. 4, 11). It typically consists of low-nitrosamine tobacco that has been air-cured, moistened, ground, and heat treated (Refs. 4, 12, 11). Swedish snus may contain up to 50 percent moisture and some flavoring but no added sugars (Refs. 13, 14, 11). Swedish snus is sold as loose tobacco or in sachets (Refs. 4, 12, 11). It is placed between the cheek and gum and does not require spitting (Refs. 1, 15).

In Sweden, all snus manufacturers must adhere to the requirements of the Swedish Food Act. In addition, a smokeless tobacco manufacturer developed the GothiaTek voluntary standard, which establishes limits for the tobacco (*e.g.,* low-nitrosamine raw tobacco that has been air-cured or sun-cured) and other ingredients as well as the manufacturing process (Refs. 11, 4). The current GothiaTek standard for NNN and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (combined) in snus is 0.95 µg/g wet weight [2] tobacco, which would be about 2 µg/g (combined NNN and NNK) dry weight tobacco (Refs. 13, 16). Swedish snus that is made using the GothiaTek standard tends to have lower levels of toxicants, including NNN, than other smokeless tobacco products in other countries (Ref. 4).

Swedish snus is usually refrigerated by retailers to maintain its quality and taste but refrigeration is not generally required to maintain stability because modern Swedish snus production techniques achieve very low levels of microbial activity and yield no new nitrosamine formation even when held at room temperature (Ref. 11). One of the methods used to limit microbial activity is pasteurization. In this process, the leaf tobacco is ground and subjected to heat treatment. The heating is achieved by combining the tobacco with water and salt, placed in closed process blenders, and using steam to achieve temperatures up to 80 to 100 °C for several hours (Ref. 11).

In recent years, some U.S. tobacco manufacturers began introducing snus products (*e.g.,* Marlboro Snus and Camel Snus) in the United States (Ref. 17). Some of the early marketing of these tobacco products emphasized the Swedish origins of snus but there is limited data available on whether the chemical composition or manufacturing processes of these products are equivalent to Swedish snus (Refs. 4, 18, 19). Studies indicate that early versions of these snus products would not comply with the current GothiaTek standard for NNN and NNK (*i.e.,* 0.95 µg/g per wet weight combined) (Ref. 13). From the limited information available, snus manufactured in the United States appears to consist of tobacco that has been air-cured or sun-cured and is pasteurized or heat treated (Refs. 20, 21). It may contain up to 34 percent moisture and may contain some flavoring, flavoring strip, and/or sweeteners (Ref. 4, 56). It is generally sold portioned in sachets or small pouches (Ref. 4).

Unlike the relatively higher moisture content of moist snuff, dry snuff usually has a moisture content of less than 10 percent (Ref. 1). Dry snuff is a powdered tobacco product that may be used orally or nasally, although nasal use is rare in the United States (Ref. 4). Typically dry snuff is made with tobacco that has been fire-cured, fermented, and finely ground or pulverized into a powder (Refs. 1, 4). A pinch or dip of dry snuff is typically held between the cheek and gum (Ref. 1).

Chewing tobacco is sold as loose leaf, plug, or twist. It is typically fire-cured or air-cured tobacco that has been fermented or aged (Refs. 4, 1). It may be flavored and sweetened and then processed into a plug, twist, or loose leaf (Refs. 4, 1). Chewing tobacco may be chewed or held in the mouth (*i.e.,* dipped) (Ref. 5).

Dissolvable tobacco products that are smokeless tobacco products are generally made of finely ground tobacco and sold as small lozenges, sticks (toothpick), or strips (Refs. 4, 5). Such dissolvable tobacco products may be flavored and may have a moisture content ranging from 1 to 20 percent, depending on the product (Refs. 9, 22, 56). As the name suggests, a dissolvable tobacco product is placed in the mouth until it dissolves.

B. Current Prevalence and Initiation Rates

In the United States, smokeless tobacco products are predominately used by men and high school age boys. According to the 2014 National Survey on Drug Use and Health, an estimated 8.7 million (3.3 percent) Americans aged 12 and over were current (any use in the past month) smokeless tobacco users (chewing tobacco or snuff) in 2014, which is generally similar to the percentage of smokeless tobacco users estimated by this study for most years from 2002 to 2013 (Ref. 23). An estimated 6.4 percent of males over the age of 12 were current smokeless tobacco users, while only 0.3 percent of females were current users (Ref. 24 at tables 2.9B, 2.10B). Among adults, the highest prevalence of current use of smokeless tobacco was observed among young adults aged 18 to 25 at 5.6 percent (Ref. 24 at 18). According to the National Youth Tobacco Survey, in 2015, there were an estimated 1.1 million middle and high school students that reported current (past 30 day) use of chewing tobacco, snuff or dip, snus, or dissolvable tobacco products (Ref. 25). The overall level of current smokeless tobacco product usage was 6 percent among high school students, and 1.8 percent among middle school students (Ref. 25). Among youth, the prevalence of smokeless tobacco use varies by sex and race. In 2015, 10 percent of male high school students reported current use of smokeless tobacco, including snus and dissolvables, compared with 1.8 percent of female high school students (Ref. 25). Among high school students, the prevalence of current use of smokeless tobacco, including snus and dissolvables, was highest among non-Hispanic White students (7.8 percent), followed by Hispanic students (4.8 percent), and non-Hispanic Black students (1.9 percent) (Ref. 25).

An estimated 1.0 million Americans aged 12 or older used smokeless tobacco for the first time in 2014 (Ref. 24 at table 4.5B). Nearly 75 percent of these new initiates were male and about 42 percent were under age 18 when they first used a smokeless tobacco product (Ref. 24 at tables 4.6B, 4.9A). The average age at first use of smokeless tobacco among recent initiates in 2014 was 19.0 years, which was similar to the 2013 estimate (Refs. 26, 24 at table 4.13B).

IV. Rationale for Developing a Standard for NNN

A. Smokeless Tobacco is Carcinogenic

The scientific evidence demonstrates that smokeless tobacco products cause certain types of cancer, and that cancer rates are higher in regions of the world where smokeless tobacco products have higher levels of NNN. In 1986, the Surgeon General of the United States released a report finding that ''users of smokeless tobacco products face a strongly increased risk of oral cancer'' (Ref. 27). In 2007, IARC classified smokeless tobacco as carcinogenic to humans (Group 1), concluding that sufficient evidence in humans demonstrate that smokeless tobacco causes cancers of the oral cavity and pancreas (Ref. 1). IARC confirmed these findings of the carcinogenicity of smokeless tobacco in a 2012 review, concluding that there is sufficient evidence in both humans and experimental animal studies that smokeless tobacco causes oral, esophageal, and pancreatic cancer (Ref. 2). The Scientific Committee on Emerging and Newly Identified Health Risks (Ref. 3) was tasked by the European Commission to evaluate the cancer risks of smokeless tobacco products, with particular attention to moist snuff, which, in the European Union is available only in Sweden, in the form of snus. It concluded in its

[2] The term ''wet weight'' refers to the weight of tobacco as used by the consumer, while the term ''dry weight'' refers to the weight of tobacco after the removal of water.

2008 review that smokeless tobacco products cause esophageal and pancreatic cancer in humans and that studies in the United States demonstrate an increased risk of oral cancer among smokeless tobacco users, however, the evidence for ''users of Swedish moist snuff (snus) is less clear'' (Ref. 3). More recently, the National Cancer Institute (NCI), National Institutes of Health, in coordination with the Centers for Disease Control and Prevention (CDC) published a report on smokeless tobacco use and health effects in 2014, concluding that smokeless tobacco use causes oral, esophageal, and pancreatic cancer (Ref. 4).

TABLE 1—CONCLUSIONS OF AUTHORITATIVE REVIEWS ON SMOKELESS TOBACCO AND CANCER RISK

Authoritative body	Year	Conclusions
Surgeon General of the United States.	1986	''In summary, users of smokeless tobacco products face a strongly increased risk of oral cancer, particularly for the tissues that come in contact with the tobacco.''
International Agency for Research on Cancer (IARC).	2007	''There is sufficient evidence in humans for the carcinogenicity of smokeless tobacco. Smokeless tobacco causes cancers of the oral cavity and pancreas.''
Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).	2008	''STP [smokeless tobacco products] are carcinogenic to humans and the pancreas has been identified as a main target organ. All STP cause localised oral lesions and a high risk for development of oral cancer has been shown for various STP but the evidence for oral cancer in users of Swedish moist snuff (snus) is less clear.''
International Agency for Research on Cancer (IARC).	2012	''There is sufficient evidence in humans for the carcinogenicity of smokeless tobacco. Smokeless tobacco causes cancers of the oral cavity, oesophagus and pancreas.''
National Cancer Institute (NCI)	2014	''There is sufficient evidence that ST [smokeless tobacco] products cause addiction, precancerous oral lesions, and cancer of the oral cavity, esophagus, and pancreas, and adverse reproductive and developmental effects including stillbirth, preterm birth, and low birth weight.''

B. NNN in Smokeless Tobacco Products is Carcinogenic

Smokeless tobacco products contain thousands of chemical constituents, including carcinogens such as TSNAs (Refs. 2, 1, 4). TSNAs are formed from nitrosation, a chemical reaction between tobacco alkaloids (nicotine, nornicotine, anatabine, and anabasine) and nitrosating agents such as nitrite (Refs. 28, 2). Because TSNAs are formed from tobacco alkaloids, they are only found in tobacco products (Ref. 28).

In smokeless tobacco, TSNAs are present at a level capable of causing cancer (Ref. 4). Of the five TSNAs identified in tobacco products, NNN and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) have been classified by IARC as carcinogenic to humans (Group 1) (Refs. 2, 4).[3]

The relatively high level of these carcinogens has led the World Health Organization (WHO) to call for limits on these constituents in tobacco products (Ref. 78). Tobacco science researchers have also called for the reduction of TSNAs in smokeless tobacco products due to their potential impact on the increased cancer risk associated with smokeless tobacco use (Refs. 175, 176).

1. Evidence for NNN Carcinogenicity in Animals

There is sufficient evidence to indicate NNN may act as both a local and systemic carcinogen in experimental animals. Studies have shown that NNN given by various routes of administration consistently causes oral and esophageal tumors in rats, as well as nasal cavity and tracheal tumors across multiple species, with noted route- and species-specific differences (Refs. 7, 178, 148, 59, 94, 149 through 160). Rats are more likely to develop tumors in the esophagus, oral and nasal cavity following oral or subcutaneous exposure to NNN (Refs. 7, 59, 94, 95, 148, 149) whereas mice develop tumors in lung, forestomach, and to a limited extent liver (Refs. 155, 156, 160). In hamsters, tracheal tumors and nasal cavity tumors are observed following oral or intraperitoneal exposure to NNN (Refs. 59, 151), with tracheal tumors also observed following subcutaneous exposure (Ref. 152). Studies in experimental animals also demonstrate that NNN can induce tumor formation in a dose-dependent manner. For example, in rats, a dose-dependent formation of nasal cavity tumors has been observed following subcutaneous or oral exposure (via gastric instillation) to NNN (Refs. 149, 161). In hamsters, NNN stimulates tumors of the nasal cavity, trachea and liver in a dose-dependent manner following subcutaneous exposure (Ref. 151).

Although a dose-dependent relationship between oral and esophageal tumor formation following exposure to NNN has not been extensively studied, chronic oral exposure to NNN via drinking water clearly identifies oral cavity and esophageal tissues as the major targets of tumorigenesis in animals (Refs. 7, 95). As indicated previously, sites of tumor formation following exposure to NNN are not limited to oral and esophageal tissues. Studies in experimental animals demonstrate oral exposure to NNN stimulates tumor formation in other tissues, such as nasal cavity, stomach, lung and liver (Refs. 151, 155, 156, 161, 178, 179). However, the number of tumors observed in oral and esophageal tissues are often greater than the number of tumors observed in other, non-target tissues. For example, a greater number of rats were reported to develop tumors in the esophagus compared with the lung following exposure to NNN in liquid diet (Ref. 94). Another study reported a similar trend, with esophageal and oral tumors observed in 35 and 18 percent of rats exposed to NNN via oral gavage, respectively, whereas only 5 percent of exposed animals developed lung tumors (Ref. 178). A more recent study by Balbo et al. (Ref. 7) found that 100 percent of rats treated orally with NNN in their drinking water developed malignant oral tumors. A high incidence of esophageal tumors has been consistently observed in rats following oral exposure to NNN across studies, with 83 percent of animals developing esophageal tumors following exposure via liquid diet (Ref. 94) and 60 to 100 percent of animals developing esophageal tumors following exposure via drinking water (Refs. 148, 95, 59, 7).

The high incidence of tumor formation in esophageal and oral tissue observed in experimental animal studies is consistent with what is known regarding the metabolism of NNN and subsequent DNA adduct formation in target tissues. NNN is a genotoxic carcinogen, it reacts with DNA and is assumed to exhibit proportional

[3] Section IV.D.3 explains why FDA is not proposing a product standard for NNK levels in smokeless tobacco at this time.

responses at low doses (Refs. 168, 169). The general understanding of the mechanism of action (MOA) of NNN-induced carcinogenicity centers around its metabolic activation. The metabolic activation of NNN leads to the formation of DNA and hemoglobin adducts and subsequent mutagenicity, ultimately resulting in cancer. NNN can be metabolized by 2′-hydroxylation and 5′-hydroxylation, with the 2′-hydroxylation the more predominant metabolic pathway (Ref. 8). The noted DNA adducts formed from NNN are POB–DNA via the 2′-hydroxylation pathway (Refs. 172, 173, 177) and py-py-dI via the 5′-hydroxylation pathway (Ref. 169). NNN has a chiral center at the 2′-position and exists in 2 enantiomeric forms, (*R*)–NNN and (*S*)–NNN, with (*S*)–NNN being the predominant enantiomer in smokeless tobacco products (Refs. 180, 181).

The MOA for NNN-induced carcinogenicity is supported by the pattern of mutagenesis and DNA adduct formation in target tissues following oral exposure to NNN in experimental animals. For example, NNN was found to be mutagenic in tongue, oral and esophageal tissue in mice following oral exposure via drinking water (Ref. 174). Both POB–DNA and py-py-dI adducts have been detected in the oral cavity, esophageal mucosa, nasal cavity, liver and lung of rats following exposure to NNN via drinking water (Refs. 169 through 173). Additionally, dose-dependent formation of POB–DNA adducts has been observed in oral, esophageal and nasal mucosa following oral exposure to NNN (Ref. 170), as has py-py-dI (Ref. 169). A greater number of DNA adduct formation has been also been observed in oral and esophageal tissues compared with other sites, consistent with previous findings of increased tumor formation in oral and esophageal tissues compared with other sites (Refs. 94, 178). For example, POB-adduct formation was greater in oral cavity and esophageal mucosa compared with lung or liver in rats following oral exposure to (*S*)-NNN via drinking water (Refs. 171, 172). These findings are consistent with previous reports of increased oral and esophageal tumor formation as compared with other tissues (Refs. 94, 178) and the reported high incidence of oral and esophageal tumors following oral exposure to NNN in rats (Refs. 7, 95).

Recent evidence has demonstrated target organ specificity for the carcinogenic effects of NNN and NNK in animals and in humans. As previously discussed, NNN's carcinogenic effects have been documented in the esophagus, nasal, and oral cavities when administered orally to animals (Refs. 7, 59, 95, 148), which provides some degree of concordance with effects observed at these sites in epidemiological studies (Refs. 77, 96). In contrast, NNK is known for being a powerful systemic lung carcinogen. NNK causes lung tumors in animals, including mice, rats, and hamsters, independent of the route of administration (Refs. 8, 149, 162 through 167). Even when animals are given NNK orally, a dose-dependent formation of lung tumors is observed (Refs. 164, 165, 166). Indeed, a recent study found 100 percent of animals receiving NNK via oral exposure developed lung tumors (Ref. 167). However, no oral cavity or esophageal tumors have been reported in animals exposed only to NNK (Ref. 8).

2. Evidence for NNN Carcinogenicity in Humans

Although the data on NNN exposure in humans is more limited, two recent epidemiological studies have found strong associations between NNN and cancer risk among cigarette smokers, providing evidence that increased exposure to NNN through use of certain tobacco products is associated with greater risk of head, neck, and esophageal cancer in tobacco users. In one nested case-control study among Chinese men, urinary levels of NNN in smokers were significantly associated with increased risk of developing esophageal cancer, but not lung cancer, after controlling urinary total NNAL (used to measure NNK exposure), smoking intensity and duration, alcohol consumption, and urinary cotinine (nicotine metabolite used to measure nicotine exposure) (Ref. 77). In the same cohort, total urinary NNAL was independently and significantly associated with increased risk of developing lung cancer (Ref. 183), whereas no association was observed between urinary total NNAL and esophageal cancer risk (Ref 77). In a second case-control study, mean levels of NNN were significantly higher in cases diagnosed with head and neck squamous cell carcinoma compared to matched controls, although no adjustment was made for potential confounding factors (Ref. 96). Although these studies were conducted among smokers, they support the significant role of NNN in cancer development in humans and are highly relevant to smokeless tobacco users, who have comparable levels of exposure to NNN and NNK as those of cigarette users (Refs. 97, 72, 98, 99). Moreover, these epidemiological findings support the target organ specificity and cancer risk associated with exposure to NNN (oral and esophageal) versus NNK (lung) that are observed in experimental animals (see section IV.B.1).

3. Geographic Differences in Cancer Risks From Smokeless Tobacco Use

Although there is some heterogeneity among particular study estimates, research on the association between smokeless tobacco use and oral cancer risk generally has found significant differences in risk by geographic region. For the United States, Boffetta et al. analyzed nine oral cancer risk estimates from seven independent studies that either adjusted for smoking or were restricted to never smokers and found a summary relative risk for smokeless tobacco use of 2.6 (Ref. 100). Lee and Hamling published a separate analysis that generated an overall relative risk estimate of 2.16 from all available U.S. studies (Ref. 114). The authors also generated estimates of never smoker oral cancer relative risks (a relative risk of 3.33) for 5 studies and smoking-adjusted oral cancer relative risks (a relative risk of 1.65) for 12 studies for U.S. smokeless tobacco users. Toombak, a smokeless tobacco product commonly used in Sudan, has been found to have a relative risk for oral cancer of 3.9 (Refs. 104, 4), while in India and Pakistan use of smokeless tobacco products, including pattiwala, naswar, khaini, and zarda, was associated with relative risks for oral cancer as high as 14 (Ref. 1 at table 71). In Scandinavia, increased oral cancer risks were observed in some but not all studies (Refs. 92, 188, 189, 191, 192).

The geographic variations in oral cancer risks are believed to be due to differences in product toxicant content (Ref. 100). TSNA concentrations in smokeless tobacco products vary by product and region; NNN levels are generally lowest in snus manufactured in Sweden, while NNN levels in smokeless tobacco products sold in the United States are typically higher (Refs. 11, 13, 5, 10). Many smokeless tobacco products sold elsewhere in the world, including in India and Sudan, contain even higher levels of NNN and other carcinogens than those in the United States (Refs. 206, 105). These analyses, in addition to the toxicological evidence demonstrating that NNN is a potent oral cavity and esophageal carcinogen, provide strong support for a relationship between smokeless tobacco use, NNN levels in these products, and oral cancer risk by geographic region. Thus, FDA believes that reducing NNN levels in smokeless tobacco products would reduce cancer risk.

C. NNN in Smokeless Tobacco Products

1. Formation of NNN in Smokeless Tobacco Products

NNN is formed either by the nitrosation of nicotine with the loss of a methyl group or by nitrosation of nornicotine, primarily during the curing of tobacco (Ref. 29). Nicotine is a tertiary amine while nornicotine is a secondary amine; the rate of nitrosation of tertiary amines is slow compared to the rate of nitrosation of secondary amines (Ref. 30). As the concentration of nicotine in smokeless tobacco products is typically three orders of magnitude larger than the TSNA concentration, NNN formation does not have a significant impact on product nicotine levels (Refs. 5, 10).

The primary nitrosating agent is nitrite (Ref. 31). Reduction of nitrate by bacteria such as halotolerant micrococci, Coryneforms, and halophilic rods during the fermentation process is the primary source of nitrite in smokeless tobacco products (Ref. 34). Nitrogen-rich fertilizer is also a source of nitrate and, upon reduction, nitrite (Ref. 41). Higher NNN levels are found in tobacco crops fertilized with nitrogen-rich fertilizers compared to fertilizers with lower nitrogen content (Refs. 42, 34). Tobacco and smokeless tobacco products with low nitrite concentrations have low levels of NNN, while products high in nitrite contain higher concentrations of NNN (Refs. 32, 31).

There is limited evidence to support that an appreciable amount of NNN is formed from nicotine or its metabolites in humans (Refs. 193, 194). The reaction of dietary precursors with nitrosating agents supplied by the diet can result in the endogenous formation of N-nitrosamines in humans (Refs. 195, 196, 197). The acidic environment in the stomach creates favorable conditions for nitrosation to occur (Ref. 198) and nitrosation of nornicotine has been observed in vitro under simulated gastric conditions, whereas nitrosation of nicotine has not been observed (Ref. 199). To date, there is not sufficient data in humans to indicate any significant in vivo NNN synthesis.

NNK is primarily formed through nitrosation of nicotine during the later stages of tobacco processing (*i.e.,* curing and fermentation) (Ref. 33). Similar to NNN, the primary nitrosating agent is nitrite and products with low nitrite concentrations have low levels of NNK while products with high nitrite concentrations have high levels of NNK (Refs. 32, 31).

2. Factors That Influence NNN Levels

NNN levels in tobacco can vary significantly from year to year, intra-year, and farm-to-farm (Ref. 34). Although tobacco plants inherently produce a small amount of NNN (Refs. 35, 1), a wide variety of factors can affect the final levels of NNN found in the finished tobacco product (Ref. 1). These factors, which can either increase or decrease NNN levels in smokeless tobacco products, include the tobacco type (*e.g.,* dark air-cured tobacco, Bright leaf tobacco, Burley tobacco), growing conditions (*e.g.,* geographic region, climate, rainfall), curing techniques (*e.g.,* fire, flue, air, sun), production process (*e.g.,* additives), and storage conditions (*e.g.,* temperature, humidity, duration) (Ref. 1). As discussed in section IV.E, because there are many factors that can influence the NNN level in smokeless tobacco products, there also are a number of options available to manufacturers to reduce and control NNN levels in order to meet the requirements of this proposed standard.

a. Tobacco Type

Studies have shown differences in NNN levels prior to curing and processing among different varieties of tobacco. Higher NNN concentrations have been found in Burley and dark tobacco compared to flue-cured Bright leaf tobacco (Ref. 36). Burley tobacco also contains more NNN compared to Virginia and Oriental types, whether grown in the same or different geographical locations (Ref. 37).

The use of selectively bred ''low converter'' tobacco seed has been shown to result in lower nornicotine (precursor to NNN) levels in tobacco (Refs. 38, 39, 40). The amount of NNN in a tobacco variety before curing or processing is dependent on the amount of its precursor nornicotine, which in turn is dependent on the amount of its precursor nicotine (Ref. 38). Nornicotine is normally present at very low levels compared to nicotine, but tobacco plants, through a process called ''conversion,'' can convert some of their nicotine to nornicotine (Ref. 39). Low converter seeds come from plants which, through selective breeding and genetic engineering, have a lower potential to convert nicotine to nornicotine (Ref. 40).

b. Growing Conditions

- *Climate.* Weather is a significant factor in NNN formation. Increased rainfall, including more frequent intense weather systems such as hurricanes, correlate with higher levels of TSNAs (Ref. 34). Specifically, wetter conditions that increase relative humidity during the growing season are more conducive to increases in total TSNA formation.
- *Fertilizer.* Nitrogen rich fertilizer can also have a profound effect on nitrate and NNN levels found in tobacco (Ref. 41). Higher NNN levels are found in crops fertilized with nitrogen-rich fertilizers compared to fertilizers with lower nitrogen content (Refs. 42, 43, 34). This is because, when nitrogen-rich fertilizer is used during tobacco growing, more nitrogen is incorporated into the leaves of the tobacco in the form of nitrate. As the tobacco leaves are cured, the nitrate acts as a substrate for microorganisms reducing the nitrate to nitrite. The nitrite reacts with alkaloids such as nicotine or nornicotine in the tobacco during curing to form higher levels of TSNAs such as NNN.

c. Curing Techniques

There are four main methods for curing tobacco: Sun, air, flue, and fire curing. Sun-cured tobacco is cured on outdoor racks exposed to the sun while air-cured tobacco is cured on racks in a well-ventilated barn under ambient temperatures (Ref. 4). Flue and fire curing occur in artificially heated and ventilated barns. Flue-cured tobacco is cured on racks in a barn or other enclosed structure with an external heat source (*e.g.,* heat exchanger, propane or diesel heaters) so the tobacco isn't exposed to smoke (Refs. 34, 200). In contrast, fire-cured tobacco is cured on racks in a barn and exposed directly to smoke from a wood fire (Ref. 201). Curing can take from a few days to several weeks depending on the curing method (Ref. 44). The curing process not only dries out and preserves the tobacco but also imparts characteristic flavor.

During the curing process, the curing method, humidity, air flow, temperature, and the fuel used for heating the tobacco influence the extent to which the NNN level changes (Refs. 45, 46). Studies have shown that flue and fire-curing tobacco results in higher NNN levels than when the same tobacco is air-cured (Refs. 47, 42, 1). In addition, air-curing during periods of high relative humidity produces tobacco with higher amounts of TSNAs and nitrite (Ref. 46). However, TSNAs in tobacco were shown to be lower when cured by reducing humidity by improving the air circulation or by using an indirect heating source to limit exposure to smoke (Refs. 46, 48). Furthermore, direct flue curing with liquid propane gas leads to higher NNN levels than fire curing or indirect flue curing (Ref. 49).

d. Production Process

During production, microorganisms (bacteria, fungi, and yeast) on tobacco play a significant role in the generation of nitrite and the subsequent formation of TSNAs (Ref. 202). The microorganisms can come from a variety of sources including the soil and surrounding environment, or unsanitary manufacturing conditions (Ref. 12).

Fermentation is commonly used in the production of U.S. smokeless tobacco products. Fermentation imparts flavor and contributes to higher nitrite and NNN levels (Ref. 50). Reduction of nitrate by bacteria during the fermentation process is the primary source of nitrite in smokeless tobacco products (Ref. 34). The increased nitrite concentration subsequently contributes to the nitrosation of amino alkaloids and the formation of NNN.

In contrast, certain processing methods have been reported to help limit the levels of NNN formed during production. For example, using non-nitrate reducing bacteria during the fermentation process (*i.e.,* through seeding or starter culture) can lower NNN yields (Refs. 34, 51). Cleaning and sanitizing all equipment used in the processing and manufacturing of smokeless tobacco products, including the fermentation equipment, can lower microorganisms on tobacco and lower NNN yields (Ref. 34). In addition, using closed process blenders at a high temperature, adding bicarbonate and carbonate salt solutions to control pH, adding humectants, and pasteurization or heat treatment can lower microbial activity during production, leading to lower NNN levels in smokeless tobacco products (Ref. 11).

e. Storage Conditions

Storage conditions (*i.e.,* temperature and humidity) and the duration of storage have been shown to influence NNN levels. Cured tobacco leaves and finished smokeless tobacco products are stored until they are processed or consumed. Tobacco leaves are often stored on farms for up to 3 months prior to sale to tobacco product manufacturers. Once sold, the tobacco may be stored for another 18 months before it is manufactured into a finished product (Ref. 41).

Researchers have reported a 2-fold increase in NNN levels in sun-cured tobacco and a 3-fold increase in NNN levels in Burley tobacco when stored at ambient temperatures over a 1-year period (Ref. 41). Further, studies have shown that storage temperatures as low as 27 °C can lead to increased NNN formation in air-cured Burley tobacco, and that the rate of increase becomes greater as the temperature is increased (Ref. 41). In addition, air-cured Burley tobacco stored at higher temperature (24 °C v. 32 °C) and higher relative humidity levels (70 v. 83 percent) showed increases in both nitrite and NNN levels (Ref. 52).

Similar to cured tobacco, high temperature, high humidity, and extended storage can cause levels of NNN to increase in smokeless tobacco products. As smokeless tobacco products ''age,'' the water content can change, leading to bacterial growth, and the pH and nicotine content can decrease, causing nitrosamine levels such as NNN to rise (Ref. 11).

Studies have shown that NNN increases in moist snuff and dry snuff when stored at 24 °C for 24 days (Refs. 53, 54). Exposing moist and dry snuff to ambient air, such as when a product is opened and closed between dips, also increases NNN concentrations (Ref. 53). Similar to cured tobacco leaves, the storage of moist snuff at low temperatures (4 °C) reduces the increase in NNN that was seen when the same product is stored at ambient conditions (Ref. 55).

Humidity levels during storage can have an even greater influence than temperature on NNN formation in finished smokeless tobacco products. Specifically, the NNN levels in moist and dry snuff can be increased just by raising the relative humidity during storage from 22 to 50 percent (Ref. 54). Moreover, the combined effects of humidity and temperature are enhanced in products with higher moisture content (Ref. 54). Yet, storage conditions do not have the same effect on all types of smokeless tobacco. Studies on storage of chewing tobacco did not show the same increase in NNN as seen with moist and dry snuff, which suggests that some tobacco blends may be less prone to producing nitrosamines during storage (Refs. 53, 54). Furthermore, although retailers are encouraged to refrigerate Swedish snus to maintain ''perceived product freshness,'' the product's low bacterial activity may stabilize the NNN level even when stored at room temperature (Ref. 11).

3. Levels of NNN in U.S. Smokeless Tobacco Products

The levels of NNN in smokeless tobacco products on the U.S. market can vary by several orders of magnitude, not only among different subcategories of products, but also among products in the same subcategory (table 2, Refs. 5, 10, 56). After measuring NNN levels in 46 different smokeless tobacco products available in the United States from 2006 and 2007, Borgerding et al. found NNN levels ranged from below the limit of quantification (0.02 µg/g) to 14.4 µg/g per dry weight (Ref. 5). As shown in table 2, the NNN levels within the class of moist snuff and dry snuff ranged from 0.6 to 12.8 µg/g per dry weight and 5.91 to 12.0 µg/g per dry weight, respectively (Ref. 5).

A more recent study by Ammann et al. examined 34 products purchased in the United States in 2015 (Ref. 10). In line with the Borgerding study, Ammann et al. found NNN levels ranged from 0.64 to 12.0 µg/g per dry weight (Ref. 10). The NNN levels for moist snuff ranged from 1.0 to 9.5 µg/g per dry weight while the NNN levels for dry snuff ranged from 5.91 to 12.0 µg/g per dry weight (Ref. 10).

The range of NNN levels described in these studies have been confirmed by numerous other studies. Stepanov et al. reported a similar range for moist snuff (3.8 to 6.9 µg/g per dry weight) with dry snuff ranging from 0.95 to 5.3 µg/g per dry weight (Ref. 13). In a separate study, Stepanov et al. reported a wide range of NNN levels in 11 dissolvables that are smokeless tobacco products (0.27 to 2.7 µg/g per dry weight) (Ref. 56). Finally, Lawler et al. reported a wide range of NNN levels in chewing tobacco (0.94 to 2.8 per wet weight which equates to 1.2 to 3.6 µg/g per dry weight) and in dry snuff (6.1 to 31 µg/g per wet weight which equates to 6.5 to 33 µg/g per dry weight) (Ref. 20).

TABLE 2—NNN CONCENTRATION AND MARKET SHARE OF SMOKELESS TOBACCO PRODUCTS SOLD IN THE UNITED STATES

Smokeless tobacco product	Mean[1] and range of NNN measured in µg/g dry weight (number of products)			Market share[2] (%)
	Stepanov et al., 2014	Borgerding et al., 2012	Amman et al., 2016	
Dissolvable	1.78; 0.27–2.66; (11)			<0.1
Chewing Tobacco (Loose leaf, plug, chew).		2.21; 0.66–5.05; (8)	2.24; 0.92–4.60; (8)	5.2
Dry Snuff		5.53; 0.81–14.42; (10)	7.50; 5.91–12.00; (4)	0.7

TABLE 2—NNN CONCENTRATION AND MARKET SHARE OF SMOKELESS TOBACCO PRODUCTS SOLD IN THE UNITED STATES—Continued

Smokeless tobacco product	Mean[1] and range of NNN measured in μg/g dry weight (number of products)			Market share[2] (%)
	Stepanov et al., 2014	Borgerding et al., 2012	Amman et al., 2016	
Moist Snuff		3.76; 0.66–12.77; (28)	3.01; 0.64–9.50; (22)	94.1
Mean NNN across product categories		3.87	3.36	
Market share adjusted mean across product subcategories[3].		3.69	3.01	

[1] Mean values were determined by averaging the NNN concentrations across a smokeless tobacco product subcategory in each of the three representative studies.

[2] Market share data was based on 2015 retail scan data from Nielsen.

[3] In order to calculate a market share adjusted mean the mean of each subcategory was multiplied by its representative market share (*e.g.,* Chewing Tobacco [NNN] × .052). These values for each subcategory were then summed to estimate a market share weighted mean across all smokeless tobacco product subcategories examined.

The range of the NNN levels in the studies discussed in this subsection suggest that there exists the potential to reduce the levels of NNN in all smokeless tobacco through manipulation of starting materials and curing processes, as well as careful control of manufacturing and storage practices.

D. Basis for the NNN Limit in the Proposed Standard

As discussed in section IV.B of this document, the scientific evidence supports that NNN is a potent carcinogenic agent found in smokeless tobacco products and that NNN in smokeless tobacco products is a major factor underlying oral and esophageal cancers. The epidemiological evidence indicates populations who use smokeless tobacco products with lower levels of NNN have lower cancer risks (Refs. 4, 100, 101). Thus, it is anticipated that reducing levels of NNN in tobacco products in the United States will reduce the incidence of oral and esophageal cancers among smokeless tobacco users.

Based on our assessment of the evidence, we are proposing that the mean level of NNN in any batch of finished smokeless tobacco products not exceed 1.0 μg/g of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by testing in compliance with § 1132.12 (proposed § 1132.10). In selecting the NNN limit in this proposed standard, FDA took into consideration the epidemiological evidence demonstrating differences in observed cancer risks between users of smokeless tobacco products manufactured in the United States and in Sweden, and the technical achievability of the proposed limit. To estimate the anticipated health benefits of the proposed standard, FDA modeled the estimated cancer risk reduction determined by reducing NNN levels in smokeless tobacco products from current levels.

As NNN appears to have a genotoxic mode of action, FDA followed the U.S. Environmental Protection Agency's (EPA's) guidance for carcinogen risk assessment and assumed a linear relationship in the low-dose region of the dose-response model (Ref. 203). Using this model, the risk of cancer is linearly reduced as exposure to NNN approaches zero. While a limit of 0.0 μg/g for NNN would maximize cancer risk reduction to smokeless tobacco users, there is limited information on NNN levels lower than the proposed standard and their technical achievability. We note, however, that an NNN level of 1.0 μg/g of tobacco has been achieved in some smokeless tobacco products sold in the United States and is thus achievable using current technology. As discussed in section II.C of this document, FDA may consider a lower NNN level in the future. In addition, FDA welcomes comments on the technical achievability of complying with the proposed standard in this rule.

FDA modelled NNN attributable cancer risk to estimate the potential benefits to public health. Specifically, FDA modelled the effect an NNN smokeless tobacco product standard would have on reducing the cancer risk to a population exposed to NNN through use of smokeless products. This analysis is described in detail in this section.

FDA also considered the epidemiological evidence demonstrating differences in observed cancer risks between users of smokeless tobacco products manufactured in the United States and in Sweden. We focused on epidemiological evidence from Sweden because Swedish smokeless tobacco products tend to have lower levels of NNN than other smokeless tobacco products (Refs. 100, 114), which helps inform our public health analysis of a product standard limiting NNN. As discussed in section IV.B of this document, epidemiological studies demonstrate a lower risk of oral cancer from the use of Swedish snus in Sweden compared to other smokeless tobacco products in other countries. It is anticipated that the proposed product standard of 1.0 μg/g dry weight would bring the NNN level in U.S. smokeless tobacco products in line with those of Swedish snus.

With respect to risk reduction, FDA assumed that changes in the growing conditions and changes in product curing and processing may be necessary to achieve lower NNN levels in smokeless tobacco products. As discussed in section IV.E, it appears that there are several options for achieving the proposed NNN limit.

We note that FDA's approach to establishing the proposed limit differs from that of other regulatory agencies, such as the EPA and the U.S. Occupational Safety and Health Administration (OSHA), which set regulatory exposure limits based upon a risk level deemed to be ''acceptable'' or ''negligible'' (Refs. 204, 205 at appendix B). FDA expects that although the cancer risks posed by smokeless tobacco products that meet the proposed standard would be lowered, use of these products would still pose increased cancer risks, including increased oral cancer risks, compared with not using smokeless tobacco products. Thus, the proposed product standard establishing a limit for NNN in smokeless tobacco products is not intended to communicate that such levels are ''acceptable'' or ''negligible'' from a public health perspective.

1. Excess Lifetime Cancer Risk of NNN in U.S. Smokeless Tobacco Products

FDA estimated the excess lifetime cancer risk (ELCR) for oral cancer associated with the current NNN levels in U.S. smokeless tobacco products and compared it to an estimate of the ELCR

under the proposed standard. We calculated the ELCR with and without the proposed product standard to estimate the extent to which the proposed standard can reduce the risk of cancer among smokeless tobacco users in the United States. Then FDA used the resulting reduction in lifetime cancer risk to estimate the potential decrease in oral cancer cases as a result of this rule.

Given the variability associated with smokeless tobacco use (frequency, quantity) and lack of data regarding the dose-response relationship for NNN in humans, FDA is using the ELCR calculation to provide an understanding of the relative, rather than absolute, risk associated with different product classes and the impact of the proposed product standard on users of smokeless tobacco.

As demonstrated by Equation 1, which FDA used to calculate the excess lifetime cancer risk, the ELCR is a unitless probability (*e.g.,* 1 in 10,000 chance). The equation is based on the U.S. Environmental Protection Agency Risk Assessment Guidance (Ref. 57). The key variables in the equation are: (1) The level of NNN in the product (*i.e.,* concentration in product as used); (2) the amount of product (mass) used each day; (3) the amount of NNN that leaves the product during use (*i.e.,* percent extracted) and the amount of the extracted NNN that is absorbed by the body (*i.e.,* absorption rate); (4) the length of time the product is used over a lifetime, which is determined by the years of use (*i.e.,* exposure duration) over the lifetime (*i.e.,* averaging time); (5) body weight of the user; and (6) the cancer slope factor (CSF), which is used to represent the dose-response relationship between NNN and cancer incidence. As each of these variables is associated with wide variability, we attempted to derive average values to estimate a population average ELCR. Below we describe the assumptions that are used in this analysis and the justification for those assumptions. Because of limitations in data, particularly with regard to data underlying the CSF, the ELCR calculation is not used to assess absolute cancer risk. Instead, the ELCR is used to estimate the percent reduction in cancer risk associated with implementing an NNN limit for smokeless tobacco products. FDA welcomes public comments on alternative assumptions that may affect the ELCR estimate. Commenters should provide explanations as to why the alternative assumptions may lead to more robust estimates of the ELCR associated with this product standard.

Equation 1—ELCR Calculation

$$ELCR = CxIR\ x\ \frac{AB\ x\ EF\ x\ ED}{BW\ x\ AT}\ x\ CSF$$

C = Concentration of NNN in product as used (µg/g wet weight)
IR = Intake rate (mg of wet (as used)) product used per day (12 g/day; 2.5 g/day for dissolvables)
AB = Absorption rate, how much of product NNN is transferred to the user (60 percent)
EF = Exposure frequency (365 days/year)
ED = Exposure duration (60 years)
BW = Body weight in kg (70 kg)
AT = Averaging time (365 days/year; 78 years)
CSF = Cancer slope factor (1.4 mg/kg/day)

As defined by the EPA guidelines, the cancer slope factor (CSF) is ''an upper bound (approximating a 95percent confidence limit) on the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg/day, is generally reserved for use in the low-dose region of the dose-response relationship; that is, for exposures corresponding to risks less than 1 in 100. This term is usually used to refer to oral slope factors (*i.e.,* slope factors used for assessing ingestion exposure).'' (Ref. 190).

For this ELCR assessment, FDA uses the CSF for NNN generated by the California Environmental Protection Agency (CalEPA) in 1992 (Ref. 93). Although this CSF has been used as the basis for several published analyses (Refs. 207, 208, 209, 74, 210, 211, 102), it has significant limitations. The CalEPA CSF of 1.4 (milligram per kilogram per day (mg/kg/day))$^{-1}$ for NNN is based upon tumor data from hamsters orally exposed to NNN in drinking water in a study conducted by Hecht et al. (Ref. 59), which compared a single dose scenario with a control group. The CalEPA thus generated a slope by drawing a line between the two points (tumor rate at a single dose and tumor rate in the control group). EPA's 2005 Cancer Guidelines and subsequent Benchmark Dose Guidance elaborate extensively on the determination of the point of departure (POD) for generating a CSF (Refs. 203, 187). More specifically, EPA recommends that the starting point for subsequent extrapolations and analyses be the lowest dose adequately supported by the data. However, in a single dose study, without an understanding of the shape of the exposure-response curve at lower doses, there is potentially significant bias in the derivation of the CSF—leading to subsequent uncertainty in the modeling of cancer risk. Thus, as noted above, FDA's ELCR calculation is only used to estimate relative risk of alternative exposure scenarios, not absolute risk. FDA welcomes public comment on whether there is a more robust CSF available for NNN.

For the concentration of NNN in the product, FDA used the Borgerding et al. and Ammann et al. data (Refs. 5, 10) to represent the range of levels of NNN in current smokeless products, which ranged from below the limit of quantification (0.02 µg/g) to 14.4 µg/g per dry weight. We chose these studies because they are the most comprehensive studies of NNN levels in U.S. smokeless tobacco products and the levels are similar to levels which have been reported by other investigators (see section IV.C.3). These studies also reported the moisture content of the smokeless tobacco products, which FDA used to determine the products wet weight NNN levels (*i.e.,* what a user would be exposed to). This calculation involves taking the dry weight NNN measurement and accounting for the moisture found in the product when used by consumers [NNN µg/g dry weight] × [1-moisture content] = [µg/g wet weight (as used)].

For the intake rate (mass of product used each day), FDA chose an average use assumption of 12 g of wet product per day, every day based on an experimental study in the United States that indicated that the range of the most common form of smokeless tobacco use, moist snuff, is between 5.1 and 42.5 g/day (Ref. 60), with an average use of 12 g/day (Ref. 60). This study is widely cited for estimating average smokeless tobacco use (Refs. 132, 212, 213). The 12 g/day assumed estimate is consistent with studies that look at use in terms of the number of tins (container holding the smokeless tobacco product) of tobacco consumed (Refs. 61 through 71). These studies' estimates ranged from 1.2 tins to 4.6 tins/week, with an average of 3.68 tins/week (0.53 tin/day. Based on an average size of a tin of 1 ounce (or slightly more than 28 g), we estimate

that the average amount of smokeless tobacco product used is approximately 15 g/day [0.53 tin/day × 28 g/tin = 14.84 g/day], which suggests an assumption of 12 g/day is not unreasonable.

Conventional moist snuff constitutes the overwhelming majority of the smokeless tobacco market in the United States (Ref. 131). The figure of 12 g/day among moist snuff users does provide a reasonable average estimate of what most U.S. smokeless tobacco users of most product subcategories consume on a daily basis. However, FDA recognizes that the amount of smokeless tobacco used in a day varies by product. In particular, some dissolvable smokeless tobacco products weigh as little as one-fifth or one-quarter as much (Ref. 56). Therefore, 2.5 g/day was used for our ELCR calculations for daily use of dissolvable products based upon a usage study by Krautter et al. (Ref. 15).

The extraction percentage, or fraction of TSNAs removed from a smokeless tobacco product while in use, has been reported to range from 10 to 85 percent (Refs. 58, 73, 74). Hecht et al. analyzed extraction and direct absorption of TSNAs in humans. A measured amount of smokeless tobacco was inserted into the oral cavity for 30 minutes. All saliva was collected during use of the product and three consecutive 24-hour urine samples were analyzed. The amount of TSNAs before and after use of the smokeless tobacco product was determined along with analysis of the expectorated saliva and urine samples. The individual subject data provided by Hecht et al. yields a median extraction of 60 percent (59 ± 23 percent) (Ref. 58). Other studies also cite 60 percent as an estimate of the amount of TSNAs extracted from smokeless tobacco (Refs. 73, 74).

FDA assumed the absorption rate for the average user to be 100 percent of the extracted 60 percent of the concentration of TSNAs found within a given smokeless product. This assumption is precautionary because it assumes that the user is exposed to the total amount of NNN extracted from the product, even though some of the NNN in saliva may be excreted without being absorbed. Therefore, the absorption rate used for the ELCR calculations is 60 percent (*i.e.,* 100 percent absorption of the 60 percent extracted NNN).

FDA used 60 years of product use as the exposure duration for the ELCR calculations assuming initiation at or near 19 years of age (Ref. 23) and an average life span of 78 years for the general population (Ref. 75). We used 78 years because it is the recommended value from the EPA (Ref. 75) to use when calculating excess lifetime cancer risk due to toxicant exposure in the absence of specific data on the population of interest (*i.e.,* smokeless tobacco users). Upon initiation, FDA assumed daily use (365 days/year) of an average mass of 12 g of wet product per day. In addition, FDA used an average adult body weight of 70 kg in the ELCR calculations, which is consistent with EPA practices (Ref. 57).

Table 3 shows the estimated ELCR calculated by using the mean NNN concentration of several different categories of smokeless tobacco products sold in the United States from table 2, using Equation 1 and the assumptions described in this section. Given the assumed linear nature of the CSF, use of products with lower NNN levels has a lower ELCR while use of products with higher NNN levels has the highest ELCR. For example, use of dissolvables with a mean level of NNN of 1.6 μg/g (as used) has a very low ELCR of 0.4 in 10,000, while use of dry snuff with a level of NNN of 5.1–7.0 μg/g (as used) has an ELCR of 5.6–7.6 in 10,000. The current market share adjusted mean NNN level of all U.S. smokeless tobacco products reported by the Borgerding and Ammann studies is 1.7–1.8 μg/g wet weight (as used), the use of which corresponds to an estimated ELCR of 1.9–2.0 in 10,000.

TABLE 3—ESTIMATED ELCR FOR SUBCATEGORIES OF U.S. SMOKELESS TOBACCO PRODUCTS

Smokeless tobacco product	ELCR (expressed as "n" in 10,000)		
	Stepanov et al., 2014	Borgerding et al., 2012	Ammann et al., 2016
Dissolvables	0.4	.....	.....
Dry Snuff	.....	5.6	7.6
Chewing Tobacco	.....	1.8	2.0
Moist Snuff	.....	2.0	1.8
Mean ELCR across product categories	.....	2.7	2.6
Market share adjusted ELCR across product subcategories	.....	2.0	1.9

[1] In order to calculate a market share adjusted mean ELCR, the mean of each subcategory was multiplied by its representative market share (table 2). These values for each subcategory were then summed to estimate a market share weighted mean across all smokeless tobacco product subcategories examined.

Using the same assumptions as above (Intake rate, NNN CSF), FDA estimated the ELCR for use of smokeless tobacco products with differing levels of NNN (dry weight, *e.g.,* 0.5, 1.0, 2.0 μg/g) and how these levels would compare to the current market estimates (table 4). FDA first carried out a moisture correction on the dry weight concentrations (0.5, 1.0, and 2.0 μg/g dry weight) to determine an ''as used'' (wet weight) NNN concentration. This estimation was based upon the moisture concentrations from the Ammann et al. study (Ref. 10), and weighted by recent subcategory market share data. As shown in table 4, we estimate that, compared to the current market, hypothetical market-wide NNN levels of 0.5, 1.0 and 2.0 μg/g dry weight would reduce the ELCR by 83.2, 66.3 and 31.6 percent, respectively.

TABLE 4—ELCR FOR HYPOTHETICAL MARKET-WIDE MEAN NNN LEVELS AND COMPARISON TO CURRENT MARKET ELCR

NNN (μg/g dry weight)	NNN (μg/g, wet weight, as used)	ELCR (n in 10,000)	% Reduction in ELCR as compared to current market [1]
0.5	0.3	0.32	83.2
1.0	0.6	0.64	66.3

TABLE 4—ELCR FOR HYPOTHETICAL MARKET-WIDE MEAN NNN LEVELS AND COMPARISON TO CURRENT MARKET ELCR—Continued

NNN (μg/g dry weight)	NNN (μg/g, wet weight, as used)	ELCR (n in 10,000)	% Reduction in ELCR as compared to current market [1]
2.0	1.2	1.3	31.6

[1] Percent reduction in ELCR compared to the market weighted mean ELCR value from Amman et al., 1.9 (table 3).

2. ELCR of NNN in Swedish Snus

As noted earlier, Swedish snus generally has a lower NNN level than other smokeless tobacco products sold in the United States, and as discussed in section IV.B.3, some epidemiological studies demonstrate a lower risk of oral cancer from the use of Swedish snus in Scandinavia when compared to the use of other smokeless tobacco products in the United States (Refs. 100, 114). Substituting the mean NNN level of 0.55 μg/g (wet weight) that is in Swedish snus (Ref. 5), into Equation 1 yields an ELCR of 0.59 in 10,000. As the proposed product standard of 1 μg/g dry weight for NNN would result in bringing U.S. smokeless tobacco products in line with NNN levels in Swedish snus, it is not surprising that the ELCR for such a hypothetical market-wide mean NNN level (table 4) would be almost the same as that estimated for Swedish snus.

Our analysis indicates that users of smokeless tobacco products would have their ELCR reduced by approximately 65 percent if the market adjusted mean of NNN in smokeless tobacco products was reduced from that of the current market to 1.0 μg/g dry weight (table 4). This value would approximate the ELCR of the Swedish snus exposure scenario which epidemiological data suggests has a lower cancer risk.

3. Conclusion

Setting the proposed limit for NNN in finished smokeless tobacco products means that, on average, in a population of daily users of smokeless tobacco products, over their life time, there would be an approximately 65 percent reduction in ELCR, compared with lifetime daily use of a population that used smokeless tobacco products with NNN levels at the current level. In section V, we calculate the impact of an estimated 65 percent reduction in cancer risk on expected incidence of oral cancer in the United States.

We note that FDA considered setting a product standard for both NNN and NNK. However, FDA is proposing a product standard for only NNN at this time because of the more limited data available on the relationship between NNK and smokeless tobacco-related cancer risk. In particular, NNK is noted for its consistent systemic lung carcinogenicity (Ref. 8). However, the relationship between smokeless tobacco use and lung cancer is a matter of ongoing investigation and a definitive association has not been established (Refs. 3, 4).

NNN and NNK constitute potent carcinogens in smokeless tobacco (Refs. 4, 78) and levels of these two TSNAs are often correlated in smokeless tobacco products (Refs. 5, 20). Because many methods available to reduce NNN also reduce NNK, there is some evidence that a product standard that requires lower NNN levels will potentially result in lower NNK levels as well (Ref. 84).

A market survey of 16 snus brands sold in Sweden in 1983, prior to the adoption of the GothiaTek voluntary quality control standard, showed average NNN levels of 3.8 μg/g of tobacco and average NNK levels of 0.8 μg/g of tobacco per wet weight (Ref. 84). In 2002, after GothiaTek was adopted, a market survey of 23 snus brands sold in Sweden showed NNN levels decreased to 0.49 μg/g of tobacco and NNK levels decreased to 0.19 μg/g of tobacco per wet weight (Ref. 84). More recent analyses of constituents in smokeless tobacco products manufactured in the United States indicate that smokeless tobacco brands that are lower in NNN content are also lower in NNK (Refs. 5, 20). Additionally a study by Song et al. (Ref. 6), examined the NNN and NNK levels of conventional and low-TSNA smokeless tobacco products on the U.S. market. NNN:NNK ratios were 3.1 and 3.7 for the conventional and low-TSNA varieties, respectively, which is in line with results from previous studies (Refs. 5, 20). Accordingly, we anticipate a potential reduction of NNK in smokeless tobacco in response to the proposed rule for NNN. We note that, in 2009, the WHO Study Group on Tobacco Product Regulation recommended a regulatory limit for NNN and NNK (combined) of 2 μg/g dry weight of tobacco (Ref. 78). Given the ratio of NNN to NNK in smokeless tobacco products, where the level of NNN is generally greater than the level of NNK, any smokeless tobacco product that meets the proposed NNN standard is likely to also meet the levels recommended by the WHO for NNN and NNK.

E. Information on Technical Achievability

Section 907(b)(1) of the Tobacco Control Act requires FDA to consider information submitted in connection with a proposed product standard regarding technical achievability of compliance with the product standard. FDA, therefore, invites public comment addressing the technical achievability of this proposed product standard, and specifically requests submission of evidence and data to support such comments. FDA has also chosen to consider available information regarding technical achievability in developing this proposed rule and it appears that there are several options for achieving the proposed NNN limit.

As described in more detail in section IV.C.2, there are many factors that can influence the level of NNN in smokeless tobacco products. Accordingly, there are a number of options available to manufacturers to reduce and control NNN levels in finished smokeless tobacco products including, but not limited to, the following:

- Using a type of tobacco with lower concentrations of NNN (*e.g.,* Bright tobacco or low-converter types of Burley tobacco);
- Using tobacco grown with limited use of nitrogen-rich fertilizer on tobacco crops;
- Using tobacco processed with a different curing method (*e.g.,* air curing instead of flue curing the same tobacco) or a modification of a currently used curing method to minimize its effect on NNN levels (*e.g.,* reducing humidity during curing by improving air circulation);
- Using tobacco that had a bacteriostatic, bactericidal, or heated solution (25 to 55 °C) applied to tobacco leaves during the growing, harvesting, or curing processes to reduce the number of bacteria in the tobacco leaves and thereby reduce the NNN level;
- Using a non-nitrate reducing bacteria ''starter culture'' for the fermentation process;
- Using cleaned and sanitized equipment for processing and

manufacturing smokeless tobacco products;

- Adding humectants, sodium chloride, or other additives to lower water activity and reduce microbial growth;
- Adding bicarbonate and carbonate salt solutions to control pH;
- Pasteurization or heat treatment;
- Storing tobacco leaves and finished smokeless tobacco products at lower temperatures and relative humidity levels; and
- Limiting the duration of storage.

For products that are already near the proposed limit, one of these options may be sufficient to bring the product into compliance with the proposed standard, while products which currently have levels of NNN well above the proposed limit may need to use a combination of options. To the extent that any change in the processing of smokeless tobacco products (*e.g.,* curing, fermentation) affects the products flavor, FDA expects that manufacturers would be able to adjust the flavor profile of finished smokeless tobacco products through minor changes in flavor ingredients. This proposed rule also could spur innovation and development of additional methods and technologies to reduce NNN levels in smokeless tobacco products.

The proposed rule does not prescribe specific methods or processes for meeting the proposed NNN level, so that smokeless tobacco product manufacturers would have flexibility in identifying appropriate methods or processes for reducing the NNN level in their products. Because certain snus, moist snuff, and chewing tobacco already contain low NNN levels, FDA expects that manufacturers of many of those products may not need to make any manufacturing changes to meet the proposed NNN level (Refs. 5, 10, 56). (Such manufacturers would remain subject to the proposed standard, including its testing, sampling, labeling, and recordkeeping requirements.) Thus, FDA expects some smokeless tobacco products may require minimal changes to the manufacturing process to meet the proposed NNN level, while other products may require extensive changes to the manufacturing process to comply with the proposed level (Ref. 56). A smokeless tobacco product that has been modified to comply with the product standard would be a ''new tobacco product'' and subject to premarket review.

F. Analytical Method

To test for the NNN limit in this product standard, FDA proposes that smokeless tobacco product manufacturers use the validated method that has been developed at FDA's Southeast Regional Laboratory (SRL) in Atlanta, GA (Determination of N-nitrosonornicotine (NNN) in Smokeless Tobacco and Tobacco Filler by HPLC–MS/MS, LIB No. 4620, January 2017) (Ref. 79). The results from the test method demonstrate a high level of specificity, accuracy, and precision in measuring a range of NNN levels across a variety of smokeless tobacco products. Requiring that a single test method be used would ensure that all of these factors are met and would permit comparison of test results among finished smokeless tobacco products and testing facilities. However, FDA is proposing that other methods may be used if they meet the requirements in § 1132.16 (Alternative test method).

Numerous methods have been published that use either high-performance liquid chromatography/mass spectrometry (LC–MS) or gas chromatography (GC), combined with thermal energy analyzer (TEA) detectors to determine the content of NNN in tobacco. The validated test method that FDA is proposing to incorporate by reference in § 1132.5(a) utilizes LC–MS and has an analysis time of 8 minutes. The method has a limit of quantification of 0.4 μg/g of NNN, a linear range of 0.4 to 1.6 μg/g, and a method detection limit of 0.1 μg/g. The method performance parameters for the standard method for NNN quantification in smokeless tobacco products do not differ significantly from the method performance parameters of other methods that are currently in use. This method uses an extraction solvent of 100 milliMolar (mM) ammonium acetate in high performance liquid chromatography (HPLC) grade water and a gradient of 5 to 50 percent of 5 mM ammonium acetate in 95 percent acetonitrile at a 0.5 milliliter per minute flow rate. Analysis is conducted after a known amount of carbon-13-labeled NNN is added to the tobacco, extracted for 5 minutes with 100 mM ammonium acetate at elevated temperature and pressure, dried, and reconstituted in methanol and ammonium acetate buffer.

The method includes the determination of NNN levels as well as moisture content, so the NNN level on a dry weight basis can be calculated. In this method, water levels are determined according to International Organization for Standardization (ISO) standards ISO 6488:2004 and ISO 6488:2004/Cor 1:2008 or ISO 16632:2013. Validation of this method was done using the smokeless tobacco reference products for snus (CRP–1) and for moist snuff (CRP–2), as well as the University of Kentucky cigarette reference product (3R4F cigarette tobacco filler). Tobacco samples with NNN levels expected to be higher than 4 μg/g tobacco were analyzed after dilution because they were too concentrated for analysis. This method was proven to be applicable for tobacco products with various moisture levels, including cigarette tobacco filler, snus, dry snuff, chewing tobacco, and moist snuff.

HPLC is favored over gas chromatography (GC) because it allows for faster analysis and sample preparation, although validated methods exist for analysis of NNN well below the level specified in § 1132.10 by either LC or GC. Mass spectrometer (MS) detection is favored over thermal energy analyzer (TEA) detection because of the possibility of using isotopically-labeled NNN as an internal standard, which controls for variation in sample preparation. In addition, instrumentation to perform LC–MS analysis is more readily available than for GC–TEA and, therefore, manufacturers or analytical laboratories wishing to establish this method themselves will have better access to equipment. The internal standard is NNN that has been specially labeled with isotopes of hydrogen and carbon, deuterium or carbon-13, respectively. The isotopic-labeling of the internal NNN standard increases the mass of the internal standard relative to naturally occurring NNN, and the internal standard appears as a distinct signal in the mass spectrometer detector. Because the analyst knows the quantity of internal standard added to the tobacco at the beginning of sample preparation, the detector signal of the internal standard can be used to quantify the amount of natural NNN present in the sample. The isotopically-labeled internal standard is chemically identical to NNN, so the internal standard used for MS controls for all variations in NNN levels that arise during sample preparation and extraction. The available scientific evidence suggests that deuterated and carbon-13-labeled internal standards are equally acceptable for NNN analysis. Internal standards used for TEA differ from internal standards used for MS because they are chemically different from NNN. Therefore, slight differences may exist between the yield of NNN and the yield of the internal standard during the extraction and sample preparation steps. The limits of detection for NNN by MS may be lower than limits of detection by TEA. However, validated methods exist

for analysis of NNN well below the level specified in § 1132.10 by either MS or TEA.

Over the years a variety of analytical methods have been developed for the detection of NNN in smokeless tobacco products. For example, the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) published CORESTA 72, an LC–MS method for determining NNN levels in smokeless tobacco using a low calibration standard of 0.015 µg/g of tobacco, extraction in 100 mM ammonium acetate, and a deuterium-labeled NNN internal standard (Ref. 80). CDC published an LC–MS method for smokeless tobacco with an extraction in ethyl acetate and use of a carbon-13-labeled NNN internal standard with an effective limit of detection of 0.072 µg/g NNN and an 8 minute analysis time (Refs. 81, 82). The Swedish National Food Administration published an LC–MS method for smokeless tobacco with extraction in ethyl acetate, a limit of detection of 0.010 µg/g NNN, a 15 minute analysis time, and quantification using an external NNN standard (Refs. 83, 84). British American Tobacco published an LC–MS method for smokeless tobacco with extraction in methanol, a deuterium-labeled NNN internal standard, and no published limit of detection (Ref. 85).

The American Health Foundation published several similar GC–TEA methods for NNN in chewing tobacco using extraction in a buffer containing ascorbic acid, a 24 minute analysis time, and confirmation by MS of the TEA signal corresponding to NNN (Refs. 86, 87, 88). Health Canada published Official Method T–309, which is a GC–TEA method for NNN in tobacco using extractions in a buffer of ascorbic acid in dichloromethane, an internal standard of N-nitrosopentyl-(3-picolyl)-amine, a lowest calibration standard corresponding to about 0.2 µg/g tobacco, and a 35-minute analysis run time (Ref. 89).

Other approaches besides LC–MS and GC–TEA have been explored to measure NNN in tobacco filler. These methods have included two ISO methods using gas chromatography with chemiluminescence detection (ISO 22303:2008 and ISO 22304:2008), an American Health Foundation method using HPLC with ultraviolet absorption detection followed by confirmation of the peak by MS (Ref. 90), and a Swedish Match method using an NNN-specific antibody in immunoassays (Ref. 91).

Although there are various methods to test for NNN, only the CORESTA 72 method has been externally validated via round-robin method validation studies in accordance with ISO 5725–2 (ISO 5725–2:1994) and only the SRL method tests on a dry weight basis. Thus, FDA concluded that levels of 1.0 µg/g or lower on a dry weight basis of NNN in tobacco could be reliably measured either by SRL's method or by optimizing existing common methods to meet the requirements of § 1132.16 (Alternative test method).

V. 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 a tobacco product standard is 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 doing 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.

As discussed in this section of the document, FDA has considered scientific evidence related to all three factors. Based on these considerations, we find that the proposed standard is appropriate for the protection of public health, because it will reduce the harm associated with the use of smokeless tobacco products and FDA does not expect that the product standard will increase the likelihood that non-users will initiate tobacco or decrease the likelihood that users will quit tobacco use in a manner that would offset the benefits of the reduced cancer risk.

A. Benefits to the Population as a Whole

As discussed in section IV, on the basis of the best available scientific evidence, FDA has determined that NNN is the predominant driver of excess oral cancer risk among smokeless tobacco users. This determination is based on multiple, consistent lines of evidence. First, several authoritative reviews have concluded smokeless tobacco products, including those currently marketed in the United States, cause cancer (Refs. 1, 2, 3, 4). Second, NNN is a potent carcinogenic agent found in smokeless tobacco and, along with NNK, another TSNA, is labeled as Group 1 (known human carcinogen) by IARC (Refs. 1, 2). Third, substantial recent evidence supports site-specific concordance of the carcinogenic effects of NNN in animal and human epidemiologic studies. In particular, oral and esophageal tissues have been identified as targets for NNN-induced carcinogenicity (Refs. 7, 95, 171, 172), with observation of tumors in the oral cavity and esophagus following oral exposure to NNN in experimental animals (Refs. 7, 59, 94, 95, 148, 178). These animal studies suggest a degree of concordance with effects observed at these sites in epidemiologic studies (Refs. 77, 96). Finally, several authoritative reviews have observed differences in the magnitude of cancer risks due to smokeless tobacco use across regions of the world, which have been found to correlate highly with variation in the levels of tobacco specific nitrosamines in smokeless products (Refs. 1, 4).

The proposed product standard is intended to reduce tobacco-related harms by requiring lower levels of NNN (and likely also leading to concomitantly lower NNK levels) in smokeless tobacco products sold in the United States. In this section, we describe the expected benefits of the proposed standard to the population as a whole, including specifically the benefits of reducing the number of new cases of and deaths from oral cancer attributable to smokeless tobacco.

In this section, FDA generates estimates of the number of new cases and fatal cases of oral cancer that would be avoided over the 20 years following implementation of the proposed product standard. We estimate that approximately 12,700 new cases of oral cancer and approximately 2,200 oral cancer deaths would be prevented in the United States. Moreover, during that 20-year period, approximately 15,200 life years would be gained as a result of the proposed standard. Because oral cancer is associated with significant health and economic impacts, we expect positive public health benefits due to prevention of new and fatal oral cancer cases. We also expect that the proposed standard would reduce the number of new and fatal cases of esophageal cancer among continuing smokeless tobacco users and may reduce the risk of pancreatic cancer as well.

1. Estimated Impact of Proposed NNN Standard on New and Fatal Oral Cancers

The analysis in section IV.C suggests that the estimated lifetime cancer risk (ELCR) would drop by approximately 65 percent under the scenario where the proposed product standard for smokeless tobacco products was fully implemented, and while assuming that all other variables remained constant (*e.g.,* user habits). Thus, over time, FDA expects implementation of the proposed product standard to reduce the number of incident cases (*i.e.,* those new cases of oral cancer that occur over time in the smokeless tobacco user population) and fatal cases of oral cancer by reducing the concentrations of a potent oral carcinogen in smokeless tobacco products (Ref. 107). To estimate the potential impact of the standard on morbidity and mortality, we first model the annual number of new cases and deaths from oral cancer that are attributable to smokeless tobacco use in the United States. We then estimate the number of these cases, both those new cases that occur (incident cases) and those that are fatal, that would be prevented as a result of the proposed standard by reducing the population attributable risk by 65 percent. Relative risk estimates used to model the population attributable risk come from a published systematic review and meta-analysis of studies of oral cancer among U.S. smokeless tobacco users (Ref. 100).

More specifically, as described in section IV.C of this document, FDA estimates, by comparing its calculation of the ELCR using the NNN levels of currently marketed U.S. smokeless tobacco products to its calculation of the hypothetical ELCR using the proposed standard, that meeting the standard would result in, on average, a 65 percent reduction in the excess lifetime cancer risk due to NNN among U.S. smokeless tobacco users. Given the apparently predominant role of nitrosamines in smokeless tobacco cancer risk, we assume that the 65 percent reduction can be applied directly to the excess oral cancer risks attributable to smokeless tobacco in general. Public comment is sought on the strength of the assumptions underlying this approach to estimate the anticipated public health effects of the rule, and whether alternative approaches may exist. Commenters should provide evidence supporting alternative assumptions or approaches to estimating likely reduction in incidence of oral cancers associated with an implementation of the proposed product standard.

The analysis quantifies the estimated public health impact of the proposed product standard in terms of new and fatal cases of oral cancer. Oral cancer is used as the endpoint of interest because of the established strong relationship between smokeless tobacco use and oral cancer risk, as well as the identification of NNN as a known, potent oral carcinogen. There are also a relatively large number of published estimates of oral cancer risk among U.S. smokeless tobacco users.

As described in this section, we also expect the standard to reduce the risk of esophageal cancer and it may reduce the risks of cancer at additional sites. However, limited data are available to permit direct quantification of this health benefit (Ref. 100). As such, we focus here on estimating the potential benefits of the proposed product standard in reducing the number of new and fatal cases of oral cancer in the United States.

We use the population attributable risk formula introduced by Levin (Ref. 108) and subsequently used extensively by the CDC in its Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) methodology for modeling smoking-attributable mortality (Ref. 109). Population attributable risk (PAR) is calculated as the proportion of cases of disease that are attributable to the risk factor as:

$$PAR = \frac{P_e(RR - 1)}{1 + P_e(RR - 1)}$$

where P_e is the prevalence of the exposure and *RR* is the relative risk of disease among the exposed compared with the unexposed. The resulting proportion is then multiplied by the total number of cases of disease in the population to estimate the number of cases that are attributable to the risk factor.

We first estimate smokeless tobacco-attributable oral cancer cases and deaths for the United States in 2010. We use this year because of the availability of all relevant data inputs, including smokeless tobacco use prevalence estimates from the same data source used in CDC's SAMMEC method for estimating cigarette smoking-attributable mortality. Because the National Survey on Drug Use and Health reports that smokeless tobacco use prevalence has been relatively consistent among youth and adults in recent years (Ref. 23), these estimates also serve as a general measure of the effects of smokeless tobacco use on oral cancer in the United States in subsequent years. We estimate the U.S. prevalence of smokeless tobacco use using 2010 National Health Interview Survey data (Ref. 111). Current smokeless tobacco use is defined as reporting having used either chewing tobacco or snuff at least 20 times in one's life and currently using that product every day or some days. Age- and sex-specific prevalence of current smokeless tobacco use is reported in table 5, along with the number of new and fatal oral cancer cases in the United States in 2010. The latter were obtained from United States Cancer Statistics data available on CDC's WONDER Web site (Refs. 112, 182, 184, 185, 186). Newly diagnosed (incident) oral cancer cases and oral cancer deaths attributable to use of smokeless tobacco products, stratified by age group and sex, are also reported in table 5. Oral cancer cases attributable to smokeless tobacco accounts for 3.4 percent of all newly diagnosed oral cancer cases.

TABLE 5—PREVALENCE OF CURRENT SMOKELESS TOBACCO USE AND NUMBER OF NEWLY DIAGNOSED AND FATAL CASES OF ORAL CANCER IN THE UNITED STATES, BY AGE GROUP AND SEX, U.S. 2010

	Smokeless tobacco use prevalence [1] (%)	Newly diagnosed oral cancer cases [2]	Oral cancer deaths [2]	Attributable oral cancer cases	Attributable oral cancer deaths	Attributable fraction (%)
Males:						

TABLE 5—PREVALENCE OF CURRENT SMOKELESS TOBACCO USE AND NUMBER OF NEWLY DIAGNOSED AND FATAL CASES OF ORAL CANCER IN THE UNITED STATES, BY AGE GROUP AND SEX, U.S. 2010—Continued

	Smokeless tobacco use prevalence [1] (%)	Newly diagnosed oral cancer cases [2]	Oral cancer deaths [2]	Attributable oral cancer cases	Attributable oral cancer deaths	Attributable fraction (%)
35–64 years	4.6	15,960	2,770	808	140	5.1
65+ years	3.9	10,351	2,997	444	128	4.3
Females:						
35–64 years	0.2	5,322	832	15	<10	0.3
65+ years	0.3	5,664	1,699	19	<10	0.3

[1] Source is the 2010 National Health Interview Survey conducted by the National Center for Health Statistics (Ref. 111).
[2] Source is CDC WONDER, 2010 for cancers of the lip, oral cavity and pharynx (Ref. 112).

In calculating the population attributable risk, FDA used summary relative risks for the relationship between smokeless tobacco use and oral cancer risk derived from a meta-analysis of epidemiology studies published by Boffetta et al. in 2008 (Ref. 100). Boffetta's analysis, based on nine relative risk estimates from seven independent studies, generated a summary relative risk of 2.6 (95 percent confidence interval of 1.3–5.2) for oral cancer associated with the use of chewing tobacco or snuff in the United States. The authors state that this meta-analysis included studies of smokeless tobacco use among non-smokers or among non-smokers and smokers with adjustment for smoking. These risks were used in estimates of the population burden of smokeless tobacco use in the United States, presented in a recent NCI and CDC report on smokeless tobacco use and global public health (Ref. 4).

One study notes that two of the estimates included in Boffetta et al.'s meta-analysis, from a study by Stockwell and Lyman examining the associations between smokeless tobacco use and mouth/gum cancers and tongue cancer, likely did not adjust for cigarette smoking and consequently yielded considerably larger risk estimates than would have likely been observed with adjustment (Refs. 103, 110). To understand the sensitivity of the overall results to this study, we replicated Boffetta et al.'s summary relative risk estimate (where relative risk was 2.6), then re-analyzed the data omitting the two estimates from Stockwell and Lyman. The latter analysis yielded a summary relative risk of 2.16 (with a 95 percent confidence interval of 1.08–4.33). This value matched the overall relative risk estimate from an independent meta-analysis of the relationship between smokeless tobacco use and oral cancer risk in the United States that was published in 2009 by Lee and Hamling (*i.e.,* a relative risk of 2.16; and a 95 percent confidence interval of 1.55–3.02), although based on different methods and a different set of studies. In this analysis, we use the relative risk of 2.16 as the summary relative risk for oral cancer among smokeless tobacco users as the relative risk in 2010 (*i.e.,* in the absence of the proposed standard). Although we believe this relative risk represents the best available estimates based on the research literature, it should be noted that the accuracy and precision of particular study estimates may be somewhat limited due to sample size and changes in study participants' smokeless tobacco use and risk over time.

Table 6 shows that an estimated 1,300 new cases of oral cancer in the United States in 2010 were attributable to smokeless tobacco use using this summary relative risk. These estimates are generally comparable to those reported in the recent NCI and CDC smokeless tobacco report (Ref. 4). The majority of these cases occur among men, which is consistent with low rates of smokeless tobacco use among women.

We use similar methods to estimate the number of oral cancer deaths in the United States in 2010 that were attributable to smokeless tobacco use, with the only difference being that we use the number of oral cancer deaths during this year, rather than new diagnoses during the year, in the population-attributable risk calculations. We also estimate the life years that were lost due to these oral cancer deaths attributable to smokeless tobacco use. We obtain the median ages at death for those dying of oral cancer by sex and age group (35–64 years and 65+ years) for the United States in 2010 (Ref. 112) and life expectancy estimates by sex at these ages from life tables for the United States in 2010 produced by the National Center for Health Statistics (Ref. 113). These life expectancy values are then multiplied by the number of attributable oral cancer deaths for each group to estimate the number of life years that were lost due to oral cancer. In this case, all future life years lost due to oral cancer deaths were assigned to the year in which the death occurred.

Table 6 shows that an estimated 300 oral cancer deaths in the United States in 2010 were attributable to smokeless tobacco use. These deaths represent an eventual loss of 4,900 life years. Consistent with the data on new cases and deaths from oral cancer shown in table 5 and with the lower rates of smokeless use among women, the majority of attributable deaths and life years lost occur among men.

TABLE 6—ESTIMATED ORAL CANCER CASES, DEATHS, AND CORRESPONDING LIFE YEARS LOST ATTRIBUTABLE TO SMOKELESS TOBACCO USE, U.S. 2010

Attributable new oral cancer cases	Attributable oral cancer deaths	Life years lost due to attributable oral cancer deaths
1,300	300	4,900

Note: Smokeless tobacco attributable oral cancer cases and deaths are rounded to the nearest hundred and estimated from information presented in table 5 including the U.S. summary relative risk value reported by Boffetta et al. (Ref. 100), as revised by FDA.

We also conducted a sensitivity analysis using other oral cancer relative risk estimates from the meta-analysis conducted by Lee and Hamling (Ref. 114). Lee and Hamling's analysis generated estimates of never smoker oral cancer relative risks (a relative risk of 3.33 and a 95 percent confidence interval of 1.76–6.32) for 5 studies and smoking-adjusted oral cancer relative risks (a relative risk of 1.65 and a 95 percent confidence interval of 1.22–2.25) for 12 studies for U.S. smokeless tobacco users. Lee and Hamling prioritized estimates for the population of smokers and nonsmokers that adjusted for smoking status over estimates for never smokers in studies that reported both types of estimates in contrast to Boffetta et al., who did the reverse. We did not use Lee and Hamling's never smoker relative risk in the main analysis because the number of studies that reported these risks is limited and only two of these estimates adjust for alcohol consumption. We also did not use Lee and Hamling's smoking-adjusted relative risk in the main analysis because smokeless tobacco risks that control for smoking may over-adjust if individuals who both smoke and use smokeless tobacco are more likely to smoke less or quit smoking compared with exclusive smokers (Refs. 192, 92). These relative risks were used to generate population-attributable risk estimates with the other inputs used above. Using these alternative relative risks yields estimates of approximately 700 to 2,500 new oral cancer cases in the United States that are attributable to smokeless tobacco use per year. Similarly, using these relative risks yields estimates of attributable oral cancer deaths ranging from approximately 200 to 500 per year.

We then use similar methods to project the effect of the proposed product standard on oral cancer attributable to smokeless tobacco use in the United States over time. The proposed standard would reduce the levels of NNN in U.S. smokeless tobacco products and is also expected to reduce NNK levels. As described in this section, the proposed standard is predicted to eventually reduce excess lifetime oral cancer risks among U.S. smokeless tobacco users by 65 percent, on average. This reduction in population cancer risk would likely occur over a period of time, given that some smokeless tobacco users may still develop oral cancer at the higher risk level after implementation of the proposed product standard due to previous exposure to higher NNN levels in smokeless tobacco products. For the purposes of generating projections, we assume that any final rule on the tobacco product standard for NNN would become effective 3 years after the date of publication of the final rule (see section VII, Proposed Effective Date) and that public health benefits would begin to accrue once the standard is in effect.

In estimating the health impact of the proposed standard on smokeless tobacco users, we begin with an oral cancer relative risk for smokeless tobacco users in the United States of 2.16 from FDA's revised meta-analysis of Boffetta et al. (Ref. 100). This relative risk indicates an increase in oral cancer risk of 116 percent among smokeless tobacco users compared with never users. We then reduce this value by 65 percent based on toxicological evidence relating the estimated average reduction in the dose of NNN to lifetime cancer risk under the proposed standard. The result is a reduction in the estimated relative risk of oral cancer to 1.41 under the proposed product standard. FDA used the following calculation: $(1 + (2.16 - 1) \times (1 - 0.65) = 1.41)$ for this determination.

We use studies of relevant cancer risks for former tobacco users by time since cessation to provide information about risk reductions over time after reductions in toxicant exposure. Due to limited data on the timing of cancer risk reduction after smokeless tobacco cessation, we applied estimates of relative risks by time since cessation for former cigarette smokers to approximate the time it takes for excess cancer risk to be eliminated after quitting smokeless tobacco. Estimates from cigarette smokers help inform our estimation of the trajectory of oral cancer risk reduction that could be expected as a result of reducing regular exposure to tobacco-related carcinogens. These studies generally find higher risks for oral cancer for former smokers during the first 10 years after smoking cessation compared to never smokers, but not necessarily thereafter (Refs. 115, 2). We therefore project that reductions in new oral cancer cases attributable to smokeless tobacco use would be fully realized over a 10-year period after manufacturers are in compliance with the product standard, with the reduction occurring in 10 percent increments until the full benefit is reached. We also assume that, in the absence of the proposed standard, new cancer cases attributable to smokeless tobacco use in the United States would remain constant over time, given that the National Survey on Drug Use and Health data show that smokeless tobacco use has remained relatively consistent among youth and adults since 2000 (Ref. 23). Using this approach and the revised Boffetta relative risk, we estimate that approximately 12,700 new cases of oral cancer would be prevented in the United States in the 20 years following implementation of the proposed product standard (table 7), which represents a 50 percent reduction in estimated smokeless-attributable oral cancer cases over that time period. We use the same approach to project the effect of the proposed standard on oral cancer deaths, once again assuming that reductions in deaths would be realized over a 10-year period but also assuming that this reduction will begin 3 years after implementation of the standard due to previously existing or developing cases of oral cancer. In this case, we assign the life years gained due to reductions in oral cancer deaths to the years in which the additional life years are actually lived. We estimate that approximately 2,200 oral cancer deaths would be prevented, and approximately 15,200 life years gained in the United States in the 20 years following implementation of the product standard (table 7). This represents a 40 percent reduction in estimated smokeless-attributable oral cancer deaths as a result of the product standard over a 20 year period.

We also conducted sensitivity analyses of these projections with the alternative summary relative risks from Lee and Hamling. Using the smoking-adjusted relative risk for oral cancer of 1.65 for U.S. smokeless tobacco users, we obtain a cumulative reduction of approximately 7,300 oral cancer cases and 1,300 oral cancer deaths over a 20-year period with the product standard. With the never smoker relative risk of 3.33, we obtain a reduction of approximately 24,000 oral cancer cases and 4,200 oral cancer deaths during the period.

We also examined possible impacts from changes to input values in these calculations. Specifically, we estimated changes in the public health benefits due to differences in smokeless tobacco prevalence and the length of time in which the full oral cancer risk reduction will be observed among U.S. smokeless tobacco users. These analyses are in the Uncertainty and Sensitivity Analysis, section II.G, of the Regulatory Impact Analysis associated with this proposed rule.

TABLE 7—PROJECTED CUMULATIVE DIFFERENCE IN NEW ORAL CANCER CASES AND ORAL CANCER DEATHS ATTRIBUTABLE TO SMOKELESS TOBACCO USE IN THE U.S. AND CORRESPONDING LIFE YEARS GAINED DUE TO IMPLEMENTATION OF THE PROPOSED STANDARD

Years after full implementation of the standard	Cumulative difference in attributable cases	Cumulative difference in attributable deaths	Cumulative life years gained
10 years	4,500	500	1,500
20 years	12,700	2,200	15,200

Note: Estimates in the table are rounded to the nearest hundred.

2. Additional Public Health Benefits From Reducing Oral Cancer

As a result of this proposed rule, we estimate considerable public health benefit to the United States resulting from reduced risk of oral cancer among smokeless tobacco users due to reductions in NNN (and concomitant reductions in NNK) levels in smokeless tobacco. The public health impact of oral cancer is estimated to be considerable in size. In the United States, about 65 percent of oral cancer patients survive at least 5 years with disease and those individuals who survive oral cancer can face profound challenges and reductions in quality of life.

Oral cancer patients and survivors can face major functional problems when performing basic tasks of daily living such as eating and talking. Treatment procedures can result in disfigurement or other serious cosmetic problems that also adversely impact quality of life (Ref. 116). Surgical treatments for head and neck cancers have been found to be associated with subsequent self-image issues and social isolation that increased with the level of disfigurement (Ref. 117). Patients with head and neck cancers also report high levels of anxiety and depressive symptoms (Ref. 116), and even long-term survivors report high levels of psychological distress (Ref. 118).

In the United States in 2010, approximately $3.63 billion annually was spent on medical treatment and followup care for all head and neck cancers (Ref. 119), which includes cancers of the oral cavity, pharynx, larynx, nasal cavity, and salivary glands (Ref. 120). The proposed standard will benefit public health by preventing thousands of new oral cancer cases and deaths caused by smokeless tobacco use over the next two decades.

3. Unquantified Potential Reductions in Other Cancers

In addition to reducing the risk of oral cancer, lower levels of NNN in smokeless tobacco under the proposed standard are expected to lower the risk of esophageal cancer. Smokeless tobacco use has been identified as a cause of esophageal cancer (Refs. 1, 2) and NNN has been directly linked to esophageal cancer in numerous animal studies (Ref. 8) and in an epidemiological study of smokers (Ref. 77). However, limited data are available, so the health benefit cannot be directly quantified.

Pancreatic cancer has also been identified as causally related to smokeless tobacco use (Refs. 1, 2). Lower levels of NNN (and potential reductions in NNK) in U.S. smokeless tobacco under the proposed standard have the potential to reduce the incidence of pancreatic cancer. Boffetta et al. reported the relative risk of pancreatic cancer from four studies of U.S. smokeless tobacco users to be elevated (*i.e.,* a relative risk of 1.4), although not statistically significant. Yet, estimates of pancreatic cancer relative risks have not consistently been reported to be higher in U.S. smokeless tobacco studies compared with Scandinavian snus product studies (Refs. 100, 114).

Lower levels of NNN in smokeless tobacco may also reduce the incidence of laryngeal and prostate cancers. Lee and Hamling's (Ref. 114) review found U.S. smokeless tobacco use was significantly associated with laryngeal cancer in four studies including one study that adjusted for cigarette smoking. More recently, Zhou et al. (Ref. 122) found that use of smokeless tobacco for 10 or more years was associated with elevated risk of laryngeal cancer. Lee and Hamling (Ref. 114) also found a statistically significant association between U.S. smokeless tobacco use and prostate cancer. Although NNN has not specifically been linked with an increased risk of these cancers, it is a potent carcinogen and smokeless tobacco product use can result in exposure throughout the human body.

Given that U.S. smokeless products contain high amounts of NNK, and NNK is a recognized systemic lung carcinogen (Ref. 8) in experimental animals, potential reductions in NNK levels in smokeless tobacco as a result of the proposed NNN standard may lead to some reduction in lung cancer risk. There is some evidence linking smokeless tobacco use to lung cancer (Ref. 121), although a definitive association has not been established in authoritative reviews (Refs. 3, 4).

B. The Likelihood That Existing Users of Tobacco Products Will Stop Using Such Products

Although data are lacking on perceptions of smokeless tobacco toxicants, including NNN, and cessation, there is some evidence on users' motivations for quitting smokeless tobacco. Some studies suggest that concerns about developing health problems are among the common motives that smokeless tobacco users provide for quitting (Refs. 123, 124). These studies suggest that if the proposed standard affects consumer perceptions about the harms of smokeless tobacco use, it may influence their cessation motivations. Specifically, if current smokeless tobacco users interpret an NNN product standard to mean the health risks from smokeless tobacco use will be lower after the standard is in effect, this might reduce some users' motivations to quit. It is worth noting, however, that while the magnitude of risk would be changed by implementation of the proposed standard, appreciable cancer risk would remain. Accordingly, users would still have a strong incentive to quit. FDA, therefore, does not expect the proposed product standard to appreciably discourage cessation of smokeless tobacco products in such a way as to offset the beneficial public health impact from reduced cancer risk.

Although data are lacking on perceptions of smokeless tobacco product toxicants, including NNN and the effect of awareness on cessation behaviors, prevalence of smokeless tobacco use would need to increase substantially in order to offset the reduction in cancer risk expected as a result of this rule. The magnitude of the change needed can be estimated using the population attributable risk calculation presented in section V.A.1 of this document. The calculation

includes the product of the excess relative risk (RR–1) and the prevalence of smokeless tobacco use. Therefore, smokeless tobacco use prevalence would need to nearly triple in order to completely offset the expected reduction in excess lifetime cancer risk to the equivalent of approximately one-third of the baseline cancer risk.

While there is evidence that exposure to media can lead to health behavior changes (Refs. 126, 127), it is unclear whether media coverage of this proposed product standard would promote sustained behavior change in the form of increased or decreased likelihood of smokeless tobacco cessation.

Methods used to reduce NNN levels as a result of this proposed rule may or may not produce changes that affect the sensory experiences of smokeless tobacco use. Consumers' sensory experiences can in turn influence their perceptions of product harms (Refs. 128, 129, 130), which can impact product use. However, for moist snuff, which constitutes the overwhelming majority of the smokeless tobacco market in the United States (Ref. 131), manufacturers have already identified ways to reduce nitrosamine content without negatively impacting the taste or user experience (see sections IV.C and IV.E of this document). Smokeless tobacco products are heavily flavored and the presence of flavors is a significant driver of consumer acceptance of these products (Ref. 70). The proposed standard does not prevent the addition of flavors to offset any changes in the taste of the product due to the methods used to reduce NNN to meet the proposed standard.

C. The Likelihood That Non-Users Will Start Using Tobacco Products

The proposed product standard is not expected to substantially increase, if at all, the likelihood that those who do not use smokeless tobacco will take up the product. Public perception is that smokeless tobacco use has some potential harms (Refs. 76, 133, 134, 135, 136). At this time we are not aware of direct scientific evidence demonstrating that the proposed smokeless tobacco product standard would influence consumers' perceptions of product appeal, relative risk, and absolute risk, or behaviors. Even if the proposed standard were to result in some changes to perceptions and behaviors, FDA believes that they would not offset the beneficial public health impact from reduced cancer risk. As described in this section, FDA estimates that the prevalence of smokeless tobacco use would have to nearly triple in order to offset the expected excess cancer risk reduction due to the proposed rule.

Data are not available on consumers' awareness and perceptions of NNN in smokeless products, although a single published study in a U.S. adult sample of smokers and non-smokers found awareness of and knowledge about NNN in cigarette smoke was low, particularly in comparison to other constituents (Ref. 125). Although there is very low awareness of NNN as a constituent, it is possible that some non-users of smokeless tobacco will be aware of the proposed standard and interpret it to mean that smokeless tobacco is less harmful than other tobacco products and this could, in turn, affect smokeless tobacco initiation. Research suggests that risk perceptions of tobacco use—that is, judgments about its harmfulness—can influence tobacco initiation (Refs. 137, 138). However, if the proposed standard were to result in additional uptake of smokeless tobacco use in the population, this could either decrease or increase the expected health benefits of the proposed standard. If cigarette smokers who would not otherwise quit smoking completely switched to smokeless tobacco products as a result of this standard, we would expect additional reduction in risk to these individual users. If cigarette smokers became dual users of cigarettes and smokeless tobacco products, this could have varying impacts depending on the extent to which such dual use led to substantial reductions in cigarette consumption or led to delayed cessation of tobacco products altogether. Conversely, the anticipated net population health benefits of the standard would be reduced if it led substantial numbers of never or former tobacco users to begin or resume using smokeless tobacco products.

In the case that some adolescents and young adults become aware that FDA is taking steps to reduce the harmfulness of smokeless tobacco products, FDA expects that any impact on smokeless tobacco initiation would be limited. First, smokeless tobacco initiation among youth has been shown to be associated with social influences such as actual or perceived peer use (Refs. 139, 140) to a greater extent than perceptions of the long-term health effects. Further, youth curiosity about smokeless tobacco is lower than curiosity about cigars or cigarettes (Ref. 141), suggesting that fewer adolescents are at risk for future use, compared to many other tobacco products. Thus, at the population level, very few adolescents are likely to be aware that FDA is taking an action related to NNN in smokeless tobacco products, and, even if there were some awareness, given that the standard is related to reducing long-term health effects, it is unlikely to have an impact on youth initiation.

It is possible that some former users could potentially relapse back to smokeless tobacco use due to perceptions of lower risk. Although specific data on relapse among smokeless users is not available, there is some data on relapse among smokers. For example, predictors of relapse for smokers who reported they had quit between study waves were assessed in one of the few studies assessing relapse in the general population and not part of a clinical trial. Neither the perceived costs of smoking (such as thoughts about the harms of smoking) nor benefits of quitting (including health benefits) were related to relapse (Ref. 142). However, nicotine dependence is related to relapse among smokers (Refs. 143, 144); and because smokeless tobacco products also deliver nicotine, FDA expects that the same reason for relapse would apply to former smokeless tobacco users and that changes to perceptions of costs and benefits would have little effect on relapse rates. Overall, the extent to which the proposed standard may influence behaviors of non-users and former users is likely to be minimal since health-related reasons are not among the main drivers of smokeless tobacco use initiation or relapse. Finally, HHS plans to continue developing and implementing public education campaigns to help prevent initiation of all tobacco products, including smokeless tobacco.

D. Conclusion

NNN is a potent carcinogenic agent found in smokeless tobacco and, along with NNK, another TSNA, is a major contributor to the elevated cancer risks associated with smokeless tobacco use. Oral and esophageal tissues have been identified as targets for NNN-induced carcinogenicity, when NNN was administered orally in animal studies, which indicates some concordance with effects observed at these sites in epidemiologic studies. NNN levels in most smokeless tobacco manufactured in the United States are higher than NNN levels in smokeless tobacco manufactured in Sweden. Oral cancer risks in U.S. smokeless tobacco users are elevated compared to the oral cancer risks in Scandinavian users. The proposed product standard is expected to reduce tobacco-related harms by reducing the levels of NNN in smokeless tobacco products sold in the United States, thereby reducing the risk of oral

cancer in smokeless users. By our estimates, in the 20 years following implementation of the proposed product standard, approximately 12,700 new cases of oral cancer and approximately 2,200 oral cancer deaths would be prevented in the United States. Moreover, during that 20-year period, approximately 15,200 life years would be gained as a result of the proposed standard. This represents a substantial benefit to the public health. Because oral cancer is associated with significant impacts on health and quality of life, we expect positive public health benefits due to prevention of new and fatal cancer cases. We also expect the proposed product standard to reduce the risk of esophageal cancer among smokeless tobacco users, and it may reduce the incidence of other cancer types; however, there is limited data available to directly quantify this health benefit.

Based on currently available evidence discussed previously, we do not anticipate the proposed standard would have behavioral impacts on smokeless tobacco initiation, cessation, switching to other products, or dual use in a way that would offset the public health benefits of the reduced cancer risk that would result from the proposed standard. Even if the proposed standard were to result in some instances of decreased smokeless tobacco cessation or increased initiation among non-users of tobacco, we would not expect the magnitude of these effects to be comparable to the public health benefits of the proposed rule. As described in this section, FDA estimates that the prevalence of smokeless tobacco use would have to nearly triple in order to offset the excess cancer risk reduction expected due to the proposed rule. In addition, to the extent that cigarette smokers who cannot or will not quit smoking are motivated to switch completely to smokeless tobacco due to perceptions of lower risk, this complete switching could result in additional benefits to public health through reduced risks to these individual users.

Accordingly, for the reasons discussed in this section, we find that the proposed standard is appropriate for the protection of public health. It would reduce the cancer risk posed by smokeless tobacco products and FDA does not expect that the product standard would increase the likelihood that non-users would initiate tobacco or decrease the likelihood that users will quit tobacco use. Even if the proposed standard were to result in some instances of decreased smokeless tobacco cessation or increased initiation among non-users of tobacco, we would not expect the magnitude of these effects to offset the benefits of the reduced cancer risk.

VI. Description of Proposed Regulation

A. General Provisions (Proposed Subpart A)

1. Scope (Proposed § 1132.1)

Proposed § 1132.1 identifies the scope of products that would be subject to this NNN product standard. FDA intends for this proposed standard to cover finished smokeless tobacco products, which are defined in proposed § 1132.3 (proposed § 1132.1(a)). This includes moist snuff, snus, dry snuff, chewing tobacco, and some dissolvables. Some dissolvable tobacco products do not meet the statutory definition of ''smokeless tobacco product'' because they do not contain cut, ground, powdered, or leaf tobacco; instead, these products contain nicotine extracted from tobacco. Dissolvable products that do not meet the statutory definition of ''smokeless tobacco product'' are not covered by this proposed rule. As previously noted, this rule focuses on smokeless tobacco products because different measures are required to address NNN in other tobacco products.

Proposed § 1132.1(b) states that no person may manufacture, distribute, sell, or offer for sale or distribution within the United States a finished smokeless tobacco product that is not in compliance with this part. For example, FDA would not consider finished smokeless tobacco products to be in compliance with this part if they exceed the NNN level set forth in proposed § 1132.10, the package label does not have a manufacturing code or expiration date, or the package label has a manufacturing code or expiration date that has been altered, mutilated, destroyed, obliterated, obstructed, concealed, or removed in whole or in part.

This provision is not intended to restrict the manufacture of smokeless tobacco products intended for export. Consistent with section 801(e)(1) of the FD&C Act, a tobacco product intended for export shall not be deemed to be in violation of section 907 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.

Proposed § 1132.1(c) explains that tobacco retailers and distributors will not be considered in violation of this part as it relates to the sale or distribution or offer for sale or distribution of finished smokeless tobacco products that exceed the NNN level set forth in § 1132.10 if they: (1) Store and transport the finished smokeless tobacco products according to the package label, (2) do not sell or distribute or offer for sale or distribution finished smokeless tobacco products past their expiration date, except to return expired products to the manufacturer, (3) do not conceal, alter, or remove the expiration date or storage conditions on the package label, and (4) do not sell or distribute or offer for sale or distribution finished smokeless tobacco products that are open or have broken seals.

FDA is proposing this exception for tobacco retailers and distributors because they cannot reasonably know or confirm by testing whether the smokeless tobacco products they are selling or distributing or offering for sale or distribution comply with the proposed NNN level. Provided that the tobacco retailers and distributors meet the requirements set forth in proposed § 1132.1(c)(1) through (4), FDA will not consider them to be in violation of part 1132 as it relates to the sale or distribution or offer for sale or distribution of products that exceed the NNN level set forth in proposed § 1132.10.

We note that tobacco retailers and distributors would need to meet all of the requirements in proposed § 1132.1(c) in order to be considered in compliance with this part as it relates to the sale or distribution or offer for sale or distribution of smokeless tobacco products that exceed the NNN level set forth in proposed § 1132.10. A retailer or distributor who, for example, covers the expiration date or storage conditions with a sticker, changes the expiration date, or scratches off the expiration date or storage conditions on the package label would not meet the requirements in proposed § 1132.1(c)(3). Furthermore, a retailer who sells finished smokeless tobacco products that are open or have broken seals would not meet the requirements in proposed § 1132.1(c)(4), because doing so could lead to changes in the NNN level, especially if it is exposed to heat or humidity.

2. Definitions (Proposed § 1132.3)

Proposed § 1132.3 provides the definitions for the terms used in the proposed rule. Several of these definitions are included in the FD&C Act or have been used in other regulatory documents.

- *Batch:* FDA proposes to define ''batch'' as a specific identified amount of a finished smokeless tobacco product produced in a unit of time or quantity and that is intended to have the same characteristics. As stated in section 910(a)(3)(B) of the FD&C Act,

characteristics means the ''materials, ingredients, design, composition, heating source, or other features of a tobacco product.''

• *Commercial distribution:* FDA proposes to define ''commercial distribution'' as any distribution of a finished smokeless tobacco product to consumers or to another person through sale or otherwise, but does not include interplant transfers of a tobacco product between registered 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.

• *Finished smokeless tobacco product:* We propose to define ''finished smokeless tobacco product'' as a smokeless tobacco product including all parts and components, packaged for consumer use, but it would not include a component, part, or accessory sold without tobacco. A product that is ''packaged for consumer use'' would have the package label on the product. For example, a tin or can of loose snuff or a pouch containing chewing tobacco, with package labels, would meet this definition.

• *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 in 2-digit numerical values in the month, day, year format (mmddyy) followed by the batch number from which the production batch can be identified. The purpose of the manufacturing code is to allow manufacturers and FDA to identify the production batch of a particular product that has been released for commercial distribution. 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 product investigation and any corrective actions that stem from the nonconforming product investigation.

• *Manufacturing date:* We propose to define ''manufacturing date'' as the month, day, and year that a smokeless tobacco product is packaged for consumer use (*i.e.,* when the package label has been added to the product). 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 product investigation.

• *N-nitrosonornicotine (NNN):* FDA proposes to define ''N-nitrosonornicotine'' as a tobacco-specific nitrosamine (TSNA) with the chemical formula C[9]H[11]N[3]O.

• *New tobacco product:* As defined in section 910(a) of the FD&C Act, the term ''new tobacco product'' means: (1) Any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or (2) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.

• *Package:* 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.

• *Performance criteria:* FDA proposes to define ''performance criteria'' as the validation requirements for the acceptability of an analytical test method, including accuracy, precision, recovery, linearity, specificity, limit of quantitation, limit of detection, robustness, and range.

• *Person:* As defined in section 201(e) of the FD&C Act, the term ''person'' includes an individual, partnership, corporation, or association.

• *Rework:* We propose to define ''rework'' as the processing of nonconforming finished smokeless tobacco products to meet the requirements of this part.

• *Smokeless tobacco:* As defined in section 900(18) of the FD&C Act, the term ''smokeless tobacco'' means any tobacco product that consists of cut, ground, powdered, or leaf tobacco and that is intended to be placed in the oral or nasal cavity. This includes moist snuff, snus, dry snuff, chewing tobacco, and some dissolvables. Some dissolvable tobacco products do not meet the statutory definition of ''smokeless tobacco product'' because they do not contain cut, ground, powdered, or leaf tobacco; instead, these products contain nicotine extracted from tobacco. Dissolvable products that do not meet the statutory definition of ''smokeless tobacco product'' are not covered by this proposed rule.

• *Source data:* FDA proposes to define ''source data'' as all information contained in original laboratory records or exact copies of original records of experimental findings, observations, or other activities used for the creation, reconstruction, and evaluation of a study or other laboratory work. Source data includes any laboratory worksheets, notebooks, correspondence, notes, and other documentation (regardless of capture medium) that are the result of original observations and activities of a laboratory study or other laboratory work.

Source data could include protocols and standard operating procedures, information regarding calibration of equipment used to measure or test samples, test standards, and the standard curves used to determine the measure of the samples being tested or of the accuracy and reliability of the test. This type of information may be needed to fully evaluate, for example, whether the product meets the product standard. In addition, if there are any problems with the data, the manufacturer and FDA would be able to use the source data to reconstruct the study or lab work, which could help identify and correct any deviations. In accordance with proposed § 1132.32, source data records would have to be maintained by the manufacturer.

• *Tobacco product:* As defined in section 201(rr) of the FD&C Act, the term ''tobacco product'' means any product that is made or derived from tobacco 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), or a combination product described in section 503(g) of the FD&C Act (21 U.S.C. 321(g)(1), 321(h), and 353(g)).

• *Tobacco product manufacturer:* As defined in section 900(20) of the FD&C Act, ''tobacco product manufacturer'' means any person, including a repacker or relabeler, who manufactures, fabricates, assembles, processes, or labels a tobacco product or imports a finished tobacco product for sale or distribution in the United States.

• *Tobacco-specific nitrosamine (TSNA):* We propose to define ''tobacco-specific nitrosamine'' to mean a chemical compound formed through the chemical reaction involving the nitrosation of nicotine, nornicotine, anabasine, or anatabine during the growing, curing, processing, or storage of tobacco.

• *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.

3. Incorporation by Reference (Proposed § 1132.5)

Proposed § 1132.5 identifies the materials that FDA proposes to incorporate by reference in this part. Information that is incorporated by reference would have the same force and effect as language explicitly stated in the codified. Under the proposed rule, a tobacco product manufacturer would be required to follow procedures and methods for testing as described in any standards incorporated by reference, unless the manufacturer meets the requirements in § 1132.16 for an alternative test method.

FDA is proposing to incorporate by reference a validated method developed by FDA's SRL to be the standard test method for NNN in smokeless tobacco products (proposed §§ 1132.5(a) and 1132.14). As discussed in section IV.F of this document, the results from the test method demonstrate a high level of specificity, accuracy, and precision in measuring a range of NNN levels across a variety of smokeless tobacco products.

If the proposed incorporation by reference is approved by the Office of the Federal Register and incorporated in the final rule, interested parties would be able to examine the incorporated material at the National Archives and Records Administration (NARA) and at FDA's Division of Dockets Management (proposed § 1132.5(b)), and obtain copies of the standard test method by contacting FDA's Center for Tobacco Products at the addresses and/or Web sites listed in proposed § 1132.5(b)(2).

If FDA subsequently determines that a test method, which has been incorporated by reference in a final rule, should be replaced with another method or updated, FDA will update the regulation in accordance with the Administrative Procedure Act (5 U.S.C. 553) and obtain approval of the change to the incorporation by reference in accordance with 1 CFR part 51.

Proposed § 1132.5(c) explains that if tobacco manufacturers or testing laboratories using these standards find an inconsistency between a material incorporated by reference in this part and definitions or methods described by FDA in proposed part 1132, the definitions or methods in proposed part 1132 take precedence.

B. Product Requirements (Proposed Subpart B)

1. NNN Level (Proposed § 1132.10)

For the reasons discussed in section IV of this document, FDA is proposing that the mean level of NNN in any batch of finished smokeless tobacco products must not exceed 1.0 µg/g of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by testing in compliance with § 1132.12. Under the proposed rule, manufacturers would be required to test their finished smokeless tobacco products using the standard test method in § 1132.14 or the alternative test method in § 1132.16.

In proposing to set the limit in terms of a batch mean, FDA has tentatively determined that the mean value is more appropriate than a limit applied to each unit produced from the entire batch of a product, given that the cancer risk is due to long term and repeated exposure, and given the variability of NNN in this agricultural product. Although we expect some degree of variability in NNN to exist in smokeless tobacco products, we recognize there may be circumstances where there could be wide ranges in the variability of NNN for some smokeless tobacco products, resulting in reduced consistency among the units produced and reduced predictability of compliance with a standard requiring that each unit meet a specific limit. FDA is requesting scientific data that could be used to determine the expected distribution of individual results for samples for a per-batch mean limit of an NNN level of 1.0 µg/g of tobacco on a dry weight basis (see proposed § 1132.10). FDA also requests comment on the compliance implications of the currently proposed approach.

NNN-related cancer risk is due to long term and repeated exposure to NNN. Under the currently proposed approach, as long as the mean of each batch consistently conforms to the NNN level of 1.0 µg/g of tobacco (on a dry weight basis) in accordance with § 1132.10, FDA expects that the long term impact from an occasional exposure to a product with slightly higher NNN level will be offset by the exposure to slightly lower levels. Therefore, any random variation that may exist is not expected to negatively impact the public health benefit of the proposed standard, which is based on reduction of excess lifetime cancer risk.

FDA also is considering an alternative approach that includes setting a standard where the specified NNN level of 1.0 µg/g of tobacco (on a dry weight basis) would apply to all units produced from the entire batch, rather than to a per-batch mean. This alternative approach would thereby require the manufacturer to ensure compliance of each unit made from a batch despite some expected random variation of the NNN level between units. This could further increase the public health benefits of this product standard. However, in instances where manufacturers determined that some units within a batch had levels of NNN above the limit and others had levels below the limit, this alternative approach could add costs for manufacturers (*e.g.,* costs of rejecting or reworking the batch) or require them to manufacture product with NNN levels lower than the NNN level of 1.0 µg/g of tobacco (on a dry weight basis) in order to minimize the risk of having to reject a batch based on random variation. FDA currently believes that this is not necessary to achieve the public health goals of the proposed standard, but invites input on this point.

We invite comments on FDA's proposed approach and on the alternative approach and their implications for compliance with the limit, and public health impact. We also invite comments or information on batch sampling methods or other approaches manufacturers might use to determine compliance with an absolute limit on all units produced from a batch given the expected variability of NNN in relevant products.

2. Product Testing (Proposed § 1132.12)

Proposed § 1132.12 contains provisions for the testing of smokeless tobacco products. FDA is proposing to require two types of testing—stability testing and batch testing.

a. *Stability testing.* Proposed § 1132.12(a) would require each tobacco product manufacturer to conduct testing to assess the stability of the NNN level in its finished smokeless tobacco products. Given the variability of NNN levels in current smokeless tobacco products (see section IV.B.1 of this document), stability testing would help ensure that the NNN level in finished smokeless tobacco products is being properly monitored and controlled and that it remains in conformance with the proposed limit through the product's labeled expiration date. The initial stability testing would establish the rate of change of the NNN level for a product and the annual stability testing would identify any changes to the rate of change of the NNN level in that product.

Manufacturers would be required to use the results of stability testing to establish and verify the product's expiration date and storage conditions

(either room temperature or refrigeration). Proposed § 1132.20 would require all finished smokeless tobacco products to have an expiration date established by stability testing. This date would have to be no later than the final date the manufacturer can demonstrate that the NNN level in the finished smokeless tobacco product conforms to § 1132.10 when the product is stored under its intended conditions (*e.g.,* room temperature or refrigeration).

When conducting stability testing, manufacturers would be required to use either the standard test method in § 1132.14 or an alternative test method that meets the requirements in § 1132.16 and samples would have to be selected in accordance with the requirements set forth in § 1132.18(a) and (c) (proposed § 1132.12(a)(1)).

Proposed § 1132.12(a)(2) would require each manufacturer to establish and maintain a written protocol for all stability testing, that fully describes the methodology used to determine the stability of the NNN level, including the test method used (the standard test method in proposed § 1132.14 or an alternative test method in accordance with proposed § 1132.16), the sampling plan and procedures required by proposed § 1132.18(a) and (c), and the storage conditions.

Proposed § 1132.12(a)(3) requires initial real-time stability testing that covers each finished smokeless tobacco product. In certain circumstances, it may not be necessary to conduct initial real-time stability testing on a particular product because the results from initial real-time stability testing conducted on another similar product apply. For example, a manufacturer who manufactures moist snuff in a tin and moist snuff in a pouch would be required to conduct initial real-time stability testing on both products, because the tin and the pouch could have different impacts on the NNN level and, thus, on the stability of the finished products. In contrast, a manufacturer who manufactures two finished products, where the only difference between them is a slight change in flavor ingredients that does not affect NNN levels, would only be required to conduct initial real-time stability testing on only one of the two products. The results from that testing would apply to both products and the testing would be considered to cover both products. Other examples of differences between products that would not require additional initial real-time stability testing, if initial real time stability testing has already been conducted on one of the products, include slight changes in acids, bases, or other pH modifiers with no resulting change in final pH. This provision is intended to reduce the burden on the manufacturer, while ensuring that there is initial real-time stability data that applies to all finished tobacco products, thus preserving the goal of the requirement.

Manufacturers would be required to use the results from initial stability testing to establish an expiration date and appropriate storage conditions (either room temperature or refrigeration) for the finished product. We believe that room temperature or refrigeration are the most likely storage conditions for smokeless tobacco products because most current smokeless tobacco products are stored at room temperature while some snus products are refrigerated. FDA does not expect that manufacturers would choose to freeze their finished smokeless tobacco products. The expiration date and storage conditions would be required to be displayed on the package label in accordance with proposed § 1132.30.

For initial real-time stability testing, FDA is proposing that, at a minimum, samples be tested within 7 days of manufacture to determine the starting NNN level and at the expected expiration date (proposed § 1132.12(a)(3)(i)). Testing the NNN level at various time points is intended to ensure that the NNN level in finished smokeless tobacco will conform to § 1132.10 through the determined expiration date under the intended storage conditions. If the proposed storage condition is room temperature, samples for initial real-time stability testing would have to be stored at 25 ± 2 degrees Celsius and 60 ± 5% relative humidity (proposed § 1132.12(a)(3)(i)(A)) and, if the proposed storage condition is refrigeration, samples would have to be stored at 5 ± 2 degrees Celsius (proposed § 1132.12(a)(3)(i)(B)).

FDA believes manufacturers will likely choose to test at several additional time points to determine the rate of NNN change, if any. Testing of additional time points could allow the manufacturer to establish an acceptable expiration date even if testing shows the finished smokeless tobacco product would exceed the level set forth in § 1132.10 at the expected expiration date. For example, a manufacturer may initially expect its product to have a conforming NNN level for a period of 8 months, based on history of experience with similar products. If instead of only testing the product at 7 days and at 8 months, the manufacturer chooses to test at 7 days, 6 months, and 8 months, that manufacturer would still be able to establish an expiration date for its product (at 6 months) if the testing results showed that the product conforms at 6 months but not at 8 months. Because NNN levels in the product would only increase over time, manufacturers would also be able to choose a shorter expiration date if they wish (Ref. 11). For instance, if stability testing demonstrated the NNN level remains in conformance with proposed § 1132.10 through at least 6 months, the manufacturer could choose to use a 4-month expiration date if the manufacturer did not want the product sold after that time period due to freshness or taste changes.

FDA is proposing to allow manufacturers to conduct accelerated stability testing concurrently with initial real-time stability testing to establish the product's expiration date and storage conditions (proposed § 1132.12(a)(3)(ii)). The manufacturer would be allowed to use an expiration date of no longer than 1 year based on initial accelerated stability testing. Accelerated stability studies provide preliminary information on NNN levels over time and are of shorter duration than long-term stability studies. By allowing manufacturers to conduct accelerated stability testing, FDA intends to reduce the time required to bring new products to market without adversely impacting public health.

Proposed § 1132.12(a)(3)(iii) would require that, at a minimum, samples for initial accelerated stability testing be tested at three time points within a 6-month period. This testing paradigm is similar to one used for stability testing for drugs. We would require the first time point be within 7 days of manufacture and the last time point at 6 months after manufacture. Because it may not always be possible to test exactly 6 months after manufacture, FDA notes that testing conducted within the week prior to or the week after the 6 month date of manufacture would be considered to meet this requirement. If the proposed storage condition is room temperature, samples for accelerated stability testing would have to be stored at 40 ± 2 degrees Celsius and 75 ± 5% relative humidity (proposed § 1132.12(a)(3)(iii)(A)) and, if the proposed storage condition is refrigeration, samples would have to be stored at 25 ± 2 degrees Celsius and 60 ± 5% relative humidity (proposed § 1132.12(a)(3)(iii)(B)). Because higher temperatures and humidity can increase the biological activity, these conditions will accelerate any increases in the NNN level, thereby providing a prediction of the stability of the NNN for a 12-month period under normal conditions.

Proposed § 1132.12(a)(3)(iv) would require the manufacturer to use the results of initial real-time stability testing to establish an expiration date and storage conditions if initial accelerated stability testing shows the NNN level in finished smokeless tobacco products will not conform to proposed § 1132.10. If the NNN levels do not conform after 6 months of accelerated testing conditions, then there will be insufficient evidence to project that NNN levels will conform after 12 months of normal conditions. Accordingly, this accelerated data may not be used to forecast an expiration date.

FDA is also proposing to require manufacturers to conduct annual real-time stability testing on each finished smokeless tobacco product to verify the results of the initial stability testing and, given the variability of NNN in tobacco, to ensure that the established expiration date and storage conditions remain appropriate and don't need to be changed (proposed § 1132.12(a)(4)). Accelerated stability testing would not be permitted for annual stability testing. We propose that accelerated stability testing be permitted for initial stability testing to reduce the time required to bring new products to market without adversely impacting public health. However, accelerated testing is unnecessary for annual stability testing because these products would already be on the market.

Proposed § 1132.12(a)(4)(i) would generally require annual real-time stability testing to begin within 12 months of the completion of initial stability testing and then annually thereafter, with no longer than 12 months between testing. When a manufacturer has not conducted initial real-time stability testing on a particular smokeless tobacco product because it has determined that the results from initial real-time stability testing conducted on another product apply, annual stability testing would have to begin when the product is first released for commercial distribution and then annually thereafter, with no longer than 12 months between testing (proposed § 1132.12(a)(4)(ii)). Samples for annual real-time stability testing, at a minimum, would have to be tested within 7 days of manufacture to determine the starting NNN level and at the established expiration date (proposed § 1132.12(a)(4)(iii)) to determine the final NNN level and provide assurance that the NNN level conforms to the standard through the expiration date. Also, similar to initial real-time stability testing, the samples would have to be stored at room temperature or refrigeration in accordance with proposed § 1132.12(a)(4)(iii)(A) and (B).

FDA proposes that, if the results of the most recent annual real-time stability testing do not support the finished smokeless tobacco product's previously established expiration date, the manufacturer must use the results of the most recent annual real-time stability testing to establish a new expiration date (proposed § 1132.12(a)(4)(iv)). After a new expiration date has been established, the package labels of all affected finished smokeless tobacco products that have not been released for commercial distribution would be required to display the new expiration date and storage conditions in accordance with proposed § 1132.30. Furthermore, if the expiration date must be shortened, the manufacturer would be required to conduct, fully document, and maintain records of an investigation to determine why the results of the most recent annual real-time stability testing do not support the product's previously established expiration date (proposed § 1132.12(a)(4)(v) and (a)(2)).

b. *Batch testing.* FDA is proposing that tobacco product manufacturers conduct testing on each batch of finished smokeless tobacco product to ensure that the products conform with proposed § 1132.10 prior to commercial distribution (proposed § 1132.12(b)). Testing each batch prior to its release into commercial distribution provides assurance to the manufacturer and FDA that each batch conforms to the proposed standard. Any problems with the NNN level that may arise during production (*e.g.,* problems due to the pasteurization equipment not heating correctly) would be detected by batch testing. In addition, finished product that does not conform to the standard would not be released for commercial distribution.

The manufacturer would be required to use either the standard test method in proposed § 1132.14 or an alternative test method that meets the requirements in proposed § 1132.16 and samples would have to be selected in accordance with the requirements set forth in § 1132.18(b) and (c) (proposed § 1132.12(b)).

FDA expects tobacco product manufacturers would use the results of batch testing and annual stability testing (proposed § 1132.12(a)) to inform their determination that a batch of finished smokeless tobacco product conforms to the proposed NNN level (proposed § 1132.10) at the time of release for commercial distribution and through the expiration date. For example, since finished smokeless tobacco products would have to conform with the proposed NNN level at batch testing and through their expiration date, the NNN level at batch testing would have to be low enough to ensure that the NNN level remains compliant until the expiration date. FDA believes that most manufacturers will develop products which have no, or minimal, changes in NNN over time. However, that is not required by this product standard. For instance, if stability testing demonstrates that the mean NNN level in a batch increases by 0.2 µg/g of tobacco on a dry weight basis over a 6 month expiration period, batch testing that demonstrates the mean NNN level is below 0.75 µg/g of tobacco on a dry weight basis would be in conformance because the mean NNN level of the batch would be expected to remain below 1.0 µg/g of tobacco on a dry weight basis at least through the expiration date of 6 months. We expect that any changes in a rate of increase would be observed and investigated during annual stability testing.

c. *Documentation of test results.* Proposed § 1132.12(c) would require the tobacco product manufacturer to maintain a full report of the source data and results of all stability and batch testing. This report would need to include the full identification of the smokeless tobacco product that is the subject of the report, including the product subcategory, brand, subbrand, package size and quantity of product (mass and, if portioned, count) and, for portioned tobacco products, the size (mass) of each portion. Subcategories of smokeless tobacco products include, for example, loose moist snuff, portioned moist snuff, loose snus, portioned snus, loose dry snuff, certain dissolvables, loose chewing tobacco, and portioned chewing tobacco.

In addition, the report would have to include the following:

- NNN level of each sample tested;
- Mean NNN level and standard deviation;
- The location, including facility name and address, from which each sample was pulled;
- The manufacturing code of each sample tested or, for samples for initial stability testing with no manufacturing code, an identifying code created by the manufacturer;
- The testing date and location, including the testing facility name and address;
- The test method and sampling procedure used;
- All tobacco product reference standard test results;

• The names and qualifications of the person(s) conducting the testing;

• The equipment used (including documentation to show that the equipment is appropriate for its intended use and has been calibrated); and

• For batch testing only, 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, including the NNN level of the individual batch and the results of the product's stability testing. For example, the criteria for accepting a batch of product whose stability testing demonstrates no change in the mean NNN level would be a batch mean NNN level less than or at 1.0 µg/g of tobacco, while the acceptance criteria for a batch of product whose stability testing demonstrates an increase of 0.2 µg in mean NNN level per gram of tobacco over the expiration period would be a batch mean NNN level at or below 0.8 µg/g of tobacco. The manufacturer would also be required to keep records, where applicable, of the decision made and justification with respect to the results of a nonconforming product investigation required under proposed § 1132.22. For example, if a batch initially tests out of compliance and a nonconforming product investigation finds the NNN levels were erroneously high because of a malfunction of the testing equipment, the manufacturer could determine that the batch is acceptable for release if the NNN levels are in conformance after the equipment has been fixed. The manufacturer would be required to keep the records of the decision made and the justification.

3. Standard Test Method (Proposed § 1132.14)

Proposed § 1132.14 states that the standard test method is the method entitled ''Determination of N-nitrosonornicotine (NNN) in Smokeless Tobacco and Tobacco Filler by HPLC–MS/MS,'' that is incorporated by reference in § 1132.5(a). The standard test method is explained in further detail in section IV.F, Analytical Method. If FDA subsequently determines that a test method, which has been incorporated by reference in a final rule, should be replaced with another method or updated, FDA will update the regulation in accordance with the Administrative Procedure Act (5 U.S.C. 553) and obtain approval of the change to the incorporation by reference in accordance with 1 CFR part 51.

4. Alternative Test Method (Proposed § 1132.16)

If a tobacco product manufacturer were to choose not to use the standard test method in § 1132.14 to test each batch, the manufacturer would be required to use a validated alternative test method that conforms to the requirements of proposed § 1132.16. The performance criteria of the alternative test method would have to meet or exceed the performance criteria of the standard test method (proposed § 1132.16). FDA would consider the following parameters to assess the performance criteria of an alternative test method: Accuracy, precision, linearity, specificity, limit of quantitation, limit of detection, robustness, and range.

Proposed § 1132.16(a) would require that, before using a validated alternative test method, the manufacturer notify the Director of the Office of Science for FDA's Center for Tobacco Products. By requiring prior notification, we hope to help manufacturers to avoid using a test method that does not meet the requirements in § 1132.16 and being unable to release for commercial distribution any product tested using that method. Notification also allows FDA to track what methods are being used, by whom, and for what products. This information can be used to inform FDA inspectors regarding the use of an alternative test method. In addition, if any issues arise with regard to a specific alternative test method, FDA would be aware of other manufacturers who may also be affected.

A manufacturer seeking to use a validated alternative test method could not begin to use this method until 60 calendar days after the date FDA receives the notification regarding the alternative test method. This would allow time for FDA to review and act on the notification. Smokeless tobacco manufacturers would be informed of FDA's receipt of the notification through the automated Document Control Center process. A manufacturer may not begin or continue using the alternative test method if FDA notifies the manufacturer that it has not been demonstrated to meet the requirements of § 1132.16.

The notification would have to contain the information required by proposed § 1132.16(b) and be in the format discussed in proposed § 1132.16(d). Proposed § 1132.16(b) provides the required contents for the notification of use of an alternative test method. The notification would be required to include the following information:

• General information;

• A comprehensive index and table of contents;

• Summary of the notification; and

• Complete description of the method.

In addition, FDA may request clarification and other relevant information, if needed (proposed § 1132.16(c)).

The set of general information would be submitted on the FDA-provided form, a draft of which FDA is making available as a reference for review and comment (Ref. 145). The form would include the following information:

• Date the manufacturer submitted the notification to FDA;

• Identification of the submission as a notification of an alternative test method;

• Manufacturer's name, address, and contact information;

• Identification of and contact information (including name, mailing address, email address, and telephone number) for an authorized representative of the manufacturer (which could be a U.S. agent for the manufacturer);

• Identification of the subcategories of finished smokeless tobacco products (*e.g.,* loose moist snuff, portioned moist snuff, loose snus, portioned snus, loose dry snuff, certain dissolvables, loose chewing tobacco, portioned chewing tobacco, or other) that can be analyzed using the alternative test method; and

• The testing facility's name and address.

The summary section of the notification would have to contain the following information:

• Identification of the standard test method for which the alternative test method is being proposed;

• A concise description of the performance criteria of the alternative test method;

• A concise explanation regarding the manufacturer's rationale for proposing to use the alternative test method; and

• A concise comparison of the similarities and differences between the alternative and standard test methods.

As stated in proposed § 1132.16(b)(4), the manufacturer would be required to provide a complete description of the method with sufficient detail to enable FDA to evaluate whether the information demonstrates that the alternative test method meets or exceeds the performance criteria of the standard test method set forth in § 1132.14. This description would have to include a complete explanation of the manner in which the alternative test method is proposed to deviate from the standard test method in § 1132.14. The

description would have to include an explanation with scientific rationale and supporting data, as well as a complete copy of the testing protocol, to demonstrate that the alternative method meets or exceeds the performance criteria established for the standard test method. In proposed § 1132.16(b)(4)(ii) and (c), the manufacturer also would have to include any data and information from other studies comparing the alternative test method to the standard test method and, if requested by FDA, any other relevant information needed to evaluate the alternative test method (*e.g.,* statistical analysis comparing the alternative test method to the standard test method, proficiency test results, or evidence of technical competence).

Proposed § 1132.16(d) provides the format for a manufacturer's notification of use of an alternative test method. First, the notification would have to be submitted using the FDA-provided form and all information would have to be organized, legible, and written in the English language. The comprehensive index and table of contents (required by proposed § 1132.16(b)) would provide sufficient organization for the document. FDA expects that the manufacturer will submit this form using the Agency's electronic system. The manufacturer's notification and all supporting information would be required to be in an electronic format that the Agency can process, review, and archive. Current information about electronic submission preparation (*e.g.,* acceptable file formats, technical specifications, data standards) and transmission requirements may be found on the FDA Web site.

FDA is proposing to require that tobacco manufacturers use the electronic format for the submission of this information to facilitate our review of the data submitted. Electronic submission of information is consistent with the Government Paperwork Elimination Act (Pub. L. 105–277), which requires that Federal Agencies allow individuals or entities to submit information or transact business with the Agency electronically.

A smokeless tobacco manufacturer that is not able to submit a notification of use of an alternative test method in an electronic format could submit a written request to the Center for Tobacco Products explaining in detail why the company cannot submit the notification in an electronic format and requesting an alternative format (as provided in proposed § 1132.16(d)(3)).

Proposed § 1132.16(d)(3) would provide that, if a manufacturer cannot submit a form electronically, the manufacturer may submit a request for a waiver. A waiver would be granted only if the use of electronic means is not reasonable. If FDA grants the manufacturer's waiver request, the Agency will provide information as to how and where to submit the notification and supporting documentation in paper format.

If a manufacturer seeks a waiver, the manufacturer must send a legible written request in the English language to the Document Control Center, with a notation ''ATTN: Office of Science,'' to the address included in our Web site at *www.fda.gov/TobaccoProducts.* The address can also be obtained by calling 1–877–CTP–2373 (1–877–287–1373). The waiver request would have to contain the following information: The name and address of the tobacco product manufacturer that wishes to submit the notification; the name and contact information of the manufacturer's authorized representative (which could be a U.S. agent for the manufacturer); and a statement and rationale as to why the creation and/or submission of information in electronic format is not reasonable (such statement must be signed by the authorized representative of the tobacco product manufacturer).

Proposed § 1132.16(e) clarifies the applicability of an alternative test method. An alternative test method could be implemented only by the tobacco product manufacturer who submitted the notification and only with respect to the subcategories of finished smokeless tobacco products that were the subject of the notification. We are proposing this approach because an alternative test method that is appropriate for one subcategory of smokeless tobacco product (*e.g.,* moist snuff) may not be generalizable to other subcategories of smokeless products (*e.g.,* chewing tobacco). Also, because some test methods may be proprietary or may have been developed by the manufacturer for a specific product, FDA believes it is important for the manufacturer to notify FDA and fully describe the method they plan to use and the products on which they intend to use it.

Other manufacturers interested in similar or identical alternative test methods would have to submit their own notification following the procedures of proposed § 1132.16. Therefore, if a manufacturer previously submitted a notification of an alternative test method and later sells the company to another manufacturer, the new manufacturer would have to submit a notification if it wished to continue using the alternative method. This would ensure that FDA is aware of which manufacturers are using an alternative test method. Similarly, if the original notification pertains to one subcategory of smokeless tobacco (*e.g.,* moist snuff), and the manufacturer also decides to use the method to test another subcategory of product (*e.g.,* dry snuff), the manufacturer would have to submit a new notification in accordance with proposed § 1132.16. A new notification would be needed because an alternative test method may not be suitable for testing of other product subcategories and the test method would need to be evaluated for them before it can be used by the manufacturer.

Proposed § 1132.16(f) indicates that FDA will acknowledge the receipt of a notification of an alternative test method. If the applicant submits the notification electronically, FDA will acknowledge receipt electronically. This provision also reiterates that there is a waiting period before a smokeless tobacco manufacturer may begin using the alternative test method. A manufacturer could start using an alternative test method beginning 60 calendar days after FDA's receipt of a complete notification unless the Agency notifies the manufacturer otherwise.

Proposed § 1132.16(f)(1) provides that, if the notification is complete when FDA receives it, the 60 calendar day waiting period would begin on the date the Agency receives the notification. If the notification did not contain all of the information required by proposed § 1132.16(b) and was, therefore, incomplete, FDA would not accept the notification and would inform the submitter (proposed § 1132.16(f)(2)). Upon notice from FDA that the notification is incomplete, the manufacturer may not supplement the submission, but rather would be required to submit a new notification that includes all the information required in proposed § 1132.16(b). Providing all of the information in one complete notification will facilitate FDA's review so that it can act expeditiously on the notification. The manufacturer would not be able to use the alternative test method until the end of the 60-day waiting period following submission of the new, complete notification, provided it has not received an FDA notification informing the submitter otherwise. If FDA informs the manufacturer during the 60 calendar day waiting period that the manufacturer has not demonstrated that the alternative test method meets or exceeds the performance criteria of the standard test method, the manufacturer would be prohibited from implementing

the alternative test method. If FDA makes this determination after the 60 calendar day period has ended and the manufacturer has already begun using the procedure, the smokeless tobacco manufacturer would have to immediately cease using the alternative test method upon receipt of FDA's notification.

Proposed § 1132.16(f)(4) explains that acceptance of a notification does not constitute a finding by the Agency that an alternative test method meets or exceeds the performance criteria of the standard test method set forth in § 1132.14.

5. Sampling Plans and Procedures (Proposed § 1132.18)

Proposed § 1132.18 would require each smokeless tobacco manufacturer to design and implement sampling plans for stability testing and batch testing. These sampling plans would be used in conjunction with the product testing required in proposed § 1132.12 (stability testing and batch testing) and would provide procedures for the manufacturer to select samples to demonstrate conformance with the proposed NNN level.

Proposed § 1132.18(a) would require each tobacco product manufacturer to design and implement a sampling plan or plans for all stability testing required in proposed § 1132.12(a) based on a valid statistical rationale to demonstrate that the finished smokeless tobacco product's expiration date is appropriate under the intended storage conditions. One sampling plan could cover multiple products (*e.g.,* different flavors of the same basic core tobacco blend and cut), but multiple plans would be needed if the products are sufficiently different from one another in processing or materials (*e.g.,* one product is expected to have a very stable NNN level, whereas in another the NNN level increases steadily over time).

The sampling plan would have to ensure that samples taken are representative and randomly selected. Furthermore, to account for the variability of NNN in the smokeless tobacco products, the following factors would have to be based on adequate statistical criteria: The confidence intervals, the level of necessary precision, and the number of finished products sampled. Finally, proposed § 1132.18(a) would require each sampling plan to fully describe the sampling methodology with scientific rationale, incorporate all sources of variability (including variability of the analytic method and the NNN levels), and describe the sample size needed (including a full description of how the sample size is calculated) consistent with the sampling design to achieve the sampling objective.

Similarly, proposed § 1132.18(b) would require each tobacco product manufacturer to design and implement a sampling plan or plans for all batch testing required in § 1132.12(b) based on a valid statistical rationale to ensure that the finished smokeless tobacco product consistently conforms to the NNN level set forth in proposed § 1132.10. One sampling plan could cover multiple products (*e.g.,* different flavors of the same basic core tobacco blend and cut), but multiple plans would be needed if the products are sufficiently different from one another in processing or materials (*e.g.,* one product is expected to have a very stable NNN level, whereas in another the NNN level increases steadily over time).

The sampling plan would have to ensure that the samples taken are representative of an entire batch and are randomly selected and collected from each batch for testing. To account for the variability of the NNN levels in the finished smokeless tobacco products, the following factors would have to be based on adequate statistical criteria: The confidence intervals, the level of necessary precision, and the number of finished products sampled. The sampling plan would also have to take into account the manufacturing quality history of the manufacturer (*e.g.,* batch testing records and nonconforming product investigations). For example, a manufacturer who has a high number of nonconforming product investigations or high number of batch rejection records may need to create a more robust sampling plan because of their history of producing nonconforming products.

In addition, the sampling plan would have to contain a full description of the sampling methodology, with scientific rationale, incorporate all sources of variability (including variability of the analytic method and the NNN levels across batches), and describe the sample size needed (including a full description of how the sample size is calculated) consistent with the sampling design to achieve the sampling objective. Finally, the sampling plan would also need to fully describe the criteria the manufacturer will use to make a decision to accept or reject each batch. For example, the criteria for accepting a batch of a product would depend on the results of the stability testing. If stability testing demonstrates no change in mean NNN level, the acceptance criteria could be a batch mean NNN level less than or at 1.0 µg/g of tobacco on a dry weight basis. If the stability demonstrates an increase of 0.2 µg of mean NNN level per gram of tobacco on a dry weight basis over the expiration period, the acceptance criteria would need to be a batch mean NNN level below 0.8 µg/g of tobacco on a dry weight basis. In those cases, the batch of product is acceptable because the manufacturer would expect the batch mean NNN level to remain at or below 1.0 µg/g of tobacco on a dry weight basis through the expiration date.

Proposed § 1132.18(c) would require that samples be collected and examined in accordance with certain procedures.

Under proposed § 1132.18(c)(1), test samples for initial real-time and accelerated stability testing would have to consist of:

- Smokeless tobacco product that has been manufactured using the same production processes as products manufactured for consumer use and packaged in the identical package that will be used for the finished smokeless tobacco product, but it need not have the product package label; or
- Finished smokeless tobacco product as it is intended to be sold or distributed to consumers.

This provision would allow flexibility for the manufacturer to determine the sample to be tested. It also recognizes that, at this early stage, a manufacturer may not want to or may not be able to create package labels for new smokeless tobacco products. For example, in accordance with § 1132.30 a package label would need to have the expiration date for the product. Prior to completing initial stability testing, the manufacturer might not know what the appropriate expiration date would be. Similarly, we expect a manufacturer of a new smokeless tobacco product would be most likely to sample smokeless tobacco that meets the requirements of § 1132.18(c)(1)(i) to minimize costs. In contrast, we would expect a manufacturer whose smokeless tobacco products may already conform to the proposed standard to test its finished smokeless tobacco product (§ 1132.18(c)(1)(ii)) rather than product that has been manufactured specifically for testing purposes.

Proposed § 1132.18(c)(2) would require that test samples for annual real-time stability testing and batch testing consist of the finished smokeless tobacco product as it is intended to be sold or distributed to consumers and not of a separate production sample. This is intended to ensure the samples tested are representative of the product to be sold or distributed to consumers.

Under proposed § 1132.18(c)(3), all test samples would need to be stored according to the intended storage

conditions for the finished smokeless tobacco product (either room temperature or refrigeration), except that test samples for initial accelerated stability testing must be stored in accordance with proposed § 1132.12(a)(3)(iii). The manufacturer would have to include all of its factories, stock rooms, warehouses, and other locations containing finished smokeless tobacco products in 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 would ensure the sample is representative of the entire population (batch) of finished smokeless tobacco products packaged for consumer use.

Proposed § 1132.18(c)(4) sets forth when samples must be taken for testing. Samples for stability testing would have to be taken within 7 days of the manufacturing date and tested in accordance with proposed § 1132.12(a). This would ensure the samples for stability testing are tested as soon as possible after manufacturing to establish the starting NNN level. It also provides sufficient time for the sample to be shipped to a laboratory for testing. Samples for batch testing would have to be taken from each batch and tested within 30 calendar days of the manufacturing date.

The amount of material acquired during sampling would have to be sufficient for the test methods in proposed §§ 1132.14 or 1132.16, including any repeats that may be necessary. For example, repeat tests would be necessary if the test material was damaged prior to or during the analysis. Samples would have to be randomly selected in accordance with the applicable sampling plan and taken within the same day. This would ensure that there has not been any degradation or change in part of the samples.

Proposed § 1132.18(c)(5) would require that sampling be performed by persons who have sufficient education, training, and experience to accomplish the assigned functions. This would allow the manufacturer the flexibility to determine the education, training, and experience needed to perform this function. For example, the manufacturer may determine that a person has the necessary education, training, and experience for the position if they have completed course work or training in statistics, been trained by the manufacturer on sampling procedures, or have prior work experience.

Under proposed § 1132.18(c)(6), each sample would have to be identified by the following information:

- Full identification of the smokeless tobacco product sampled, including product subcategory, brand, and subbrand, package size and quantity of the product (mass and, if portioned, count) and, for portioned tobacco products, the size (mass) of each portion;
- Manufacturing code or, for samples for initial stability testing with no manufacturing code, an identifying code created by the manufacturer;
- 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 stored and tested (including the facility name and address).

This information would be generated at the time the samples are pulled for testing.

The purpose of this information is to fully identify each sample, including what the product is, and when and where it was taken. These records would serve dual purposes. First, they can be used to verify that a company is following its sampling plan and the procedures required under this part, including the number of samples pulled, when they are pulled, and the locations from where they are pulled. Second, these records can be used to generate some of the information for the report required under proposed § 1132.18(c)(9). The records also document the start of sampling process.

Proposed § 1132.18(c)(7) provides packing requirements for samples that are sent for testing. Samples would have to be packed securely to protect against damage that might occur during shipment to the testing facility, including mechanical damage or severe changes in humidity or temperature that may affect the NNN level. The samples would have to be sent to the testing facility by the most expeditious means in order to arrive no later than 3 calendar days after shipment. This is intended to minimize the potential for damage to or contamination of the samples and would help to ensure that the testing is completed within the specified time periods. The smokeless tobacco manufacturer would also have to send, under separate cover, a list of the samples (identified by the relevant information required by proposed § 1132.18(c)(6)) included in each shipment to the testing facility. This would ensure the laboratory receives a complete list of the samples to be tested.

Proposed § 1132.18(c)(8) would require that all the samples for a specific stability or batch test be tested at the same testing facility to ensure consistency among the procedures used and to protect against sample degradation.

Proposed § 1132.18(c)(9) provides sampling requirements for the testing facility responsible for testing the manufacturer's samples. Once the samples arrive at the testing facility, a representative of the facility would have to ensure that the samples are inspected, accounted for, and stored under the finished smokeless tobacco product's intended storage conditions (*e.g.,* room temperature or refrigeration) except that test samples for initial accelerated stability testing must be stored in accordance with § 1132.12(a)(3)(iii). The facility would then be responsible for generating a report for the stability or batch test that includes the following information:

- Full identification of the smokeless tobacco product sampled, including product subcategory, brand, and subbrand, package size and quantity of the product (mass and, if portioned, count) and, for portioned tobacco products, the size(mass) of each portion;
- Manufacturing code or, for samples for initial stability testing with no manufacturing code, an identifying code created by the manufacturer;
- The date when the samples were taken from the batch, if available;
- Locations where samples were drawn (including the address and specific locations within any facilities where the samples were taken), if available;
- The number of test samples drawn; 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 samples arrive at the testing facility. Unlike the information required under proposed § 1132.18(c)(6), 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 § 1132.18(c)(6), would be to establish the chain of custody for the samples from the time they were taken up through their transfer to the testing facility where they will be tested. The smokeless tobacco manufacturer would be required to maintain the sampling information in accordance with proposed § 1132.32. Thus, the manufacturer would be responsible for obtaining this information from the

testing facility. FDA also expects that this information would be integrated into the records required by proposed § 1132.12(c) to provide information across the batch.

Proposed § 1132.18(c)(10) explains that the manufacturer would be required to withhold from commercial distribution each batch until it has been sampled and tested, and the tobacco product manufacturer has made a decision to accept and release the batch. The manufacturer would be required to reject any nonconforming products as discussed in proposed § 1132.22.

6. Expiration Date (Proposed § 1132.20)

Proposed § 1132.20 would require all finished smokeless tobacco products to have an expiration date established by stability testing. The expiration date would be required to be set no later than the final date the manufacturer can demonstrate the finished smokeless tobacco product will not exceed the NNN limit in proposed § 1132.10 when stored under its intended conditions (*i.e.,* either room temperature or refrigeration). FDA considered requiring manufacturers to determine the time point at which the NNN level exceeds the limit. However, FDA rejected this approach because manufacturers may develop products with stable NNN levels that do not exceed the NNN limit for a prolonged period (*e.g.,* 5 years) and requiring manufacturers to conduct stability testing for that entire period would be unnecessary. FDA also considered mandating a specific expiration period (*e.g.,* 6 months or 1 year) but determined this may be too restrictive and stifle innovation. Accordingly, FDA believes the proposed approach would provide manufacturers more flexibility in establishing an expiration date that conforms to the NNN level.

Requiring an expiration date that is established by stability testing provides assurance that the NNN level will remain in conformance with the product standard for the specified time period. The expiration date also informs retailers that the manufacturer has not demonstrated compliance with the product standard beyond that date and the product cannot be sold to consumers. The expiration date also allows FDA inspectors to quickly determine if products for sale in a retail establishment purport to be in conformance with the product standard.

7. Nonconforming Product (Proposed § 1132.22)

Proposed § 1132.22 would require manufacturers to establish procedures for handling nonconforming smokeless tobacco products. Proposed § 1132.22(a) would require tobacco product manufacturers to establish and maintain procedures to identify, investigate, segregate, and make disposition decisions (*i.e.,* acceptance, rejection, or rework) about nonconforming finished smokeless tobacco products to prevent their release for commercial distribution. FDA interprets ''establish and maintain'' for purposes of proposed § 1132.22(a) to mean define, document (in writing or electronically), implement, follow, and, when necessary, update. This section allows manufacturers the flexibility to determine how they will perform these activities.

Proposed § 1132.22(b) would require tobacco product manufacturers to conduct an investigation if:

- The mean of the representative samples from any batch of finished smokeless tobacco product is determined to be out of conformance with the requirements of § 1132.10,
- A finished smokeless tobacco product's expiration date must be shortened due to the results of annual real-time stability testing, or
- FDA notifies the smokeless tobacco manufacturer that a distributed finished smokeless tobacco product does not conform to the requirements of part 1132.

The purpose of a nonconforming product investigation would be to determine the extent and the cause, if possible, of the nonconformity so that, if identified early, the product is not processed further or released for commercial distribution. In addition, it would help to prevent recurrence of the nonconformity.

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 the 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, operations, records, complaints, any corrective actions taken, and any other relevant 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 nonconformity of the affected batch.

The manufacturer would have to fully document any investigation, including any materials reviewed, 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 the manufacturer has adequately performed an investigation.

Proposed § 1132.22(c) would require tobacco product manufacturers to reject any batch of a finished smokeless tobacco product if the mean of the representative samples from the batch does not meet the requirements of § 1132.10 unless a disposition decision and justification to release the batch is made after an investigation shows the batch meets the requirements of part 1132. Manufacturers would not be able to simply resample a batch until the mean conforms with the proposed NNN limit in § 1132.10 if a previous mean did not meet the requirements of part 1132. If the initial mean was not in conformance, the manufacturer must conduct a nonconforming product investigation. If the manufacturer, for instance, determines the NNN levels were erroneously high because of a malfunction of the testing equipment, and the batch tests in conformance after repair of the equipment, the manufacturer could determine that the batch is acceptable for release into commercial distribution.

Proposed § 1132.22(d) would allow smokeless tobacco manufacturers to rework a batch of a nonconforming finished smokeless tobacco product, which does not conform to the requirements of part 1132, to bring it into conformance with all the requirements of the part before it may be released for commercial distribution. However, FDA thinks it is unlikely that a manufacturer would rework nonconforming finished smokeless tobacco product because this would likely require removing the product from its container and then mixing it with smokeless tobacco product with very low NNN levels to ensure that the final product did not exceed the

proposed NNN limit.[4] We welcome information and comments on this provision.

C. Labeling and Recordkeeping Requirements (Proposed Subpart C)

1. Package Label Requirements (Proposed § 1132.30)

Proposed § 1132.30 would require that the package label of all finished smokeless tobacco products include a manufacturing code, expiration date, and, if applicable, storage conditions. FDA is proposing to require that the labels of finished smokeless tobacco products contain a manufacturing code, expiration date, and, if applicable, storage conditions for the finished smokeless tobacco product (proposed § 1132.30) so that FDA can determine whether a product on store shelves purports to be in conformance with the product standard and link the product to records that substantiate its conformance. These requirements would also help ensure that the product is handled and stored under appropriate conditions so that the product remains in compliance with the standard and would help FDA verify that retailers are storing products appropriately. The information would be required to be printed on or permanently affixed to the package in a manner that assures it will remain on the packaging or label through the expected duration of use of the product by the consumer. In addition, it would have to appear clearly, legibly, and indelibly in the English language.

The purpose of the manufacturing code is to allow manufacturers and FDA to be able to link the product to a specific batch that has been released for commercial distribution, which would be helpful in the event of a nonconforming product investigation or in the event that corrective or preventive actions should be taken. The manufacturing code could also help determine the history of the manufacturing, processing, packaging, labeling, holding, and initial distribution of the tobacco product from records maintained by the smokeless tobacco product manufacturer. The expiration date on the package label would have to appear in two-digit numerical values in the following format: ''Expires on month/day/year.'' The expiration date informs retailers that the manufacturer has not demonstrated compliance with the product standard beyond that date and the product cannot be sold to consumers. The expiration date also allows FDA inspectors to quickly determine if products for sale in a retail establishment purport to be in conformance with the product standard and if retailers are selling expired products.

Storage conditions would be required to be on the label if the finished smokeless tobacco product must be kept in refrigerated storage to conform with the product standard until the expiration date (as determined by stability testing) and the package label would be required to bear the wording: ''Keep Refrigerated.'' However, no wording would be required to be on the package label if the product's intended storage condition is room temperature. We note that proposed § 1132.1 states that retailers and distributers would not be in violation of part 1132 as it relates to the sale or distribution or offer for sale or distribution of smokeless tobacco products that exceed the NNN limit if they, among other things, store and transport the finished tobacco product according to the package label and do not sell or distribute or offer for sale or distribution finished smokeless tobacco products past their expiration date. Requiring package labels with an expiration date and storage conditions would allow retailers and distributers to handle the product in accordance with the manufacturer's intent so the product remains in conformance with the product standard.

2. Recordkeeping Requirements (Proposed § 1132.32)

Proposed § 1132.32 includes two recordkeeping requirements. This information is necessary for FDA to ascertain and confirm that smokeless tobacco products are in compliance with the proposed standard.

First, proposed § 1132.32(a) would require that each facility that manufactures finished smokeless tobacco products establish and maintain records containing the following information:

1. Full documentation of stability testing protocols and the results of initial and annual stability testing under § 1132.12(a), including all information specified in § 1132.12(c).

2. All investigations under § 1132.12(a)(4)(v).

3. The source data and results of batch testing conducted to determine conformance with § 1132.10, including all information specified in § 1132.12(c).

4. All notifications of an alternative test method and all related correspondence under § 1132.16;

5. All source data for the alternative test method validation;

6. All sampling plans and reports under § 1132.18;

7. Documentation that the persons performing sampling under § 1132.18 have sufficient education, training, and experience to accomplish the assigned functions;

8. All identification, investigation, segregation, and disposition decision procedures under § 1132.22(a); and

9. All nonconforming product investigations and rework under § 1132.22(b) and (d).

Second, proposed § 1132.32(b) provides certain specifications for these records. The records would have to be legible and written in English. 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. All records would be required to be readily available for inspection and copying or other means of reproduction by FDA upon request during an inspection.[5] Requested records that are maintained offsite would have to be made available within 24 hours or, if that is not feasible, as soon as possible before the close of the inspection. While we expect that most records can be made available to FDA within 24 hours, we recognize 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.

In addition, proposed § 1132.32(c) would require that the records kept under this part be retained for at least 4 years from the date of commercial

[4] Based on comments provided by the Alcohol and Tobacco Tax and Trade Bureau (TTB), we understand that this process would likely constitute the manufacture of tobacco products for purposes of the Internal Revenue Code. Under the Internal Revenue Code, the manufacture of tobacco products requires a permit as a manufacturer of tobacco products from TTB. As we understand TTB's permitting requirements, entities lacking a manufacturing permit, including importers, may not engage in manufacturing activities. We also understand that certain provisions of the Internal Revenue Code prohibit importers of tobacco products from repackaging tobacco products after such products are released from customs custody.

[5] Several laws govern the confidentiality of information submitted under sections 907 and 909 of the FD&C Act, including sections 301(j) and 906(c) of the FD&C Act (21 U.S.C. 331(j) and 387f(c)), the Trade Secrets Act (18 U.S.C. 1905), and the Freedom of Information Act (FOIA) (5 U.S.C. 552), as well as FDA's regulations in 21 CFR part 20.

distribution of the finished smokeless tobacco product that is the subject of the record. However, for records relating to alternative test methods under § 1132.16, the required 4-year retention period would be for a period not less than 4 years after the last date the method that is the subject of the record is used (*e.g.,* 4 years from the last date the manufacturer used an alternative test method). 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 considered not requiring specific recordkeeping requirements and, instead, allowing the manufacturer to determine recordkeeping needs but, FDA believes that detailed recordkeeping requirements are necessary to confirm that the finished smokeless tobacco products are in compliance with the proposed standard. For example, requiring manufacturers to fully document their stability testing protocols and test results will enable FDA to confirm that the manufacturer's test method and protocols are adequate to meet the requirements of part 1132. In addition, requiring nonconforming product records will help the manufacturer and FDA determine the extent of the nonconformity and, as applicable, the locations where the nonconforming products have been distributed, in the event of a recall or enforcement action (*e.g.,* seizure).

VII. Proposed Effective Date

FDA proposes that any final rule on the tobacco product standard for NNN that may issue based on this proposal become effective 3 years after the date of publication of the final rule. FDA believes this approach would allow adequate time for developing any necessary changes in technology to achieve the NNN level, for any changes made to manufacturers' tobacco purchasing choices and curing methods, and for any preparation or changes needed in facilities. In addition, FDA believes that it will provide adequate time for manufacturers to seek and obtain marketing authorization from FDA for their new tobacco products. New tobacco products are subject to enforcement if they are on the market without FDA authorization.

Therefore, after the effective date of a final rule for this proposed tobacco product standard, no person would be allowed to manufacture, distribute, sell, or offer for sale or distribution within the United States any finished smokeless tobacco product that does not comply with the rule. After the effective date of the final rule, manufacturers would not be allowed to introduce into domestic commerce any finished smokeless tobacco product that does not comply with the requirements of the final rule, irrespective of the date of manufacture. However, retailers would be permitted to sell-off existing inventory of noncompliant finished smokeless tobacco products manufactured before the effective date for 60 days after the effective date of the final rule. FDA notes that keeping products with higher NNN levels on the market for an extended period of time after the effective date of the rule is not in the interest of public health.

VIII. Incorporation by Reference

FDA is proposing to incorporate by reference the test method entitled, ''Determination of N-nitrosonornicotine (NNN) in Smokeless Tobacco and Tobacco Filler by HPLC–MS/MS,'' LIB No. 4620, January 2017 (Ref. 79). You may obtain a free copy of the material proposed to be incorporated from the Docket at *www.regulations.gov* or from the Food and Drug Administration, Center for Tobacco Products, 10903 New Hampshire Ave., Silver Spring, MD 20993, 1–888–463–6332.

This is a technical document developed by FDA specifically for use in tobacco testing facilities. FDA developed this test method for NNN in order to streamline the testing process and reduce testing costs. Other available methods test for all TSNAs while this test method is limited to NNN. As such it is a highly specific method that reduces testing costs while ensuring that the results from the test method demonstrate a high level of specificity, accuracy, and precision in measuring a range of NNN levels across a variety of smokeless tobacco products.

This test method relies on several ISO standards for determining moisture content in tobacco and tobacco products—ISO 6488:2004, ISO 6488:2004/Cor 1:2008, and ISO 16632:2013. FDA is not proposing to incorporate these standards by reference. You may purchase a copy of the ISO standards from the International Organization for Standardization, 1, ch. de la Voie-Creuse, Case Postale 56, CH–1211, Geneva 20, Switzerland, or from the American National Standards Institute, 1899 L Street NW., 11th Floor, Washington, DC 20036, or on the Internet at *http://www.iso.org* or *www.ansi.org.* We note that these ISO standards are relatively inexpensive (about $50 each) and may already be used by tobacco testing facilities.

For the reasons set forth in this section, FDA considers the test method proposed to be incorporated by reference to be reasonably available and usable by testing facilities (see 1 CFR 51.5(a) and 51.7).

IX. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, 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 and 13563 direct us to assess all costs and benefits 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. We believe that this proposed rule is an economically significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because many smokeless tobacco products may need to be reformulated, and reformulation represents the main driver of the costs of the rule, we tentatively find that the proposed rule would 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 current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would result in an expenditure in any year that meets or exceeds this amount.

The proposed rule would establish a product standard for all finished smokeless tobacco products. Specifically, the proposed rule would require that all finished smokeless tobacco products comply with a limit for NNN in such products in order to be marketed and distributed for sale in the United States. This proposed product standard would require that the mean level of NNN in any batch of finished

smokeless tobacco products not exceed 1.0 µg/g of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by product testing. The proposed standard also includes requirements on the sale and distribution of smokeless tobacco products, product testing, labeling, and recordkeeping.[6]

The costs of the proposed rule, when finalized, will be due to affected entities ensuring that the smokeless tobacco products comply with the proposed product standard. We have estimated that the annualized costs associated with the proposed rule over 20 years to be between $17.91 million and $42.72 million using a 3 percent discount rate, with a primary value of $30.31 million, and between $20.11 million and $50.57 million, with a primary value of $35.34 million using a 7 percent discount rate. The primary estimate for the present value of total quantified costs over 20 years is approximately $450.97 million at a 3 percent discount rate and $374.36 million at a 7 percent discount rate.

NNN is a carcinogenic agent found in smokeless tobacco products. As described in the preamble, on the basis of the available scientific evidence, FDA has determined that NNN is the predominant driver of excess oral cancer risk among smokeless tobacco users.

We quantify benefits associated with the proposed rule in the form of reduced oral cancer morbidity and mortality attributable to smokeless tobacco. As described in section V.A.3 of the preamble of the proposed rule, we also expect the standard to reduce the risk of esophageal cancer and it may reduce the risks of other cancers such as pancreatic, laryngeal, prostate, and lung cancer. However, there is more limited information to directly quantify these health benefits. As such, we only consider reductions in oral cancer as the quantified benefit of the proposed product standard.

Most of the estimated benefits arise from quality life-years gains gained from reduced oral cancer mortality. The annualized value over 20 years of quality adjusted life-years gained from reduced oral cancer mortality ranges from $228.66 million to $2.46 billion at a 3 percent discount rate, with a primary value of $858.46 million. Using a 7 percent discount rate, the annualized value of quality life-years gained from averted deaths ranges from $182.01 million to $1.96 billion, with a primary value of $683.34 million. The primary estimate of the present value of mortality reductions quantified over 20 years is $12.77 billion at a 3 percent discount rate and $7.24 billion at a 7 percent discount rate. The annualized value over 20 years of quality adjusted life-years gained from reduced oral cancer mortality and morbidity ranges from approximately $283.95 million to $3.05 billion at a 3 percent discount rate, with a primary value of $1.06 billion, and approximately $246.40 million to $2.65 billion, with a primary value of $0.92 billion at a 7 percent discount rate. The primary estimate of the present value of total quantified benefits over 20 years is approximately $15.86 billion at a 3 percent discount rate and $9.80 billion at a 7 percent discount rate for reductions in oral cancer alone. These values are likely an underestimate of the benefits associated with the proposed rule, as we do not quantify reductions in mortality and morbidity from cancers other than oral cancer. Costs and benefits are summarized in table 8.

The full analysis of economic impacts is available in the docket for this proposed rule (Ref. 146) and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

TABLE 8—SUMMARY OF BENEFITS, COSTS AND DISTRIBUTIONAL EFFECTS OF PROPOSED RULE

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Benefits:							
Annualized Monetized millions/year.	$924.91	$246.40	$2,647.21	2015	7	20	Most of the health benefits included in the totals would be realized more than 20 years after publication of the final rule, but the risk reductions associated with these benefits occur during the 20-year period beginning at publication of the final rule.
	$1,065.92	$ 283.95	$3,051.09	2015	3	20	
Annualized					7	20	
Quantified					3	20 years	
Qualitative							Potential cost savings from net life-time reduction in medical care utilization; additional health benefits from reduction in other toxicants correlated with NNN; reduction in cancers, other than oral cancers
Costs:							
Annualized	$35.34	$20.11	$50.57	2015	7	20	
Monetized millions/year	$30.31	$17.91	$42.72	2015	3	20	
Annualized					7	20	
Quantified					3	20	
Qualitative							
Transfers:							
Federal Annualized				7	20		
Monetized $millions/year					3	20	
	From:			To:			
Other Annualized					7	20	

[6] The proposed product standard includes a number of requirements in addition to the actual NNN limit, including requirements related to product testing, recordkeeping, and sale and distribution restrictions. However, generally, this analysis uses the term product standard as shorthand for the NNN limit requirement. Similarly when we discuss anticipated compliance status and compliant versus noncompliant products, we generally refer to compliance with the NNN limit requirement.

TABLE 8—SUMMARY OF BENEFITS, COSTS AND DISTRIBUTIONAL EFFECTS OF PROPOSED RULE—Continued

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Monetized $millions/year	.....	.....	.....	.....	3	20	.....
	From:			To:			
Effects	*State, Local or Tribal Government:* None estimated. *Small Business:* The average cost per small entity is largest in Year 1 and range between $2.67 million and $7.97 million. Reformulation costs and stability testing represent the largest proportion of costs—up to 60 percent of average sales for entities with fewer than 50 employees and up to 13 percent of average sales for entities with 50–100 employees. *Wages:* None estimated. *Growth:* None estimated.						

X. 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, contained in an environmental assessment, may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday. 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.

XI. 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. 3501–3520). 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.

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; and (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.

Title: Tobacco Product Standard: NNN Level in Finished Smokeless Tobacco Products.

Description: FDA is proposing a product standard to establish a limit of NNN in finished smokeless tobacco products sold in the United States. Products with higher NNN levels pose higher risks of cancer and FDA finds that establishing a NNN limit in finished smokeless tobacco products is appropriate for the protection of the public health. Proposed § 1132.10 would require that the mean level of NNN in any batch of finished smokeless tobacco products not exceed 1.0 µg/g of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by testing in compliance with § 1132.12. Proposed §§ 1132.12, 1132.14, 1132.16, and 1132.18 would establish product testing and sampling plan requirements. Proposed § 1132.12 would require two types of testing for smokeless tobacco products—stability testing and batch testing. Proposed § 1132.12(a) would require initial and annual stability testing to assess the stability of the NNN level in finished smokeless tobacco products and to establish and verify the product's expiration date and storage conditions (either room temperature or refrigeration). Proposed § 1132.12(b) would require manufacturers to conduct batch testing on each batch of finished smokeless tobacco product to determine whether the products conform to the proposed NNN limit. Proposed § 1132.12(c) would require the tobacco product manufacturer to document all testing.

Proposed §§ 1132.14 and 1132.16 would establish the standard and alternative test methods. If a tobacco product manufacturer were to choose not to use the standard test method in § 1132.14 to test its smokeless tobacco products, the manufacturer would be required to use a validated alternative test method that conforms to the requirements of proposed § 1132.16. Proposed § 1132.16(a) would require that, before using a validated alternative test method, the manufacturer notify the Center for Tobacco Products.

Proposed§ 1132.18 would establish the sampling requirements for all testing. These sampling requirements would be used in conjunction with the product testing required in proposed § 1132.12 (stability testing and batch testing) and would provide procedures for the manufacturer to select samples to demonstrate conformance with the proposed NNN limit.

Proposed § 1132.22 would require tobacco product manufacturers to establish and maintain procedures to identify, investigate, segregate, and make disposition decisions about nonconforming finished smokeless tobacco products in order to prevent their release for commercial distribution and to conduct investigations related to nonconforming products.

Under proposed § 1132.30, the labels of finished smokeless tobacco products would be required to contain a manufacturing code, expiration date, and, if applicable, storage conditions for the finished smokeless tobacco product. The information would have to be printed on or permanently affixed to the package assuring that the label remains intact through the expected duration of use. It must appear clearly, legibly, and indelibly in the English language. The expiration date must appear on the packaging in two-digit numerical values. If the manufacturer determines by stability testing that meets the requirements in § 1132.12 that the finished smokeless tobacco product must be stored in a refrigerator, the package label must state ''Keep Refrigerated.'' The manufacturing code would provide a history of the manufacturing, processing, packaging, labeling, holding, and initial

distribution of the product from records maintained by the tobacco product manufacturer.

Proposed § 1132.32 would require that tobacco product manufacturers maintain records regarding the product testing (*i.e.,* stability and batch testing), including protocols and a full report of the source data and results; records regarding investigations related to shortening of expiration dates based on results of annual stability testing; all notifications of an alternative test method and source data for alternative test method validation; all sampling plans and reports; documentation that the persons performing sampling have sufficient education, training, and experience to accomplish the assigned functions; all identification, investigation, segregation, and disposition procedures related to nonconforming products; and all nonconforming product investigations and rework (*i.e.,* the processing of nonconforming finished smokeless tobacco products to meet the requirements of part 1132). FDA is also proposing to require copies of all records be retained for a period of not less than 4 years from the date of commercial distribution of the finished smokeless tobacco product that is the subject of the record, except that certain records relating to alternative test methods would be required to be retained for a period of not less than 4 years after the last date the method is used. 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.

Description of Respondents: The provisions of this standard would apply to finished smokeless tobacco products. Finished smokeless tobacco product means a smokeless tobacco product, including all parts and components, packaged for consumer use, except for components, parts, or accessories sold without tobacco. The respondents are therefore manufacturers of smokeless tobacco products.

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

TABLE 9—ESTIMATED ANNUAL REPORTING BURDEN [1]

21 CFR part	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
§ 1132.16 Alternative Test Method (FDA Form 3979)	23	1	23	20	460
§ 1132.16 Waiver from Electronic Submission	2	1	2	.75	2
Total					462

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The burden in the reporting chart corresponds to table 23 ''Estimated Costs to Industry Associated with Notifications to FDA Regarding Use of Alternative Testing Methods'' in the RIA.

TABLE 10—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

Activity (units)	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
Change in process (Formulations)	68	1	68	8	544
Ingredient change (Formulations)	28	1	28	8	224
No change (Formulations)	60	1	60	4	240
Labeling records, annual after year 1 (UPCs)	1255	1	1255	2	2,510
Initial Stability Testing records (Manufacturers)	23	8	184	4	736
Annual Stability Testing records (Manufacturers)	23	3	69	4	276
Batch Testing (products)	784	28	21,952	4	87,808
Batch Testing records (Manufacturers)	23	1	23	4	92
Procedures for nonconforming products and related investigations (Manufacturers)	23	1	23	4	92
Notifications, alternate testing methods (Manufacturers)	23	2	46	0.75	35
Total [1]					92,557

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The burden in the recordkeeping chart corresponds to table 24 ''Estimated Recordkeeping Costs to Industry'' and table 13 ''Estimated Number of Batch Tests'' in the RIA.

TABLE 11—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN [1]

Activity (units)	Number of respondents	Number of disclosures per respondent	Total annual disclosures	Average burden per disclosure	Total hours
Package Labeling Change Minor (UPCs)	459	1	459	10	4,590
Package Labeling Change Major (UPCs)	8	1	8	23	184
Initial Stability Testing (one time) (Products)	784	168	131,712	2	263,424
Initial Stability Testing (recurring) (Products)	784	6.72	5,268	2	10,536
Annual Stability Testing (Products)	784	60.48	47,416	2	94,832
Sampling Plans (Products)	784	1	784	2	1,568
Total [1]					370,360

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The burden in the third-party disclosure chart corresponds to table 12 ''Estimated Costs Associated with Proposed Stability Testing Requirements'' and table 15 ''Products with Expiration and Storage Information'' in the RIA.

FDA's burden estimates are based on the regulatory impact analysis, Agency expertise, registration and listing data, company revenue information from Dunn & Bradstreet, and comparing to other online sources in order to categorize the entities and number of products.

Table 9 describes the annual reporting burden as a result of the requirements proposed in § 1132.16 submitting a notification of an alternative test method and requesting a waiver from electronic submission of such a notification. FDA estimates that it will receive 23 notifications for alternative test methods using FDA Form 3979 (Ref. 145) for a total of 460 hours. Because some of the manufacturers may currently be conducting these reports, the RIA anticipates that there would be between 1 and 23 manufacturers affected. For PRA purposes we have used the high estimate of 23. FDA also estimates that 2 respondents will submit a waiver request from electronic submission. Therefore, the total estimated reporting burden for this proposed rule is 462 hours.

Table 10 outlines the recordkeeping requirements that are proposed in § 1132.32. We note that recordkeeping time burden activities are derived from the respective models (RTI International, 2015a; RTI International, 2015a; RTI International, 2015(b). FDA estimates recordkeeping time burden related to product reformulation (change in process, ingredient change, and no change) to involve 156 formulations for total of 1,008 hours. For recordkeeping burden related to certain labeling records, FDA estimates that after year one 1,255 affected Universal Product Code (UPC) records will be kept annually for a total of 2,510 hours. The number of UPCs subject to these recordkeeping requirements is determined by multiplying the number of UPCs in each product category by the percent of products with expiration date information.

We estimate that batch testing will be conducted for 784 products (21,952 tests per year) for a total of 87,808 hours. Proposed § 1132.32 requires records to be maintained for stability and batch tests. FDA estimates that 23 manufacturers will maintain records related to initial stability testing, annual stability testing, and batch testing for a total of 1104 hours. Records are also required to be maintained of procedures for nonconforming products and related investigations. We estimate that 23 manufacturers will maintain these records for a total of 92 hours. Proposed § 1132.32 requires manufacturers to maintain all notifications of an alternative test method. We estimate that 23 manufacturers will maintain these records for a total of 35 burden hours. Therefore, the total estimated recordkeeping hours are 92,557.

Table 11 represents third party disclosures (package labeling) that a respondent must display. This table also covers the proposed stability testing that must occur for the label. Labeling burden is estimated by using data on the number of active UPCs from Nielsen Inc., and the estimated percentage of products with expiration and storage information come from FDA Registration and Listing database (as of March 1, 2016). To derive the number of UPCs subject to a labeling change that includes storage information, we assume that only those products that are currently refrigerated but for which we did not find evidence that the labeling exists would incur such labeling change. Thus, we estimate that these different products that would likely be affected by labeling changes would include up to 467 UPCs (derived by assuming that each product would be associated with one unique UPC).

Since all products already have either an expiration date or a manufactured on date, adding an expiration date or storage conditions to labeling would be considered a minor change if product label redesign is not needed and major if product label redesign is needed. FDA believes that labeling changes associated with adding storage information is assumed to be ''major'' to incorporate uncertainty regarding product label redesign. We estimate that 459 affected UPCs will undergo minor labeling changes for a total of 4,590 hours. Additionally, FDA estimates that 8 affected UPCs will undergo major labeling changes regarding storage information for a total of 184 hours.

Since establishing and verifying a product's expiration date and storage conditions on a label requires actual stability testing we categorize this burden under third party disclosures. For PRA purposes we have categorized stability testing under third party disclosures. For example, in accordance with § 1132.30 a package label would need to have the expiration date for the product. Prior to completing initial stability testing, the manufacturer might not know what the appropriate expiration date would be. Since the testing will inform the label we believe it is appropriate for the burden to fall under this category. We estimate that 784 products would undergo initial stability testing, and annual stability testing each year thereafter. FDA estimates that in year 1 there would be 131,712 initial tests for a total of 263,424 hours. After the first year we estimate that there would be 5,268 initial tests for a total of 10,536 hours. After the initial testing we expect 47,416 annual tests per year for total of 94,832 hours.

FDA included sampling plans in the third party disclosure chart because each tobacco product manufacturer would be required to demonstrate that the finished smokeless tobacco product's expiration date (on the label) is appropriate under the intended storage conditions, and to do so the manufacturer would conduct testing pursuant to sampling plans. In developing a sampling plan for NNN in smokeless tobacco products a manufacturer must take into account the size of a batch, the variation of NNN in their product, the margin of error around their analytical techniques, and any other variables they can justify as pertinent to their calculation. While the development of a sampling plan would require some data analysis and determination of assumptions, we believe that the development of a sampling plan could cover multiple products. In addition once a sampling plan had been developed we believe that there would be significant redundancy in the development of subsequent plans which would reduce the time needed to complete them. Ultimately we have estimated that the time for the development of a sampling plan would average 2 hours per product for a total of 1,568 hours. Therefore, the total third party disclosure burden is estimated to be 370,360 hours.

FDA estimates that the total burden imposed by these proposed requirements will be 463,379 hours (462 reporting, 92,557 recordkeeping, and 370,360 third party disclosures).

This proposed rule also refers to previously approved collections of information found in FDA regulations. The collections of information in section 905(j) of the FD&C Act (substantial equivalence reports) have been approved under OMB control number 0910–0673.

To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB (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)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will

publish a notice concerning OMB approval of these requirements in the **Federal Register**.

XII. Executive Order 13132

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would 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 proposed 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.

XIII. Executive Order 13175

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively concluded that the rule does not contain policies that would 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. The Agency solicits comments from tribal officials on any potential impact on Indian tribes from this proposed action.

XIV. References

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

1. International Agency for Research on Cancer, ''Smokeless Tobacco and Some Tobacco-specific N-nitrosamines,'' *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* 89, 2007, available at *http://monographs.iarc.fr/ENG/Monographs/vol89/mono89.pdf.*
2. International Agency for Research on Cancer, ''Personal Habits and Indoor Combustions: A Review of Human Carcinogens,'' *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* 100(e), 2012, available at *http://monographs.iarc.fr/ENG/Monographs/vol100E/mono100E.pdf.*
3. European Commission, Scientific Committee on Emerging and Newly Identified Health Risks, ''Health Effects of Smokeless Tobacco Products,'' 2008.
4. National Cancer Institute, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, ''Smokeless Tobacco and Public Health: A Global Perspective,'' 2014, available at *http://cancercontrol.cancer.gov/brp/tcrb/global-perspective/SmokelessTobaccoAndPublicHealth.pdf.*
5. Borgerding, M.F., J.A. Bodnar, G.M. Curtin, et al., ''The Chemical Composition of Smokeless Tobacco: A Survey of Products Sold in the United States in 2006 and 2007,'' *Regulatory Toxicology and Pharmacology,* 64(3):367–387, 2012.
6. Song, M., C. Marian, T.M. Brasky, et al., ''Chemical and Toxicological Characteristics of Conventional and Low-TSNA Moist Snuff Tobacco Products,'' *Toxicology Letters,* 245:68–77, 2016.
7. Balbo, S., S. James-Yi, C.S. Johnson, et al., ''(S)-N′-nitrosonornicotine, a Constituent of Smokeless Tobacco, is a Powerful Oral Cavity Carcinogen in Rats,'' *Carcinogenesis,* 34(9):2178–2183, 2013.
8. Hecht, S.S., ''Biochemistry, Biology, and Carcinogenicity of Tobacco-specific N-nitrosamines,'' *Chemical Research in Toxicology,* 11(6):559–603, 1998.
9. Stepanov, I., L. Biener, A. Knezevich, et al., ''Monitoring Tobacco-specific N-nitrosamines and Nicotine in Novel Marlboro and Camel Smokeless Tobacco Products: Findings From Round 1 of the New Product Watch,'' *Nicotine & Tobacco Research,* 14(3):274–281, 2012.
10. Ammann, J.R., K.S. Lovejoy, M.J. Walters, et al., ''A Survey of N′-nitrosonornicotine (NNN) and Total Water Content in Select Smokeless Tobacco Products Purchased in the United States in 2015,'' *Journal of Agricultural and Food Chemistry,* 64(21):4400–4406, 2016.
11. Rutqvist, L.E., M. Curvall, T. Hassler, et al., ''Swedish Snus and the GothiaTek® Standard,'' *Harm Reduction Journal,* 8:11, 2011.
12. Foulds, J., L. Ramstrom, M. Burke, et al., ''Effect of Smokeless Tobacco (Snus) on Smoking and Public Health in Sweden,'' *Tobacco Control,* 12:349–359, 2003.
13. Stepanov, I., J. Jensen, D. Hatsukami, et al., ''New and Traditional Smokeless Tobacco: Comparison of Toxicant and Carcinogen Levels,'' *Nicotine & Tobacco Research,* 10(12):1773–1782, 2008.
14. McNeill, A., R. Bedi, S. Islam, et al., ''Levels of Toxins in Oral Tobacco Products in the UK,'' *Tobacco Control,* 15(1):64–67, 2006.
15. Krautter, G.P., P.X. Chen, and M.F. Borgerding, ''Consumption Patterns and Biomarkers of Exposure in Cigarette Smokers Switched to Snus, Various Dissolvable Products, Dual Use, or Tobacco Abstinence,'' *Regulatory Toxicology and Pharmacology,* 71(2):186–197, 2015.
16. Swedish Match, ''Gothiatek® Limits for Undesired Components,'' March 7, 2016.
17. Rogers, J.D., L. Biener, and P.I. Clark, ''Test Marketing of New Smokeless Tobacco Products in Four U.S. Cities,'' *Nicotine &Tobacco Research,* 12(1):69–72, 2010.
18. Bahreinifar, S., N.M. Sheon, and P.M. Ling, ''Is Snus the Same as Dip? Smokers' Perceptions of New Smokeless Tobacco Advertising,'' *Tobacco Control,* 22(2):84–90, 2013.
19. Foulds, J. and H. Furberg, ''Is Low-Nicotine Marlboro Snus Really Snus?'' *Harm Reduction Journal,* 5:9, 2008.
20. Lawler, T.S., S.B. Stanfill, L. Zhang, et al., ''Chemical Characterization of Domestic Oral Tobacco Products: Total Nicotine, pH, Unprotonated Nicotine and Tobacco-specific N-nitrosamines,'' *Food and Chemical Toxicology,* 57:380–386, 2013.
21. Savage, L., ''Experts Fear Swedish Snus Sales in the U.S. Could Thwart Anti-tobacco Measures,'' *Journal of the National Cancer Institute,* 99(18):1358–1359, 1365, 2007.
22. Belushkin, M., G. Jaccard, and A. Kondylis, ''Considerations for Comparative Tobacco Product Assessments Based on Smoke Constituent Yields,'' *Regulatory Toxicology and Pharmacology,* 73(1):105–113, 2015.
23. Substance Abuse and Mental Health Services Administration, ''Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health,'' 2015, available at *http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.htm.*
24. Substance Abuse and Mental Health Services Administration, ''Results From the 2014 National Survey on Drug Use and Health: Detailed Tables,'' 2015, available at *http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.htm.*
25. Centers for Disease Control and Prevention, ''Tobacco Use Among Middle and High School Students—United States 2011–2015,'' *Morbidity and Mortality Weekly Report,* 65(14):361–367, April 15, 2016, available at *http://www.cdc.gov/mmwr/volumes/65/wr/mm6514a1.htm.*
26. Substance Abuse and Mental Health Services Administration, ''Results From the 2013 National Survey on Drug Use and Health,'' 2014.
27. U.S. Department of Health and Human Services, ''The Health Consequences of Using Smokeless Tobacco,'' A Report of the Advisory Committee to the Surgeon General, 1986.
28. World Health Organization, ''The Scientific Basis of Tobacco Product Regulation,'' Third Report of a WHO Study Group, WHO Technical Report Series 955, 2009.
29. Fisher, S., B. Spiegelhalder, J. Eisenbarth, et al., ''Investigations on the Origin of Tobacco-specific Nitrosamines in Mainstream Smoke of Cigarettes,'' *Carcinogenesis,* 11(5):723–730, 1990.
30. Brunnemann, K.D., B. Prokopczyk, M.V. Djordjevic, et al., ''Formation and Analysis of Tobacco-specific N-nitrosamines,'' *Critical Reviews in Toxicology,* 26(2):121–137, 1996.

31. Hoffmann, D., M.V. Djordjevic, J. Fan, et al., ''Five Leading U.S. Commercial Brands of Moist Snuff in 1994: Assessment of Carcinogenic N-nitrosamines,'' *Journal of National Cancer Institute,* 87(24):1862–1869, 1995.
32. Burton, H.R., L.P. Bush, and M.V. Djordjevic, ''Influence of Temperature and Humidity on the Accumulation of Tobacco Specific Nitrosamines in Stored Burley Tobacco,'' *Journal of Agricultural and Food Chemistry,* 37:1372–1377, 1989.
33. Spiegelhalder, B. and S. Fischer, ''Formation of Tobacco-specific Nitrosamines,'' *Critical Reviews in Toxicology,* 21(4):241, 1991.
34. Fisher, M.T., C.B. Bennett, A. Hayes, et al., ''Sources of and Technical Approaches for the Abatement of Tobacco Specific Nitrosamine Formation in Moist Smokeless Tobacco Products,'' *Food and Chemical Toxicology,* 50(3–4):942–948, 2012.
35. Brunnemann, K.D., S.S. Hecht, and D. Hoffmann, ''N-nitrosamines: Environmental Occurrence, in vivo Formation and Metabolism,'' *Journal of Toxicology: Clinical Toxicology,* 19(6–7):661–688, 1982.
36. Burton, H.R., N.K. Dye, and L.P. Bush, ''Relationship Between Tobacco-specific Nitrosamines and Nitrite from Different Air-Cured Tobacco Varieties,'' *Journal of Agricultural and Food Chemistry,* 42(9), 2007–2011, 1994.
37. Fischer, S., B. Spiegelhalder, and R. Preussmann, ''Preformed Tobacco-specific Nitrosamines—Role of Nitrate and Influence of Tobacco Type,'' *Carcinogenesis,* 10(8):1511–1517, 1989.
38. De Roton, C., A. Wiernik, I. Wahlberg, et al., ''Factors Influencing the Formation of Tobacco-specific Nitrosamines in French Air-Cured Tobaccos in Trials and at the Farm Level,'' *Beiträge zur Tabakforschung International,* 21(6): 305–320, 2005.
39. Siminszky, B., L. Gavilano, S. Bowen, et al., ''Conversion of Nicotine to Nornicotine in Nicotiana Tabacum is Mediated by CYP82E4, a Cytochrome P450 Monooxygenase,'' *Proceedings of the National Academy of Sciences of the United States of America,* 102(41):14919–14924, 2005.
40. Gavilano, L.B., N.P. Coleman, L.E. Burnley, et al., ''Genetic Engineering of Nicotiana Tabacum for Reduced Nornicotine Content,'' *Journal of Agricultural and Food Chemistry,* 54(24):9071–9078, 2006.
41. Shi, H., R. Wang, L.P. Bush, et al., ''Changes in TSNA Contents During Tobacco Storage and the Effect of Temperature and Nitrate Level on TSNA Formation,'' *Journal of Agricultural and Food Chemistry,* 61(47):11588–11594, 2013.
42. Chamberlain, W.J. and O.T. Chortyk, ''Effects of Curing and Fertilization on Nitrosamine Formation in Bright and Burley Tobacco,'' *Beiträge zur Tabakforschung International,* 15(2):87–92, 1992.
43. Hecht, S.S., C.B. Chen, M. Dong, et al., ''Chemical Studies on Tobacco Smoke,'' *Beiträge zur Tabakforschung International,* 9(11), 1977.
44. Geiss, O. and D. Kotzias, ''Tobacco, Cigarettes and Cigarette Smoke, An Overview,'' Institute for Health and Consumer Protection, European Commission Joint Research Centre, 2007.
45. Bush, L.P., M. Cui, H. Shi, et al., ''Formation of Tobacco-specific Nitrosamines in Air-Cured Tobacco,'' *Recent Advances in Tobacco Science,* 27:23–46, 2001.
46. Staaf, M., S. Back, A. Wiernik, et al., ''Formation of Tobacco-specific Nitrosamines (TSNA) During Air-curing: Conditions and Control,'' *Beiträge zur Tabakforschung International,* 21(6):321–330, 2005.
47. Andersen, R.A., P.D. Fleming, H.R. Burton, et al., ''Levels of Alkaloids and Their Derivatives in Air- and Fire-cured KY 171 Dark Tobacco During Prolonged Storage: Effects of Temperature and Moisture,'' *Tobacco International,* 192(10):49–55, 1990.
48. Morin, A., A. Porter, A. Ratavicius, et al., ''Evolution of Tobacco Specific Nitrosamines and Microbial Populations During Flue-Curing of Tobacco Under Direct and Indirect Heating,'' *Beiträge zur Tabakforschung International,* 21(1):40–46, 2004.
49. Nestor, T.B., J.S. Gentry, D.M. Peele et al., ''Role of Oxides of Nitrogen in Tobacco-specific Nitrosamine Formation in Flue-cured Tobacco,'' *Beiträge zur Tabakforschung International,* 20(7):467–475, 2003.
50. Rodu, B. and C. Jansson, ''Smokeless Tobacco and Oral Cancer: A Review of the Risks and Determinants,'' *Critical Reviews in Oral Biology and Medicine,* 15(50):252–263, 2004.
51. Parsons, L.L., M.S. Smith, J.L. Hamilton, et al., ''Nitrate Reduction During Curing and Processing of Burley Tobacco,'' *Tobacco Science,* 30:100–103, 1986.
52. Burton, H.R., G.H. Childs, R.A. Andersen, et al., ''Changes in Chemical Composition of Burley Tobacco During Senescence and Curing .3. Tobacco-specific Nitrosamines,'' *Journal of Agricultural and Food Chemistry,* 37(2):426–430, 1989.
53. Andersen, R.A., H.R. Burton, P.D. Fleming, et al., ''Effect of Storage Conditions on Nitrosated, Acylated, and Oxidized Pyridine Alkaloid Derivatives in Smokeless Tobacco Products,'' *Cancer Research,* 49(21):5895–5900, 1989.
54. Andersen, R.A., P.D. Fleming, H.R. Burton, et al., ''Nitrosated, Acylated, and Oxidized Pyridine Alkaloids During Storage of Smokeless Tobaccos: Effects of Moisture, Temperature, and Their Interactions,'' *Journal of Agricultural Food Chemistry,* 39(7):1280–1287, 1991.
55. Djordjevic, M.V., J. Fan, L.P. Bush, et al., ''Effects of Storage Conditions on Levels of Tobacco-specific N-nitrosamines and N-nitrosamino Acids in U.S. Moist Snuff,'' *Journal of Agricultural and Food Chemistry,* 41(10):1790–1794, 1993.
56. Stepanov, I., L. Biener, K. Yershova, et al., ''Monitoring Tobacco-specific N-nitrosamines and Nicotine in Novel Smokeless Tobacco Products: Findings from Round II of the New Product Watch,'' *Nicotine & Tobacco Research,* 16(8):1070–1078, 2014.
57. U.S. Environmental Protection Agency, ''Risk Assessment Guidance for Superfund,'' 1989, available at *https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part.*
58. Hecht S.S., S.G. Carmella, Stepanov, I., et al., ''Metabolism of the Tobacco-specific Carcinogen 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanone to Its Biomarker Total NNAL in Smokeless Tobacco Users,'' *Cancer Epidemiology, Biomarkers & Prevention,* 17(3): 732–735, 2008.
59. Hecht, S.S., R. Young, and Y. Maeura, ''Comparative Carcinogenicity in F344 Rats and Syrian Golden Hamsters of N′-nitrosonornicotine and N'-nitrosonornicotine-1–N-oxide,'' *Cancer Letters,* 20(3):333–340, 1983.
60. Hatsukami, D.K., R.M. Keenan, and D.J. Anton, ''Topographical Features of Smokeless Tobacco Use,'' *Psychopharmacology,* 96(3):428–429, 1988.
61. Ary, D.V., E. Lichtenstein, and H.H. Severson, ''Smokeless Tobacco Use Among Male Adolescents: Patterns, Correlates, Predictors, and the Use of Other Drugs,'' *Preventive Medicine,* 16(3):385–401, 1987.
62. Andersson, G. and T. Axell, ''Clinical Appearance of Lesions Associated with the Use of Loose and Portion-bag Packed Swedish Moist Snuff: A Comparative Study,'' *Journal of Oral Pathology & Medicine,* 18(1):2–7, 1989.
63. Digard, H., G. Errington, A. Richter, et al., ''Patterns and Behaviors of Snus Consumption in Sweden,'' *Nicotine & Tobacco Research,* 11(10):1175–1181, 2009.
64. Hatsukami, D.K., D. Anton, A. Callies, et al., ''Situational Factors and Patterns Associated With Smokeless Tobacco Use,'' *Journal of Behavioral Medicine,* 14(4):383–396, 1991.
65. Boyle, R.G., M.A. Gerend, C.B. Peterson, et al., ''Use of Smokeless Tobacco by Young Adult Females,'' *Journal of Substance Abuse,* 10(1):19–25, 1998.
66. Lemmonds, C.A., S.S. Hecht, J.A. Jensen, et al., ''Smokeless Tobacco Topography and Toxin Exposure,'' *Nicotine & Tobacco Research,* 7(3):469–474, 2005.
67. Ferketich, A.K., A.G. Wee, J. Shultz, et al., ''Smokeless Tobacco Use and Salivary Cotinine Concentration,'' *Addictive Behaviors,* 32(12):2953–2962, 2007.
68. Hatsukami, D.K., J.O. Ebbert, R.M. Feuer, et al., ''Changing Smokeless Tobacco Products New Tobacco-delivery Systems,'' *American Journal of Preventive Medicine,* 33(6 Suppl): S368–S378, 2007.
69. Caraway, J.W. and P.X. Chen, ''Assessment of Mouth-level Exposure to Tobacco Constituents in U.S. Snus Consumers,'' *Nicotine & Tobacco Research,* 15(3):670–677, 2013.
70. Oliver, A.J., J.A. Jensen, R.I. Vogel, et al., ''Flavored and Nonflavored Smokeless

Tobacco Products: Rate, Pattern of Use, and Effects,'' *Nicotine & Tobacco Research,* 15(1):88–92, 2013.
71. Jitnarin, N., W.S.C. Poston, C.K. Haddock, et al., ''Tobacco Use Pattern Among a National Firefighter Cohort,'' *Nicotine & Tobacco Research,* 17(1):66–73, 2015.
72. Hecht, S.S., S.G. Carmella, A. Edmonds, et al., ''Exposure to Nicotine and a Tobacco-specific Carcinogen Increase with Duration of Use of Smokeless Tobacco,'' *Tobacco Control,* 17(2):128–131, 2008.
73. Nilsson, R., ''A Qualitative and Quantitative Risk Assessment of Snuff Dipping,'' *Regulatory Toxicology and Pharmacology,* 28(1):1–16, 1998.
74. Ayo-Yusuf, O.A. and G.N. Connolly, ''Applying Toxicological Risk Assessment Principles to Constituents of Smokeless Tobacco Products: Implications for Product Regulation,'' *Tobacco Control,* 20(1):53–57, 2011.
75. U.S. Environmental Protection Agency, ''Exposure Factors Handbook,'' Chapter 18, 2011, available at *http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=526181.*
76. Berg, C.J., E. Stratton, G.L. Schauer, et al., ''Perceived Harm, Addictiveness, and Social Acceptability of Tobacco Products and Marijuana Among Young Adults: Marijuana, Hookah, and Electronic Cigarettes Win,'' *Substance Use and Misuse,* 50(1): 79–89, 2015.
77. Yuan, J.M., A.D. Knezevich, R. Wang, et al., ''Urinary Levels of the Tobacco-specific Carcinogen N′-nitrosonornicotine and its Glucuronide are Strongly Associated with Esophageal Cancer Risk in Smokers,'' *Carcinogenesis,* 32(9):1366–1371, 2011.
78. World Health Organization, ''The Scientific Basis of Tobacco Product Regulation 2nd Report,'' 2008.
79. U.S. Food and Drug Administration, ''Determination of N-nitrosonornicotine (NNN) in Smokeless Tobacco and Tobacco Filler by HPLC–MS/MS,'' LIB No. 4620, January 2017, available at *http://www.fda.gov/ScienceResearch/FieldScience/ucm231463.htm.*
80. CORESTA, ''Recommended Method No 72: Determination of Tobacco-specific Nitrosamines in Smokeless Tobacco Products by LC–MS/MS.'' 2016.
81. Wu, W., D. Ashley, and C. Watson, ''Simultaneous Determination of Five Tobacco-specific Nitrosamines in Mainstream Cigarette Smoke by Isotope Dilution Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry,'' *Analytical Chemistry,* 75(18):4827–4832, 2003.
82. Richter, P., K. Hodge, S. Stanfill, et al., ''Surveillance of Moist Snuff: Total Nicotine, Moisture, pH, Un-ionized Nicotine, and Tobacco-specific Nitrosamines,'' *Nicotine & Tobacco Research,* 10(11):1645–1652, 2008.
83. Jansson, C., A. Paccou, and B. Österdahl, ''Analysis of Tobacco-specific N-nitrosamines in Snuff by Ethyl Acetate Extraction and Liquid Chromatography—tandem Mass Spectrometry,'' *Journal of Chromatography A,* 1008(2):135–143, 2003.
84. Osterdahl, B., C. Jansson, and A. Paccou, ''Decreased Levels of Tobacco-specific N-nitrosamines in Moist Snuff on the Swedish Market,'' *Journal of Agricultural and Food Chemistry,* 52(16):5085–5088, 2004.
85. Digard, H., N. Gale, G. Errington, et al., ''Multi-analyte Approach for Determining the Extraction of Tobacco Constituents From Pouched Snus by Consumers During Use,'' *Chemistry Central Journal,* 7:55, 2013.
86. Adams, J.D., K.D. Brunnemann, and D. Hoffmann, ''Chemical Studies on Tobacco Smoke,'' *Journal of Chromatography A,* 256(2):347–351, 1983.
87. Brunnemann, K.D., L. Genoble, and D. Hoffmann, ''Identification and Analysis of a New Tobacco-specific N-nitrosamine, 4-(Methylnitrosamino)-4-(3-Pyridyl)-1-Butanol,'' *Carcinogenesis,* 8(3):465–469, 1987.
88. Djordjevic, M.V., K.D. Brunnemann, and D. Hoffmann, ''Identification and Analysis of a Nicotine-Derived N-nitrosamino Acid and Other Nitrosamino Acids in Tobacco,'' *Carcinogenesis,* 10(9):1725–1731, 1989.
89. Health Canada, ''Official Method T–309: Determination of Nitrosamines in Whole Tobacco,'' 1999.
90. Hecht, S.S., R.M. Ornaf, and D. Hoffmann, ''Determination of N′-nitrosonornicotine in Tobacco by High Speed Liquid Chromatography,'' *Analytical Chemistry,* 47(12):2046–2048, 1975.
91. Brown, M.C., D.V. Onisk, J.W. Stave, et al., ''Tobacco-specific Nitrosamine Detection Assays and Reagents,'' U.S. Patent Application No. 20050043515 A1, 2005.
92. Roosaar, A., A.L. Johansson, G. Sandborgh-Englund, et al., ''Cancer and Mortality Among Users and Nonusers of Snus,'' *International Journal of Cancer,* 123(1):168–173, 2008.
93. California Environmental Protection Agency, ''Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens,'' 1992.
94. Castonguay, A., A. Rivenson, N. Trushin, et al., ''Effects of Chronic Ethanol Consumption on the Metabolism and Carcinogenicity of N′-nitrosonornicotine in F344 Rats,'' *Cancer Research,* 44(6):2285–2290, 1984.
95. Stoner, G.D. C. Adams, L.A. Kresty, et al., ''Inhibition of N′-nitrosonornicotine-induced Esophageal Tumorigenesis by 3-phenylpropyl isothiocyanate,'' *Carcinogenesis,* 19(12):2139–2143, 1998.
96. Khariwala, S.S., S.G. Carmella, I. Stepanov, et al., ''Elevated Levels of 1-hydroxypyrene and N′-nitrosonornicotine in Smokers with Head and Neck Cancer: A Matched Control Study,'' *Head & Neck,* 35(8):1096–1100, 2013.
97. Rostron, B.L., C.M. Chang, D.M. van Bemmel, et al., ''Nicotine and Toxicant Exposure Among U.S. Smokeless Tobacco Users: Results From 1999 to 2012 National Health and Nutrition Examination Survey Data,'' *Cancer Epidemiology, Biomarkers & Prevention,* 24(12):1829–1837, 2015.
98. Hecht, S.S., S.G. Carmella, SE. Murphy, et al., ''Similar Exposure to a Tobacco-specific Carcinogen in Smokeless Tobacco Users and Cigarette Smokers,'' *Cancer Epidemiology, Biomarkers & Prevention,* 16(8):1567–1572, 2007.
99. Stepanov, I., and S.S. Hecht, ''Tobacco Specific Nitrosamines and Their Pyridine-N-glucoronides in the Urine of Smokers and Smokeless Tobacco Users,'' *Cancer Epidemiology, Biomarkers & Prevention,* 14(4), 885–891, 2005.
100. Boffetta, P., S.S Hecht, N. Gray, et al., ''Smokeless Tobacco and Cancer,'' *Lancet Oncology,* 9(9):822, 2008.
101. Pednekar, M.S., P.C. Gupta, B.B. Yeole, et al., ''Association of Tobacco Habits, Including Bidi Smoking, With Overall and Site-specific Cancer Incidence: Results From the Mumbai Cohort Study,'' *Cancer Causes and Control,* 22(6):859–868, 2011.
102. Haussmann, H., ''Use of Hazard Indices for a Theoretical Evaluation of Cigarette Smoke Composition,'' *Chemical Research in Toxicology,* 25(4):794–810, 2012.
103. Lee, P.N. and J. Hamling, ''The Relation Between Smokeless Tobacco and Cancer in Northern Europe and North America. A Commentary on Differences Between the Conclusions Researched by Two Recent Reviews,'' *BMC Cancer,* 9:256, 2009.
104. Idris, A.M., H. Ahmed, and M. Malik, ''Toombak Dipping and Cancer of the Oral Cavity in the Sudan: A Case-Control Study,'' *International Journal of Cancer,* 63(4):477–480, 1995.
105. Idris, A.M., J. Nair, H. Ohshima, et al., ''Unusually High Levels of Carcinogenic Tobacco-specific Nitrosamines in Sudan Snuff (Toombak),'' *Carcinogenesis,* 12(6):1115–1118, 1991.
106. U.S. Department of Health and Human Services, ''How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General,'' Chapter 3, 2010, available at *https://www.ncbi.nlm.nih.gov/books/NBK53017/.*
107. Hecht, S.S., I. Stepanov, and S. Carmella, ''Exposure and Metabolic Activation Biomarkers of Carcinogenic Tobacco-specific Nitrosamines,'' *Accounts of Chemical Research,* 49(1):106–114, 2016.
108. Levin, M.L., ''The Occurrence of Lung Cancer in Man,'' *Acta: Unio Internationalis Contra Cancrum,* 9(3):531–541, 1953.
109. U.S. Department of Health and Human Services, ''The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General,'' Chapter 12, 2014, available at *https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html.*
110. Stockwell, H.G. and Lyman, G.H, ''Impact of Smoking and Smokeless

Tobacco on the Risk of Cancer of the Head and Neck,'' *Head & Neck Surgery,* 9(2):104–110, 1986.
111. Centers for Disease Control and Prevention, ''2010 National Health Interview Survey,'' 2011, available at *http://www.cdc.gov/nchs/nhis/nhis_2010_data_release.htm.* Accessed on April 11, 2016.
112. United States Cancer and Cancer Mortality Statistics: 1999–2013, WONDER Online Database. United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2016, available at *http://wonder.cdc.gov/cancer.html.* Accessed on April 11, 2016.
113. Centers for Disease Control and Prevention, National Vital Statistic Report, U.S. Life Tables 2010, available at *http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_07.*
114. Lee, P.N. and J. Hamling, ''Systematic Review of the Relation Between Smokeless Tobacco and Cancer in Europe and North America,'' *BMC Medicine,* 7:36, 2009.
115. International Agency for Research on Cancer, ''Tobacco Control: Reversal of Risk After Quitting Smoking,'' *IARC Handbooks of Cancer Prevention,* 2007.
116. Chandu, A., A.C.H. Smith, and S.N. Rogers, ''Health-related Quality of Life in Oral Cancer: A Review,'' *Journal of Oral and Maxillofacial Surgery,* 64(3):495–502, 2006.
117. Gamba, A. M. Romano, I.M. Grosso, et al., ''Psychosocial Adjustment of Patients Surgically Treated for Head and Neck Cancer,'' *Head & Neck,* 14(3):218–223, 1992.
118. Bjordal, K. and S. Kaasa, ''Psychological Distress in Head and Neck Cancer Patients 7–11 Years After Curative Treatment,'' *British Journal of Cancer,* 71(3):592–597, 1995.
119. National Cancer Institute, ''Cancer Prevalence and Cost of Care Projections,'' 2015, available at *http://costprojections.cancer.gov/graph.php.* Accessed on April 11, 2016.
120. National Cancer Institute, ''A Snapshot of Head and Neck Cancer,'' 2014, available at *http://www.cancer.gov/research/progress/snapshots/head-and-neck.* Accessed on April 11, 2016.
121. Henley, S.J., M.J. Thun, C. Connell, et al., ''Two Large Prospective Studies of Mortality Among Men Who Use Snuff or Chewing Tobacco (United States),'' *Cancer Causes and Control,* 16(4):347–358, 2005.
122. Zhou, J., D.S Michaud, S.M Langevin, et al., ''Smokeless Tobacco and Risk of Head and Neck Cancer: Evidence From a Case-control Study in New England,'' *International Journal of Cancer,* 132(8):1911–1917, 2013.
123. Agaku, I., A.O Akinyele, and U. Omaduvie, ''Evaluation of Factors Influencing Intention To Quit Smokeless and Cigarette Tobacco Use Among Nigerian Adolescents,'' *Nigerian Medical Journal,* 53(1):31–36, 2012.
124. Chakravorty, B. and S. Chakravorty, ''Cessation Related Perceptions and Behavior of Former and Current Smokeless Tobacco Users,'' *Journal of American College of Health,* 46(3):133–138, 1997.
125. Hall, M.G., K.M. Ribisl, and N. Brewer, ''Smokers' and Nonsmokers' Beliefs About Harmful Tobacco Constituents: Implications for FDA Communication Efforts,'' *Nicotine & Tobacco Research,* 16(3):343–350, 2014.
126. Yanovitzky, I. and C.L. Blitz, ''Effect of Media Coverage and Physician Advice on Utilization of Breast Cancer Screening by Women 40 Years and Older,'' *Journal of Health Communication,* 5(2):117–134, 2000.
127. Cram, P., A. Fendrick, J. Inadomi, et al., ''The Impact of a Celebrity Promotional Campaign on the Use of Colon Cancer Screening—The Katie Couric Effect,'' *Archives of Internal Medicine,* 163(13):1601–1605, 2003.
128. Johnson, SE., C. Choiniere, G. Tessman, et al., ''How Do Young Adult Consumers Evaluate and Compare the Harmfulness of Cigarettes and Smokeless Tobacco? A Focus Group Study,'' In B. Apelberg (Chr.), *Youth and Young Adult Use and Risk Perception of Tobacco Products: Research to Inform FDA Regulations, 2013,* Symposium conducted at the annual meeting of the Society for Research on Nicotine and Tobacco (SRNT), Boston, MA.
129. Loewenstein, G., ''Out of Control: Visceral Influences on Behavior,'' *Organizational Behavior and Human Decision Processes,* 65(3):272–292, 1996.
130. Mutti, S., D. Hammond, R. Borland, et al., ''Beyond Light and Mild: Cigarette Brand Descriptors and Perceptions of Risk in the International Tobacco Control (ITC) Four Country Survey,'' *Addiction,* 106(6):1166–1175, 2011.
131. Delnevo, C.D., O.A. Wackowski, D.P. Giovenco, et al., ''Examining Market Trends in the United States Smokeless Tobacco Use: 2005–2011,'' *Tobacco Control,* 23(2):107–112, 2014.
132. Alpert, H.R., H. Koh, and G.N. Connolly, ''Free Nicotine Content and Strategic Marketing of Moist Snuff Tobacco Products in the United States: 2000–2006,'' *Tobacco Control,* 17(5):332–338, 2008.
133. O'Connor, R.J., A. McNeill, R. Borland, et al., ''Smokers' Beliefs About the Relative Safety of Other Tobacco Products: Findings From the ITC Collaboration,'' *Nicotine & Tobacco Research,* 9(10):1033–1042, 2007.
134. Borland, R., J. Cooper, A. McNeill, et al., ''Trends in Beliefs About the Harmfulness and Use of Stop-smoking Medications and Smokeless Tobacco Products Among Cigarettes Smokers: Findings From the ITC Four-country Survey,'' *Harm Reduction Journal,* 8, 2011.
135. Smith, S.Y., B. Curbow, and F.A. Stillman, ''Harm Perception of Nicotine Products in College Freshmen,'' *Nicotine & Tobacco Research,* 9(9): 977–982, 2007.
136. Tomar, S.L. and D.K. Hatsukami, ''Perceived Risk of Harm From Cigarettes or Smokeless Tobacco Among U.S. High School Seniors,'' *Nicotine & Tobacco Research,* 9(11):1191–1196, 2007.
137. Krosnick, J.A, L. Chang, S.J. Sherman, et al., ''The Effects of Beliefs About the Health Consequences of Cigarette Smoking on Smoking Onset,'' *Journal of Communication,* 56(S1):S18–S37, 2006.
138. Song, A.V., H.E.R. Morrell, J.L. Cornell, et al., ''Perceptions of Smoking-related Risks and Benefits as Predictors of Adolescent Smoking Initiation,'' *American Journal of Public Health,* 99(3):487–492, 2009.
139. Boyle, R.G., A.J. Claxton, and J.L. Forster, ''The Role of Social Influences and Tobacco Availability on Adolescent Smokeless Tobacco Use,'' *Journal of Adolescent Health,* 20(4):279–285, 1997.
140. Nemeth, J.M., S.T. Liu, E.G. Klein, et al., ''Factors Influencing Smokeless Tobacco Use in Rural Ohio Appalachia,'' *Journal of Community Health,* 37(6):1208–1217, 2012.
141. Portnoy, D.B., C.C. Wu, C. Tworek, et al., ''Youth Curiosity about Cigarettes, Smokeless Tobacco, and Cigars: Prevalence and Associations with Advertising,'' *American Journal of Preventive Medicine,* 47(2 Suppl 1):S76–S86, 2014.
142. Herd, N., R. Borland, and A. Hyland, ''Predictors of Smoking Relapse by Duration of Abstinence: Findings From the International Tobacco Control (ITC) Four Country Survey,'' *Addiction,* 104(12):2088–2099, 2009.
143. Ockene, J.K., K.M. Emmons, R.J. Mermelstein, et al., ''Relapse and Maintenance Issues for Smoking Cessation,'' *Health Psychology,* 19(1, Suppl):17–31, 2000.
144. Killen, J.D. and S.P. Fortmann, ''Craving is Associated with Smoking Relapse: Findings From Three Prospective Studies,'' *Experimental and Clinical Psychopharmacology,* 5(2):137–142, 1997.
145. Draft FDA Form 3979 (Alternative Test Method Notification).
146. Food and Drug Administration, Preliminary Regulatory Impact Analysis; Initial Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis; Tobacco Product Standard for N-nitrosonornicotine Level in Finished Smokeless Tobacco Products; Proposed Rule.
147. Hoffmann, D. and S.S. Hecht, ''Advances in Tobacco Carcinogenesis,'' Handbook of Experimental Pharmacology, 63–102, 1990.
148. Hoffmann, D., R. Raineri, S.S. Hecht, et al., ''A Study of Tobacco Carcinogenesis. XIV. Effects of N′-nitrosonornicotine and N′-nitrosonanabasine in Rats,'' *Journal of the National Cancer Institute,* 55(4):977–981, 1975.
149. Hoffmann D., A. Rivenson, S. Amin, et al., ''Dose-response Study of the Carcinogenicity of Tobacco-specific N-nitrosamines in F344 Rats,'' *Journal of Cancer Research and Clinical Oncology,*'' 108(1):81–86, 1984.
150. Prokopczyk, B., A. Rivenson, and D. Hoffmann, ''A Study of Betel Quid

Carcinogenesis. IX. Comparative Carcinogenicity of 3-(methylnitrosamino)propionitrile and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone upon Local Application to Mouse Skin and Rat Oral Mucosa,'' *Cancer Letters,* 60(2):153–157, 1991.
151. McCoy, G.D., S.S. Hecht, S. Katayama, et al., ''Differential Effect of Chronic Ethanol Consumption on the Carcinogenicity of N-nitrosopyrrolidine and N′-nitrosonornicotine in Male Syrian Golden Hamsters,'' *Cancer Research,* 41(7):2849–2854, 1981.
152. Hilfrich, J., S.S. Hecht, and D. Hoffmann, ''A Study of Tobacco Carcinogenesis. XV. Effects of N′-nitrosonornicotine and N′-nitrosoanabasine in Syrian Golden Hamsters,'' *Cancer Letters,* 2(3):169–175, 1977.
153. Koppang, N., A. Rivenson, A. Reith, et al., ''A Study of Tobacco Carcinogenesis XLVIII. Carcinogenicity of N′-nitrosonornicotine in Mink (Mustela vison),'' *Carcinogenesis,* 13(11):1957–1960, 1992.
154. Koppang, N., A. Rivenson, H.K. Dahle, et al., ''A Study of Tobacco Carcinogenesis, LIII: Carcinogenicity of N′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in Mink (Mustela vison),'' *Cancer Letters,* 111(1–2):167–171, 1997.
155. Padma, P.R., V.S. Lalitha, A.J. Amonkar, et al., ''Anticarcinogenic Effect of Betel Leaf Extract Against Tobacco Carcinogens,'' *Cancer Letters,* 45(3):195–202, 1989.
156. Padma, P.R., V.S. Lalitha, A.J. Amonkar, et al., ''Carcinogenicity Studies on the two Tobacco-specific N-nitrosamines, N′-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone,'' *Carcinogenesis,* 10(11):1997–2002, 1989.
157. Hecht, S.S., C.B. Chen, R.M. Ornaf, et al., ''Chemical Studies on Tobacco Smoke LVI. Tobacco Specific Nitrosamines: Origins, Carcinogenicity and Metabolism,'' *IARC Scientific Publications,* (19):395–413, 1978.
158. Hecht, S.S. and D. Hoffmann, ''Tobacco-specific Nitrosamines, an Important Group of Carcinogens in Tobacco and Tobacco Smoke,'' *Carcinogenesis,* 9(6):875–884, 1988.
159. Peterson, L.A. and S.S. Hecht, ''0^6-Methylguanine is a Critical Determinant of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone Tumorigenesis in A/J Mouse Lung,'' *Cancer Research,* 51(20): 5557–5564, 1991.
160. Castonguay, A., D. Lin, G.D. Stoner, et al., ''Comparative Carcinogenicity in A/J Mice and Metabolism by Cultured Mouse Peripheral Lung of N′-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and their Analogues,'' *Cancer Research,* 43(3):1223–1229, 1983.
161. Griciute, L., M. Castegnaro, J.C. Bereziat, et al., ''Influence of Ethyl Alcohol on the Carcinogenic Activity of N-nitrosonornicotine,'' *Cancer Letters,* 31(3):267–275, 1986.
162. Chung, F.L., G. Kelloff, V. Steele, et al., ''Chemopreventive Efficacy of Arylalkyl Isothiocyanates and N-acetylcysteine for Lung Tumorigenesis in Fischer Rats,'' *Cancer Research,* 56(4):772–778, 1996.
163. Boorman, G.A., R. Hailey, S. Grumbein, et al., ''Toxicology and Carcinogenesis Studies of Ozone and 4-(N-nitrosomethylamino)-1-(-3-pyridyl)-1-butanone in Fischer-344/N Rats,'' *Toxicologic Pathololgy,* 22(5): 545–554, 1994.
164. Rivenson, A., D. Hoffmann, B. Prokopczyk, et al., ''Induction of Lung and Exocrine Pancreas Tumors in F344 Rats by Tobacco-specific and *Areca*-derived N-nitrosamines,'' *Cancer Research,* 48(23):6912–6917, 1988.
165. Hecht, S.S., N. Trushin, J. Rigotty, et al., ''Complete Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induced Rat Lung Tumorigenesis and Favorable Modification of Biomarkers by Phenethyl Isothiocyanate,'' *Cancer Epidemiology, Biomarkers & Prevention,* 5(8):645–652, 1996.
166. Hoffmann, D., A. Rivenson, R. Abbi, et al., ''A Study of Tobacco Carcinogenesis: Effect of the Fat Content of the Diet on the Carcinogenic Activity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in F344 Rats,'' *Cancer Research,* 53(12):2758–2761, 1993.
167. Balbo, S., C.S. Johnson, R.C. Kovi, et al., ''Carcinogenicity and DNA Adduct Formation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and Enantiomers of its Metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in F-344 Rats,'' *Carcinogenesis,* 35(12): 2798–2806, 2014.
168. Pool-Zobel, B.L., R.G. Klein, U.M. Liegibel, et al., ''Systemic Genotoxic Effects of Tobacco-related Nitrosamines Following Oral and Inhalational Administration to Sprague-Dawley Rats,'' *Clinical Investigation,* 70(3–4):299–306, 1992.
169. Zarth, A.T., P. Upadhyaya, J. Yang, et al., ''DNA Adduct Formation from Metabolic 5′-Hydroxylation of the Tobacco-specific Carcinogen N′-nitrosonornicotine in Human Enzyme Systems and in Rats,'' *Chemical Research in Toxicology,* 29(3):380–389, 2016.
170. Yang, J., P.W. Villalta, P. Upadhyaya, et al., ''Analysis of 0^6-[4-(3-Pyridyl)-4-oxobut-1-yl]-2′-deoxyguanosine and Other DNA Adducts in Rats Treated with Enantiomeric or Racemic N′-nitrosonornicotine,'' *Chemical Research in Toxicology,* 29(1):87–95, 2016.
171. Zhao, L., S. Balbo, M. Wang, et al., ''Quantitation of Pyridyloxobutyl-DNA Adducts in Tissues of Rats Treated Chronically with (R)- or (S)-N′-nitrosonornicotine (NNN) in a Carcinogenicity Study,'' *Chemical Research in Toxicology,* 26(10):1526–1535, 2013.
172. Zhang, S., M. Wang, P.W. Villalta, et al., ''Quantitation of Pyridyloxobutyl DNA Adducts in Nasal and Oral Mucosa of Rats Treated Chronically with Enantiomers of N′-nitrosonornicotine,'' *Chemical Research in Toxicology,* 22(5):949–956, 2009.
173. Lao, Y., N. Yu, F. Kassie, et al., ''Analysis of Pyridyloxobutyl DNA Adducts in F344 Rats Chronically Treated with (R)- and (S)-N′-nitrosonornicotine,'' *Chemical Research in Toxicology,* 20(2):246–256, 2007.
174. von Pressentin, M.M., W. Kosinska, and J.B. Guttenplan, ''Mutagenesis Induced by Oral Carcinogens in lacZ Mouse (MutaMouse) Tongue and Other Oral Tissues,'' *Carcinogenesis,* 20(11):2167–2170, 1999.
175. Hatsukami, D., I. Stepanov, H. Severson, et al., ''Evidence Supporting Product Standards for Carcinogens in Smokeless Tobacco Products,'' *Cancer Prevention Research,* 8(1):20–26, 2015.
176. Hecht, S.S., I. Stepanov, and D. Hatsukami, ''Major Tobacco Companies Have Technology to Reduce Carcinogen Levels But Do Not Apply It to Popular Smokeless Tobacco Products,'' *Tobacco Control,* 20(6):443, 2011.
177. McIntee, E.J. and S.S. Hecht, ''Metabolism of N′-nitrosonornicotine Enantiomers by Cultured Rat Esophagus and In Vivo in Rats,'' *Chemical Research in Toxicology,* 13(3):192–199, 2000.
178. Nachiappan, V., S.I. Mufti, A. Chakravarti, et al., ''Lipid Peroxidation and Ethanol-related Tumor Promotion in Fischer-344 Rats Treated With Tobacco-specific Nitrosamines,'' *Alcohol and Alcoholism,* 29(5):565–574, 1994.
179. Singer, G.M. and H.W. Taylor, ''Carcinogenicity of N′nitrosonornicotine in Sprague Dawley Rats,'' *Journal of the National Cancer Institute,* 57(6):1275–1276, 1976.
180. Carmella, S.G., E.J. McIntee, M. Chen, et al, ''Enantiomeric Composition of N′-nitrosonornicotine and N′-nitrosoanatabine in tobacco,'' *Carcinogenesis,* 21(4):839–43, 2000.
181. Stepanov, I., K. Yershova, S. Carmella, et al., ''Levels of (S)-N′-nitrosonornicotine in U.S. Tobacco Products,'' *Nicotine & Tobacco Research,* 15(7):1305–10, 2013.
182. United States Cancer Statistics (USCS). United States Department of Health and Human Services, Centers for Disease Control and Prevention; 2016, available at *https://www.cdc.gov/cancer/npcr/uscs/technical_notes/contributors/.*
183. Yuan, J.M., W.P. Koh, S.E. Murphy, et al., ''Urinary Levels of Tobacco-specific Nitrosamine Metabolites in Relation to Lung Cancer Development in Two Prospective Cohorts of Cigarette Smokers,'' *Cancer Research,* 69(7):2990–2995, 2009.
184. National Program of Cancer Registries. United States Department of Health and Human Services, Centers for Disease Control and Prevention; 2016, available at *https://www.cdc.gov/cancer/npcr/.*
185. Surveillance, Epidemiology, and End Results Program. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2016, available at *https://seer.cancer.gov/.*
186. National Vital Statistics System. United States Department of Health and Human

Services, Centers for Disease Control and Prevention; 2016, available at *https://www.cdc.gov/cancer/npcr/uscs/technical_notes/contributors/nvss.htm.*
187. U.S. Environmental Protection Agency, ''Guidelines for Carcinogen Risk Assessment,'' 2012, available at *https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf.*
188. Lewin, F., S.E. Norell, H. Johansson, et al., ''Smoking Tobacco, Oral Snuff, and Alcohol in the Etiology of Squamous Cell Carcinoma of the Head and Neck: A Population-Based Case-Referent Study in Sweden,'' *Cancer,* 82:1367–1375, 1998.
189. Schildt, B.B., M. Eriksson, L. Hardell, et al., ''Oral Snuff, Smoking Habits, and Alcohol Consumption in Relation to Oral Cancer in a Swedish Case-Control Study,'' *International Journal of Cancer,* 77:341–346, 1998.
190. Definition of ''cancer slope factor'' from the U.S. Environmental Protection Agency's Thesaurus of Terms Used in Microbial Risk Assessment available at *https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=MRA%20Thesaurus* (type in ''cancer slope factor'').
191. Boffetta, P., B. Aagnes, E. Weiderpass, et al., ''Smokeless Tobacco Use and Risk of Cancer of the Pancreas and Other Organs,'' *International Journal of Cancer,* 114:992–995, 2005.
192. Luo, J., W. Ye, K. Zendehdel, et al., ''Oral Use of Swedish Moist Snuff (Snus) and Risk of Cancer of the Mouth, Lung, and Pancreas in Male Construction Workers: A Retrospective Cohort Study,'' *Lancet,* 369:2015–2020, 2007.
193. Ziebarth, D., B. Spiegelhalder and H. Bartsch, ''N-nitrosation of Medicinal Drugs Catalysed by Bacteria from Human Saliva and Gastro-intestinal Tract, including Helicobacter Pylori,'' *Carcinogenesis,* 18(2):383–389, 1997.
194. Knezevich, A., J. Muzic, D.K. Hatsukami, et al., ''Nornicotine Nitrosation in Saliva and its Relation to Endogenous Synthesis of N′-nitrosonornicotine in Humans,'' *Nicotine & Tobacco Research,* 15(2):591–595, 2013.
195. Bartsch, H., H. Ohshima, B. Pignatelli, et al., ''Human Exposure to Endogenous N-nitroso Compounds: Quantitative Estimates in Subjects at High Risk for Cancer of the Oral Cavity, Oesophagus, Stomach and Urinary Bladder,'' *Cancer Surveys,* 8(2):335–362, 1989.
196. Marletta, M.A., ''Mammalian Synthesis of Nitrite, Nitrate, Nitric Oxide, and N-nitrosating Agents,'' *Chemical Research in Toxicology,* 1(5):249–257, 1988.
197. Mirvish, S.S., ''Role of N-nitroso compounds (NOC) and N-nitrosation in Etiology of Gastric, Esophageal, Nasopharyngeal and Bladder Cancer and Contribution to Cancer of Known Exposures to NOC,'' *Cancer Letters,* 93(1):17–48, 1995.
198. Mirvish, S.S., ''Formation of N-nitroso compounds: Chemistry, Kinetics, and In Vivo Occurrence,'' *Toxicology and Applied Pharmacology,* 31(3):325–351, 1975.
199. Tricker, A.R., R. Haubner, B. Spiegelhalder, et al., ''The Occurrence of Tobacco-specific Nitrosamines in Oral Tobacco Products and Their Potential Formation under Simulated Gastric Conditions,'' *Food Chemistry and Toxicology,* 26(10):861–865, 1988.
200. Peedin, G.F. ''Production Practices: Flue-cured Tobacco'' *Tobacco: Production, Chemistry, and Technology,* 104–142, 1999.
201. Miller, R.D. and D.J. Fowlkes, ''Dark Fire-cured Tobacco,'' *Tobacco: Production, Chemistry, and Technology,* 164–182, 1999.
202. Wiernik, A., A. Christakopoulos, L. Johansson, et al., ''Effect of Air-curing on the Chemical Composition of Tobacco,'' *Recent Advances in Tobacco Science,* 21:39–80, 1995.
203. U.S. Environmental Protection Agency, ''Guidelines for Carcinogen Risk Assessment,'' 2005, available at *https://www.epa.gov/sites/production/files/2013–09/documents/cancer_guidelines_final_3-25-05.pdf.*
204. U.S. Environmental Protection Agency, ''Environmental Fact Sheet: The Delaney Paradox and Negligible Risk,'' January 1990.
205. National Research Council, ''Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to Deployed Personnel.'' Washington, DC: The National Academies Press, 2004, available at *www.nap.edu/catalog/10974/html.*
206. Stepanov, I., S.S. Hecht, S. Ramakrishnan, et al., ''Tobacco-specific Nitrosamines in Smokeless Tobacco Products Marketed in India,'' *International Journal of Cancer,* 116(1):16–19, 2005.
207. Menzie Cura Associates, Inc., ''Estimating Risk to Cigarette Smokers From Smoke Constituents in Proposed 'Testing and Reporting of Constituents of Cigarette Smoke' Regulations,'' August 1999. Prepared for: Massachusetts Tobacco Control Program, Boston, Massachusetts.
208. Fowles, J. and M. Bates, ''The Chemical Constituents in Cigarettes and Cigarette Smoke: Priorities for Harm Reduction,'' A Report to the New Zealand Ministry of Health, March 2000, available at *http://www.health.govt.nz/publication/chemical-constituents-cigarettes-and-cigarette-smoke-priorities-harm-reduction.*
209. Fowles, J. and E. Dybling, ''Application of Toxicological Risk Assessment Principles to the Chemical Constituents of Cigarette Smoke,'' *Tobacco Control,* 12(4):424–430, 2003.
210. Watanabe, K.H., M.V. Djordjevic, S.D. Stellman, et al., ''Incremental Lifetime Cancer Risks Computed for Benzo[a]pyrene and Two Tobacco-specific N-nitrosamines in Mainstream Cigarette Smoke Compared with Lung Cancer Risks Derived from Epidemiologic Data,'' *Regulatory Toxicology and Pharmacology,* 55(2):123–133, 2009.
211. Pankow, J.F., K.H. Watanabe, P.L. Toccalino, et al., ''Calculated Cancer Risks for Conventional and 'Potentially Reduced Exposure Product' Cigarettes,'' *Cancer Epidemiology Biomarkers & Prevention,* 16(3):584–592, 2007.
212. Boyle, R.G., J. Jensen, D.K. Hatsukami, et al., ''Measuring Dependence In Smokeless Tobacco Users,'' *Addictive Behaviors,* 20(4):443–450, 1995.
213. Mushtaq, N., L.A. Beebe, and S.K. Vesely, ''Determinants of Salivary Cotinine Concentrations Among Smokeless Tobacco Users,'' *Nicotine & Tobacco Research,* 14(10): 1229–1234, 2012.

List of Subjects in 21 CFR Part 1132

Administrative practice and procedure, Incorporation by reference, Labeling, Smokeless 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 1132 to subchapter K to read as follows:

PART 1132—PRODUCT STANDARD: DETERMINATION OF N-NITROSONORNICOTINE (NNN) LEVEL IN FINISHED SMOKELESS TOBACCO PRODUCTS

Subpart A—General Provisions

Subpart B—Product Requirements

Subpart C—Labeling and Recordkeeping Requirements

Authority: 21 U.S.C. 331, 371, 374, 387b, 387c, 387f(d), 387g, 387i.

Subpart A—General Provisions

§ 1132.1 Scope.

(a) This part sets forth the requirements for the maximum level of N-nitrosonornicotine (NNN) in finished smokeless tobacco products. The provisions of this standard apply to finished smokeless tobacco products as defined in § 1132.3.

(b) No person may manufacture, distribute, sell, or offer for sale or distribution within the United States a

finished smokeless tobacco product that is not in compliance with this part.

(c) Tobacco retailers and distributors will not be considered in violation of this part as it relates to the sale or distribution or offer for sale or distribution of finished smokeless tobacco products that exceed the NNN level set forth in § 1132.10 if they:

(1) Store and transport the finished smokeless tobacco products according to the package label;

(2) Do not sell or distribute or offer for sale or distribution finished smokeless tobacco products past their expiration date, except to return expired products to the manufacturer;

(3) Do not conceal, alter, or remove the expiration date or storage conditions on the package label; and

(4) Do not sell or distribute or offer for sale or distribution finished smokeless tobacco products that are open or have broken seals.

§ 1132.3 Definitions.

For purposes of this part:

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

Commercial distribution means any distribution of a finished smokeless tobacco product to consumers or to another person through sale or otherwise, but does not include interplant transfers of a tobacco product between registered 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.

Finished smokeless tobacco product means a smokeless tobacco product, including all parts and components, packaged for consumer use, except for components, parts, or accessories sold without tobacco. An example of a finished smokeless tobacco product is a tin or can of loose snuff or a pouch containing chewing tobacco.

Manufacturing code means any distinctive sequence or combination of letters, numbers, or symbols that begins with the manufacturing date in 2-digit numerical values in the month, day, year format (mmddyy) followed by the batch number from which the production batch can be identified.

Manufacturing date means the month, day, and year that a smokeless tobacco product is packaged for consumer use (*i.e.,* when the package label has been added to the product).

N-nitrosonornicotine (NNN) means a tobacco-specific nitrosamine (TSNA) with the chemical formula C[9]H[11]N[3]O.

New tobacco product means:

(1) Any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or

(2) Any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.

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.

Performance criteria means the validation requirements for the acceptability of an analytical test method, including accuracy, precision, recovery, linearity, specificity, limit of quantitation, limit of detection, robustness, and range.

Person includes an individual, partnership, corporation, or association.

Rework means the processing of nonconforming finished smokeless tobacco products to meet the requirements of this part.

Smokeless tobacco means any tobacco product that consists of cut, ground, powdered, or leaf tobacco and that is intended to be placed in the oral or nasal cavity.

Source data means all information contained in original laboratory records or exact copies of original records of experimental findings, observations, or other activities used for the creation, reconstruction, and evaluation of a study or other laboratory work. Source data includes any laboratory worksheets, notebooks, correspondence, notes, and other documentation (regardless of capture medium) that are the result of original observations and activities of a laboratory study or other laboratory work.

Tobacco product, as stated in section 201(rr) of the Federal Food, Drug, and Cosmetic Act in relevant part:

(1) Means any product made or derived from tobacco 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); and

(2) Does not mean an article that is a drug defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act, a device defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, or a combination product described in section 503(g) of the Federal Food, Drug, and Cosmetic Act.

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.

Tobacco-specific nitrosamine (TSNA) means a chemical compound formed through the chemical reaction involving the nitrosation of nicotine, nornicotine, anabasine, or anatabine during the growing, curing, processing, or storage of tobacco.

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.

§ 1132.5 Incorporation by reference.

(a) The Director of the Federal Register approves this material for incorporation by reference into this part in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain a copy of the material from the sources listed below. You may inspect a copy at the U.S. Food and Drug Administration, Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 or the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

(b) Center for Tobacco Products, U.S. Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993; 1–888–463–6332.

(1) ''Determination of N-nitrosonornicotine (NNN) in Smokeless Tobacco and Tobacco Filler by HPLC–MS/MS,'' LIB No. 4620, January 2017; into § 1132.14. (Also available at *http://www.fda.gov/ScienceResearch/FieldScience/ucm231463.htm.*)

(2) [Reserved]

Subpart B—Product Requirements

§ 1132.10 NNN level.

The mean level of NNN in any batch of finished smokeless tobacco product

must not exceed 1.0 microgram per gram (μg/g) of tobacco (on a dry weight basis) at any time through the product's labeled expiration date as determined by testing in compliance with § 1132.12.

§ 1132.12 Product testing.

(a) *Stability testing.* Each tobacco product manufacturer must conduct testing to assess the stability of the NNN level in its finished smokeless tobacco products. The results of stability testing must be used to establish and verify the product's expiration date and storage conditions (either room temperature or refrigeration).

(1) *Test method.* The manufacturer must use either the standard test method in § 1132.14 or an alternative test method that meets the requirements set forth in § 1132.16. Samples for testing must be selected in accordance with the requirements set forth in § 1132.18(a) and (c).

(2) *Written protocol.* Each manufacturer must establish and maintain a written protocol that addresses all stability testing. The protocol must fully describe the methodology used to determine the stability of the NNN level, including the test method used (the standard test method in § 1132.14 or an alternative test method in accordance with § 1132.16), the sampling plan and procedures required by § 1132.18(a) and (c), and the storage conditions.

(3) *Initial stability testing.* A manufacturer must conduct initial real-time stability testing that covers each finished smokeless tobacco product and use the results to establish an expiration date and appropriate storage conditions (either room temperature or refrigeration) for the product. The expiration date and storage conditions must be displayed on the package label in accordance with § 1132.30.

(i) For initial real-time stability testing, at a minimum, samples must be tested within 7 days of manufacture and at the expected expiration date.

(A) If the proposed storage condition is room temperature, samples for initial real-time stability testing must be stored at 25 ± 2 degrees Celsius and 60 ± 5% relative humidity.

(B) If the proposed storage condition is refrigeration, samples for initial real-time stability testing must be stored at 5 ± 2 degrees Celsius.

(ii) If initial real-time stability testing is in progress but not yet complete, the manufacturer may concurrently conduct accelerated stability testing to establish the product's expiration date and storage conditions. The manufacturer may use an expiration date of no longer than 1 year based on initial accelerated stability testing.

(iii) For initial accelerated stability testing, at a minimum, samples must be tested at three time points within a 6 month period. The first time point must be within 7 days of manufacture and the last time point at 6 months after manufacture.

(A) If the proposed storage condition is room temperature, samples for initial accelerated stability testing must be stored at 40 ± 2 degrees Celsius and 75 ± 5% relative humidity.

(B) If the proposed storage condition is refrigeration, samples for initial accelerated stability testing must be stored at 25 ± 2 degrees Celsius and 60 ± 5% relative humidity.

(iv) If initial accelerated stability testing shows the NNN level in the finished smokeless tobacco products will not conform to § 1132.10, the manufacturer must establish an expiration date and storage conditions, as determined by the results of initial real-time stability testing.

(4) *Annual stability testing.* A manufacturer must conduct annual real-time stability testing on each finished smokeless tobacco product to verify the results of the initial stability testing and to ensure that the expiration date and storage conditions remain appropriate. Accelerated stability testing may not be used for annual stability testing.

(i) Except as provided in paragraph (a)(4)(ii) of this section, annual real-time stability testing must begin within 12 months of the completion of initial stability testing and then annually thereafter, with no longer than 12 months between testing.

(ii) When a manufacturer has not conducted initial real-time stability testing on a particular smokeless tobacco product because it has determined that the results from initial real-time stability testing conducted on another product apply, annual real-time stability testing must begin when the product is first released for commercial distribution and then annually thereafter, with no longer than 12 months between testing.

(iii) For annual real-time stability testing, at a minimum, samples must be tested within 7 days of manufacture and at the established expiration date.

(A) If the intended storage condition is room temperature, samples for annual real-time stability testing must be stored at 25 ± 2 degrees Celsius and 60% ± 5% relative humidity.

(B) If the intended storage condition is refrigeration, samples for annual real-time stability testing must be stored at 5 ± 2 degrees Celsius.

(iv) If the results of the most recent annual real-time stability testing do not support the finished smokeless tobacco product's expiration date, the manufacturer must use those results to establish a new expiration date. After a new expiration date has been established, the package labels of all affected finished smokeless tobacco products that have not been released for commercial distribution must display the new expiration date and storage conditions, in accordance with § 1132.30.

(v) If the finished smokeless tobacco product's expiration date must be shortened due to the results of the annual real-time stability testing, the manufacturer must conduct an investigation to determine why the results of the most recent stability testing do not support the product's previously established expiration date. The investigation must be fully documented and the records maintained in accordance with § 1132.32.

(b) *Batch testing.* Tobacco product manufacturers must conduct testing on each batch of finished smokeless tobacco product to ensure that the products conform with § 1132.10. The manufacturer must use either the standard test method in § 1132.14 or an alternative test method that meets the requirements set forth in § 1132.16. Samples for testing each batch to determine if a product conforms with § 1132.10 must be selected in accordance with the requirements set forth in § 1132.18(b) and (c).

(c) *Documentation of test results.* A full report of the source data and results of all stability and batch testing must be maintained by the tobacco product manufacturer in accordance with § 1132.32, including the following:

(1) Full identification of the smokeless tobacco product that is the subject of the report, including product subcategory, brand, subbrand, package size and quantity of product (mass and, if portioned, count) and, for portioned tobacco products, the size (mass) of each portion;

(2) NNN level of each sample tested;

(3) Mean NNN level and standard deviation;

(4) The batch manufacturing date and location, including facility name and address;

(5) The location, including facility name and address, from which each sample was pulled;

(6) The manufacturing code of each sample tested or, for samples for initial stability testing with no manufacturing code, an identifying code created by the manufacturer;

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

(8) The test method and sampling procedure used;

(9) All tobacco product reference standard test results;

(10) The names and qualifications of the person(s) conducting the testing;

(11) The equipment used (including documentation to show that the equipment is appropriate for its intended use and has been calibrated); and

(12) For batch testing only, 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, including, where applicable, the NNN level of the individual batch, the results of the product's stability testing, and the decision made and justification with respect to the results of a nonconforming product investigation under § 1132.22.

§ 1132.14 Standard test method.

(a) The standard test method for this part is the method entitled ''Determination of N-nitrosonornicotine (NNN) in Smokeless Tobacco and Tobacco Filler by HPLC–MS/MS,'', incorporated by reference in § 1132.5.

(b) In the event of an inconsistency between a material incorporated by reference and the definitions and methods described in this part, definitions and methods in this part will apply.

§ 1132.16 Alternative test method.

Tobacco product manufacturers may use a validated alternative test method in accordance with this section, only if the alternative method meets or exceeds the performance criteria of the standard test method set forth in § 1132.14.

(a) *Notice requirement.* Tobacco product manufacturers who intend to use a validated alternative test method to that listed in § 1132.14 for determining conformance with § 1132.10 must notify the Director, Office of Science, Center for Tobacco Products, before beginning use of the alternative test method. Manufacturers may begin using the alternative test method 60 calendar days after FDA receives the notification as set forth in paragraph (f) of this section unless FDA notifies the manufacturer that the alternative test method has not been demonstrated to meet or exceed the performance criteria of the standard test method set forth in § 1132.14.

(b) *Contents of notification of an alternative test method.* The manufacturer must include in the notification of an alternative test method the following information:

(1) *General information.* The following information must be submitted using the form that FDA provides:

(i) The date the manufacturer submitted the notification to FDA;

(ii) Identification of the submission as a notification of an alternative test method;

(iii) The manufacturer's name, address, and contact information;

(iv) Identification of and contact information for an authorized representative of the manufacturer (which could be a U.S. agent for the manufacturer), including name, address (mailing and email), and telephone number;

(v) Identification of the subcategories of finished smokeless tobacco products that can be analyzed using the alternative test method; and

(vi) The testing facility's name and address.

(2) *Index and table of contents.* A comprehensive index and table of contents.

(3) *Summary.* The notification must include a summary section that contains the following information:

(i) Identification of the standard test method for which the alternative test method is being proposed;

(ii) A concise description of the performance criteria of the alternative test method;

(iii) A concise explanation of why the manufacturer is proposing to use the alternative test method; and

(iv) A concise comparison of the similarities and differences between the alternative test method and the standard test method.

(4) *Complete description.* The notification must describe the alternative test method in sufficient detail to enable FDA to evaluate whether the information provided demonstrates that the alternative test method meets or exceeds the performance criteria of the standard test method set forth in § 1132.14. This description must include:

(i) A complete description of the manner in which the alternative test method is proposed to deviate from the standard test method and a complete explanation, with scientific rationale and supported by appropriate data, including a complete copy of the testing protocol, to demonstrate that the alternative test method meets or exceeds the performance criteria of the standard test method set forth in § 1132.14; and

(ii) Any data and information from other studies comparing the alternative test method to the standard test method.

(c) *Relevant information.* If requested by FDA, the manufacturer must submit any other relevant information needed to evaluate the alternative test method.

(d) *Format for notifications of an alternative test method.*

(1) *General requirements.* All notifications must be submitted using the form that FDA provides and must be well-organized and legible, and written in English.

(2) *Electronic format requirement.* Except as provided in paragraph (d)(3) of this section, notifications of an alternative test method must be submitted using the Agency's electronic system. The notification and all supporting information must be in an electronic format that the Agency can process, review, and archive.

(3) *Waivers from electronic format requirement.* If a notification cannot be submitted electronically, a waiver may be requested. Waivers will be granted only if use of electronic means is not reasonable for the tobacco product manufacturer requesting the waiver. If FDA grants the waiver request, FDA will provide information on where to send the notification in paper form. To request a waiver, manufacturers must send a written request that is legible and in English to the Document Control Center (ATTN: Office of Science) at the address included on our Web site. The written request must contain the following information:

(i) The name and address of the tobacco product manufacturer that wishes to submit the notification, the name of an authorized representative of the manufacturer (which could be a U.S. agent for the manufacturer), and their contact information.

(ii) A statement that creation and/or submission of information in electronic format is not reasonable for the manufacturer requesting the waiver, and an explanation of why creation and/or submission in electronic format is not reasonable. This statement must be signed by a person who is authorized to make the declaration on behalf of the tobacco product manufacturer.

(e) *Applicability of an alternative test method.* An alternative test method may be implemented only by the tobacco product manufacturer that submitted the notification and only with respect to the subcategories of finished smokeless tobacco products that were the subject of the notification. Other manufacturers interested in similar or identical alternative test methods must submit their own notifications following the procedures of this section.

(f) *Action on notifications.* FDA will acknowledge the receipt of a notification of an alternative test

method. Manufacturers may implement an alternative test method beginning 60 calendar days after FDA receives the notification of alternative test method unless FDA notifies them otherwise.

(1) If a notification is complete when received, the 60 calendar day period begins on the date FDA receives the notification.

(2) If any element required under paragraph (b) of this section is missing from a notification, FDA will not accept the notification submission and will inform the manufacturer.

(3) If FDA determines that an alternative test method has not been demonstrated to meet or exceed the performance criteria of the standard test method set forth in § 1132.14, FDA will inform the submitter. If FDA informs the submitter during the 60 calendar day period, the submitter must not implement the alternative test method. If FDA determines that an alternative test method does not comply with this section after the 60 calendar day period, FDA will provide a written determination to the submitter and the submitter must immediately cease using the alternative test method.

(4) Acceptance of a notification submission does not constitute a finding by the Agency that the alternative test method meets or exceeds the performance criteria of the standard test method set forth in § 1132.14.

§ 1132.18 Sampling plans and procedures.

(a) *Sampling plan for stability testing.* Each tobacco product manufacturer must design and implement a sampling plan or plans for all stability testing required in § 1132.12(a) based on a valid statistical rationale to demonstrate that the finished smokeless tobacco product's expiration date is appropriate under the intended storage conditions. The sampling plan must ensure that samples taken are representative and randomly selected. To account for the variability of the NNN in smokeless 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. Each sampling plan must fully describe the sampling methodology, with scientific rationale, incorporate all sources of variability (including variability of the analytic method and NNN levels), and describe the sample size needed (including a full description of how the sample size is calculated) consistent with the sampling design to achieve the sampling objective.

(b) *Sampling plan for batch testing.* Each tobacco product manufacturer must design and implement a sampling plan or plans for all batch testing required in § 1132.12(b) based on a valid statistical rationale to ensure that the finished smokeless tobacco product consistently conforms to the NNN level set forth in § 1132.10. The sampling plan must ensure that samples taken are representative of an entire batch and are randomly selected and collected from each batch for testing. To account for the variability of NNN in the finished smokeless 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. Each sampling plan must fully describe the sampling methodology, with scientific rationale, incorporate all sources of variability (including variability of the analytic method and the NNN levels), and describe the sample size needed (including a full description of how the sample size is calculated) consistent with the sampling design to achieve the sampling objective. The sampling plan must also fully describe the criteria the manufacturer will use to make a decision to accept or reject each batch.

(c) *Sampling procedures.* Test samples must be collected and examined in accordance with the following procedures:

(1) Test samples for initial real-time and accelerated stability testing are to consist of:

(i) Smokeless tobacco product that has been manufactured using the same production processes as products manufactured for consumer use and packaged in the identical package that will be used for the finished smokeless tobacco product, but it need not have the product package label; or

(ii) Finished smokeless tobacco product as it is intended to be sold or distributed to consumers.

(2) Test samples for annual real-time stability testing and batch testing are to consist of the finished smokeless tobacco product as it is intended to be sold or distributed to consumers and not of a separate production sample.

(3) All test samples must be stored according to the intended storage conditions for the finished smokeless tobacco product, except that test samples for initial accelerated stability testing must be stored in accordance with § 1132.12(a)(3)(iii). A tobacco product manufacturer must include all of its factories, stock rooms, warehouses, and other locations containing finished smokeless tobacco products in the population to be sampled.

(4) Test samples for stability testing must be taken within 7 days of the manufacturing date and tested in accordance with § 1132.12(a). Test samples for batch testing 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 the test methods in §§ 1132.14 or 1132.16, including any repeats that may be necessary (*e.g.,* because test material was damaged prior to or during analysis). Samples must be randomly selected in accordance with the applicable sampling plan and the samples must be taken within the same day.

(5) Sampling must be performed by persons who have sufficient education, training, and experience to accomplish the assigned functions.

(6) Each test sample must be identified so that the following information can be determined:

(i) Full identification of the smokeless tobacco product sampled, including product subcategory, brand, subbrand, package size and quantity of product (mass and, if portioned, count) and, for portioned tobacco products, the size (mass) of each portion;

(ii) The manufacturing code or, for samples for initial stability testing with no manufacturing code, an identifying code created by the manufacturer;

(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 stored and tested (including the facility name and address).

(7) Samples sent for testing must be packed securely with adequate protection against damage (*e.g.,* mechanical damage, severe changes in humidity or temperature) and sent to the testing facility by the most expeditious means, arriving no later than 3 calendar days after shipment. A list of the samples in each shipment must be sent to the testing facility under separate cover.

(8) All samples for a specific stability or batch test must be tested at the same facility.

(9) Once test samples arrive at the testing facility they must be inspected, accounted for, and stored under the finished smokeless tobacco product's intended storage conditions (*e.g.,* room temperature or refrigeration) except that

test samples for initial accelerated stability testing must be stored in accordance with § 1132.12(a)(3)(iii), and a report that includes the following information must be generated for the stability or batch test and be maintained by the tobacco product manufacturer in accordance with § 1132.32:

(i) Full identification of the smokeless tobacco product, including product subcategory, brand, subbrand, package size and quantity of product (mass and, if portioned, count) and, for portioned tobacco products, the size (mass) of each portion;

(ii) The manufacturing code or, for samples for initial stability testing with no manufacturing code, an identifying code created by the manufacturer;

(iii) The date on which samples were taken, if available;

(iv) The locations where samples were drawn (including the address and specific locations within any facilities where samples were taken), if available;

(v) The number of test samples drawn;

(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.

(10) For batch testing only, 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 may be released for commercial distribution.

§ 1132.20 Expiration date.

All finished smokeless tobacco products must have an expiration date established by stability testing. The expiration date must be set no later than the final date the manufacturer can demonstrate the finished smokeless tobacco product conforms to § 1132.10 when stored under its intended conditions (*e.g.,* room temperature or refrigeration).

§ 1132.22 Nonconforming product.

(a) *General requirements.* Tobacco product manufacturers must establish and maintain procedures to identify, investigate, segregate, and make disposition decisions about nonconforming finished smokeless tobacco products in order to prevent their release for commercial distribution.

(b) *Investigation.* The tobacco product manufacturer must conduct an investigation to determine the extent of the nonconformity and, as applicable, the locations where the nonconforming products have been distributed if the mean of the representative samples from any batch of finished smokeless tobacco product is determined to be out of conformance with the requirements of § 1132.10, or a finished smokeless tobacco product's expiration date must be shortened due to the results of annual real-time stability testing, or if FDA notifies a tobacco product manufacturer that a distributed finished smokeless tobacco product does not conform to the requirements of this part. The investigation must include, but is not limited to, examination of all relevant processes, operations, records, complaints, any corrective actions taken, and any other relevant sources of information concerning the nonconforming product. The investigation must be fully documented, including any materials reviewed, name of the person(s) making the disposition decisions, justification for the disposition decisions, results of retesting, decisions with respect to reworking, and followup resulting from the investigation.

(c) *Rejection of nonconforming product.* Tobacco product manufacturers must reject a batch of a finished smokeless tobacco product if the mean of the representative samples 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 shows that the batch meets the requirements of this part.

(d) *Rework of nonconforming product.* If appropriate, a manufacturer may rework a batch of a finished smokeless tobacco product that does not conform to the requirements of this part. The reworked batch of finished smokeless tobacco product must be determined to conform to all the requirements of this part with a disposition decision and justification before it may be released for commercial distribution.

Subpart C—Labeling and Recordkeeping Requirements

§ 1132.30 Package label requirements.

The package of a finished smokeless tobacco product must have a label that includes the manufacturing code, expiration date, and, if applicable, storage conditions for the smokeless tobacco product as follows:

(a) The information must be printed on or permanently affixed to the package in a manner that assures it will remain on the packaging or label through the expected duration of use of the product by the consumer. It must appear clearly, legibly, and indelibly in the English language.

(b) The expiration date must appear on the packaging in two-digit numerical values in the following format: ''Expires on month/day/year.''

(c) If the manufacturer determines by stability testing that meets the requirements in § 1132.12 that the finished smokeless tobacco product must be stored in a refrigerator, the package label must state ''Keep Refrigerated.''

(d) It must be possible to determine from the manufacturing code the history of the manufacturing, processing, packaging, labeling, holding, and initial distribution of the product from records maintained by the tobacco product manufacturer.

§ 1132.32 Recordkeeping requirements.

(a) Each facility that manufactures tobacco products subject to this part must establish and maintain records of the following information:

(1) Full documentation of stability testing protocols and the results of initial and annual stability testing under § 1132.12(a), including all information specified in § 1132.12(c);

(2) All investigations under § 1132.12(a)(4)(v);

(3) The source data and results of batch testing conducted to determine conformance with § 1132.10, including all information specified in § 1132.12(c);

(4) All notifications of an alternative test method and all related correspondence under § 1132.16;

(5) All source data for alternative test method validation;

(6) All sampling plans and reports under § 1132.18;

(7) Documentation that the persons performing sampling under § 1132.18 have sufficient education, training, and experience to accomplish the assigned functions;

(8) All identification, investigation, segregation, and disposition decision procedures under § 1132.22(a); and

(9) All nonconforming product investigations and rework under § 1132.22(b) and (d).

(b) The records must be legible and written in English. Documents that have been translated from a foreign language into English must 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. All records must be readily available for inspection and copying or other means of reproduction by FDA upon request during an inspection. Requested records that are maintained offsite must be made available within 24 hours or, if that is not feasible, as soon as possible before

the close of the inspection. Records that can be immediately retrieved from another location, including by computer or other electronic means, meet the requirements of this paragraph.

(c) Copies of all records required under this part must be retained for a period of not less than 4 years from the date of commercial distribution of the finished smokeless tobacco product that is the subject of the record, or, for records relating to alternative test methods under § 1132.16, for a period of not less than 4 years after the last date the method that is the subject of the record is used.

Dated: January 12, 2017.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2017–01030 Filed 1–19–17; 8:45 am]

BILLING CODE 4164–01–P

• CSU retail sales or shipments, especially information about the type of CSUs sold and the number of units sold in recent years;
• the number of CSUs in use;
• studies, tests, or descriptions of technologies or design changes that address tip-over injuries and estimates of costs associated with those features, including manufacturing costs and wholesale prices;
• the expected impact of technologies or design changes that address tip-over injuries on manufacturing costs or wholesale prices;
• the potential impact of design changes to address CSU stability on consumer utility; and
• information about whether any stability requirements for CSUs in ether a voluntary standard or potential mandatory rule could have a disparate impact on small entities, such as small manufacturers or importers.

In addition, the Commission invites interested parties to submit any existing standards, or portions of them, for consideration as a consumer product safety standard. The Commission also invites interested persons to submit a statement of intention to modify or develop a voluntary consumer product safety standard addressing the risk of injury associated with CSU tip overs, including a description of the plan to develop or modify such a standard.

Please submit comments in accordance with the instructions in the **ADDRESSES** section at the beginning of this ANPR.

Alberta E. Mills,

Acting Secretary, Consumer Product Safety Commission.

[FR Doc. 2017–25779 Filed 11–29–17; 8:45 am]

BILLING CODE 6355–01–P

DEPARTMENT OF ENERGY

Federal Energy Regulatory Commission

18 CFR Part 40

[Docket No. RM16–22–000]

Coordination of Protection Systems for Performance During Faults and Specific Training for Personnel Reliability Standards

Correction

Proposed Rule document 2017–25586 beginning on page 56186 was incorrectly published in the issue of Tuesday, November 28, 2017.

[FR Doc. C1–2017–25586 Filed 11–29–17; 8:45 am]

BILLING CODE 1505–01–D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 15

[Docket No. FDA–2017–N–6529]

The Food and Drug Administration's Approach To Evaluating Nicotine Replacement Therapies; Public Hearing; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing a public hearing on FDA's approach to evaluating the safety and efficacy of nicotine replacement therapy (NRT) products, including how they should be used and labeled.

DATES: The public hearing will be held on Friday, January 26, 2018, from 9 a.m. to 5 p.m. The public hearing may be extended or may end early depending on the level of public participation. Persons seeking to attend or to present at the public hearing must register by Tuesday, January 2, 2018. Section II provides attendance and registration information. Electronic or written comments will be accepted after the public hearing until Thursday, February 15, 2018.

ADDRESSES: The public hearing will be held at the FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room A, Silver Spring, MD 20993–0002. Entrance for public hearing participants (non-FDA employees) is through Building 1 where routine security check procedures will be performed. For parking and security information, please refer to *https://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm.*

You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before February 15, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of February 15, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

• *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*

• If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

• *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

• For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked, and identified as confidential if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2017–N–6529 for ''FDA's Approach to Evaluating Nicotine Replacement Therapies''; Public Hearing; Request for Comments. Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential

with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov*. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.fda.gov/regulatoryinformation/dockets/default.htm*.

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

FOR FURTHER INFORMATION CONTACT: Allison Hoffman, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 1314, Silver Spring, MD 20993, 301–796–9203, *OMPTFeedback@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

A majority (roughly 70%) of adult smokers in the United States report that they want to quit, and nearly half of them make a quit attempt each year. Many of those quit attempts involve the use of NRT products, which are designed to help people quit smoking by supplying controlled amounts of nicotine to ease their withdrawal symptoms. FDA has approved two types of prescription [1] NRT products—a nicotine nasal spray and nicotine inhaler—and three types of over-the-counter (OTC) NRT products—a nicotine gum, transdermal nicotine patch, and nicotine lozenge (see Appendix A). Most of these products have been approved for over 20 years.[2] The use of approved prescription and OTC NRT products is generally considered to double the likelihood of a successful quit attempt, although there is variation in efficacy among the types of products.

Although the formulations and routes of administration of currently approved NRT products have remained relatively unchanged for decades, there have been developments in research regarding NRT products and corresponding changes in the regulatory landscape. For example, in 2013, FDA recommended changing the statements on concomitant use and duration of use in the labeling for OTC NRT products because evidence gathered since 1984—the year the first NRT product was approved—suggested that the statements were no longer necessary to ensure the safe use of OTC NRT products for smoking cessation.[3] Specifically, the Agency recommended that the statement in the labeling for OTC NRT products warning consumers that they should not use an NRT product if they are still smoking, or using any other product that contains nicotine—including another NRT—be removed. FDA also recommended that the directions in the labeling for OTC NRT products be modified to remove the statement advising consumers to stop using the product at the end of the labeled duration of use. Instead of this statement, FDA recommended that consumers be advised to talk to their health care provider if they feel the need to use the product for longer than the labeled duration of use to keep from smoking. To facilitate these labeling changes, FDA invited the submission of supplemental new drug applications (labeling supplements).

On July 28, 2017, the FDA announced a new comprehensive plan that places nicotine, and the issue of addiction, at the center of the Agency's tobacco regulation efforts. This plan will serve as a multi-year roadmap to better protect children and significantly reduce tobacco-related disease and death in the United States. One of the first actions of this comprehensive approach will be an advanced notice of proposed rulemaking (ANPRM) to seek input on the potential impacts of reducing nicotine levels in cigarettes to minimally or non-addictive levels. A key piece of the FDA's comprehensive plan is a recognition that nicotine—while highly addictive—is delivered through products that represent a continuum of risk and is most harmful when delivered through combustible tobacco products. Accordingly, the Agency is committed to increasing access to and use of nicotine replacement therapy, which could help more smokers quit. Therefore, the Agency is seeking public input on its approach to evaluating the safety and efficacy of NRT products.

As a part of its mission to protect and promote public health, FDA is responsible for ensuring that approved drugs, including NRT products, are safe and effective.[4] For FDA to approve a new drug, it must find that the applicant has submitted ''substantial evidence'' of effectiveness based on adequate and well-controlled studies [5] and that the drug is safe for use under the conditions set forth in the labeling.[6] Generally, the safety of a product is assessed by determining whether its benefits outweigh its risks. The benefit–risk assessment takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in a marketing application as well as many other factors.[7]

II. Purpose and Scope of the Public Hearing

To enable a thorough assessment of its approach for evaluating the safety and efficacy NRT products and how they should be used and labeled, FDA is holding a public hearing to receive information and comments from a broad group of stakeholders, including the public health community, researchers, health care professionals, manufacturers, interested industry and professional organizations, and the public, on the appropriate study designs and methods for evaluating the safety and efficacy of OTC NRT drug products. FDA is also seeking input on the warnings and directions sections of the Drug Facts labeling (among other

[1] Non-nicotine prescription medications are also available to aid in smoking cessation, but are beyond the scope of this document.

[2] Only the lozenge formulation has been approved for less than 20 years; it was approved in 2002.

[3] See the **Federal Register**, available at *https://www.federalregister.gov/documents/2013/04/02/2013-07528/modifications-to-labeling-of-nicotine-replacement-therapy-products-for-over-the-counter-human-use*. Recommendations also included other language revisions that were not related to dosing or duration.

[4] Section 1003(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 393(b).

[5] Section 505(d) of the FD&C Act; 21 U.S.C. 355(d).

[6] 21 U.S.C. 355(d). FDA also noted in the preamble to the final rule on new drug approvals (NDA final rule) that the new drug approval process and the supplemental application requirements ''are intended to ensure that the drug is safe, that its benefits outweigh its risks, and that it is effective.'' See 50 FR 7452, 7469 (February. 22, 1985).

[7] See FDA's *Structured Approach to Benefit–Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA V Implementation Plan*—February 2013, Fiscal Years 2013–2017, available at *https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf*.

aspects) for approved OTC NRT products, specifically regarding the possible impact of current warnings on likelihood of use. The Agency has determined that a public hearing is the most appropriate way to ensure public engagement on these important public health issues. FDA believes it is critical to obtain input across the research and medical fields, the tobacco and pharmaceutical industries, and among public health stakeholders regarding how evolving science could influence FDA's approach to evaluating the safety and effectiveness of NRT products.

Questions for Commenters To Address

Although FDA welcomes all feedback on any public health, scientific, regulatory or legal considerations relating to NRT products and their use in tobacco use cessation, we encourage commenters to consider the following questions as they prepare their comments or statements. Responses to questions should include supporting scientific justification.

1. Might there be ways to improve upon the currently available delivery systems to yield new OTC NRT products that might be more effective? If so, what evidence would be needed to support such changes, and how should they be evaluated?

2. Are there additional indications or regimens for OTC NRT products that could be explored? Concepts to consider could include relapse prevention, craving reduction, maintenance, reduce to quit, use of short- and long-acting products in combination, or cessation of non-cigarette tobacco products. What evidence would be needed to support each indication or regimen?

3. What data would be required to demonstrate health benefits of reduction in consumption of combustible tobacco products?

4. Are there OTC NRT products that could be studied for use in combination that might result in reduced tobacco-related health impacts? What evidence would be needed to support the safety and efficacy of these products when used in combination?

5. Is there other information that could be added to labeling for currently approved or new dosage forms of OTC NRT products that would maximize their ability to be used to support smoking cessation? Please consider the various sections of the Drug Facts labeling, including the Uses, Warnings, and Directions sections.

6. Generally, the labeling of OTC NRT products contains a dosing schedule based on duration of use, and FDA has recommended the labeling on OTC NRT products be modified to include the following: ''If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider.'' What is the impact of longer term NRT treatment? What is the impact on likelihood of cessation or relapse prevention? What data would support an affirmative recommendation to use approved OTC NRT products for durations that exceed those currently included in the Drug Facts labeling of approved OTC NRT products, or would support a chronic or maintenance drug treatment indication for such products?

Registration and Requests for Oral Presentations: The FDA Conference Center at the White Oak location is a Federal facility with security procedures and limited seating. Attendance will be free and on a first-come, first-served basis. If you wish to attend (either in person or by webcast (see *Streaming Webcast of the Public Hearing*)) and/or present at the hearing, please register for the hearing and/or make a request for oral presentations or comments by email to *OMPTfeedback@fda.hhs.gov* by Tuesday, January 2, 2018. The email should contain complete contact information for each attendee (*i.e.,* name, title, affiliation, address, email address, and telephone number). For those wishing to present at the hearing, the email should also include a presentation title. Those without email access can register by contacting Allison Hoffman at 301–796–9203 by Tuesday, January 2, 2018 (see **FOR FURTHER INFORMATION CONTACT**).

FDA will try to accommodate all persons who wish to make a presentation. Individuals wishing to present should identify the number of the specific question, or questions, they wish to address. This will help FDA organize the presentations. Individuals and organizations with common interests should consolidate or coordinate their presentations and request time for a joint presentation. FDA will notify registered presenters of their scheduled presentation times. The time allotted for each presentation will depend on the number of individuals who wish to speak. Presenters are encouraged to submit an electronic copy of their presentation to *OMPTfeedback@fda.hhs.gov* on or before Friday, January 19, 2018. Persons registered to make an oral presentation are encouraged to arrive at the hearing room early and check in at the onsite registration table to confirm their designated presentation time. An agenda for the hearing and any other background materials will be made available 5 days before the hearing at *https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm580561.htm.*

If you need special accommodations because of a disability, please contact *OMPTFeedback@fda.hhs.gov* (see **FOR FURTHER INFORMATION CONTACT**) no later than Tuesday, January 2, 2018, at 12 noon Eastern Time.

Streaming Webcast of the Public Hearing: For those unable to attend in person, FDA will provide a live webcast of the hearing. To join the hearing via the webcast, please go to *https://collaboration.fda.gov/part15nicotine.*

Transcripts: Please be advised that as soon as a transcript is available, it will be accessible at *https://www.regulations.gov.* It may be viewed at the Dockets Management Staff (see **ADDRESSES**).

III. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with 21 CFR part 15. The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner, the Center for Drug Evaluation and Research, and the Center for Tobacco Products. Under § 15.30(f), the hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members can pose questions; they can question any person during or at the conclusion of each presentation. Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (21 CFR part 10, subpart C). Under § 10.205, representatives of the media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in § 15.30(b) (see *Transcripts*). To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

IV. References

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

Register, but Web sites are subject to change over time.

1. Babb S, Malarcher A, Schauer G, Asman K, and Jamal A. 2017. Quitting Smoking Among Adults—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 65:1457–1464.
2. Etter J-F and Stapleton JA. 2006. Nicotine Replacement Therapy for Long-Term Smoking Cessation: A Meta-Analysis. *Tobacco Control* 15:280–285.
3. Silagy C, Mant D, Fowler G, and Lodge M. 1994. Meta-Analysis on Efficacy of Nicotine Replacement Therapies in Smoking Cessation. *Lancet* 343:139–142.

Appendix A: Summary of FDA-Approved Active New Drug Applications (NDAs) of Nicotine Replacement Therapies (September 18, 2017)

Product name (NDA #; holder)	OTC or Rx (date approved; date Rx→OTC)	Route (doses)	Indication	Labeled treatment duration and schedule
Nicorette gum (nicotine polacrilex) (NDA 018612 for 2 mg, NDA 020066 for 4 mg; GSK).	Approved as prescription on 1/13/84 for 2 mg; 6/8/92 for 4 mg; Rx→OTC for both on 2/9/16.	Oral (2, 4 mg gum).	Reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking (under Directions: If you are under 18 years of age ask a doctor before use).	12 weeks: • Wk 1–6: 1 per 1–2 hr. • Wk 7–9: 1 per 2–4 hr. • Wk 10–12: 1 per 4–8 hr. If smoke 1st cigarette within 30 min of waking up, use 4 mg; if more than 30 min, use 2 mg.
NicoDerm CQ (nicotine) (NDA 020165; GSK, Sanofi Aventis).	Approved as prescription on 11/7/91; Rx→OTC on 8/2/96.	Patch (7, 14, 21 mg).	Same use as above	10 weeks and 8 weeks: If >10 cigarettes/day: • Wk 1–6: one 21 mg/day. • Wk 7–8: one 14 mg/day. • Wk 9–10: one 7 mg/day. If ≤10 cigarettes/day: • Wk 1–6: one 14 mg/day. • Wk 7–8: one 7 mg/day.
Habitrol (nicotine) (NDA 020076; Ciba-Geigy, Novartis, Dr. Reddy's).	Approved as prescription on 11/27/91; Rx→OTC on 11/12/99.	Patch (7, 14, 21 mg).	Same use as above	8 weeks: If >10 cigarettes/day: • Wk 1–4: one 21 mg/day. • Wk 5–6: one 14 mg/day. • Wk 7–8: one 7 mg/day. If ≤10 cigarettes/day: • Wk 1–6: one 14 mg/day. • Wk 7–8: one 7 mg/day.
Nicotrol NS (nicotine) (NDA 020385; Pfizer).	Prescription (3/22/96; N/A) ...	Nasal spray	• Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. • Should be used as a part of a comprehensive behavioral smoking cessation program.	The label does not specify the recommended duration of treatment, but notes the following in the Indications and Usage section: The safety and efficacy of the continued use of Nicotrol NS for periods longer than 6 months have not been adequately studied and such use is not recommended.
Nicotrol Inhaler (nicotine) (NDA 020714; Pharmacia and Upjohn).	Prescription (5/2/97; N/A)	Inhalant	• Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. • Recommended for use as part of a comprehensive behavioral smoking cessation program.	The recommended duration of treatment is 3 months, after which patients may be weaned from the inhaler by gradual reduction of the daily dose over the following 6 to 12 weeks. The safety and efficacy of the continued use of Nicotrol Inhaler for periods longer than 6 months have not been studied and such use is not recommended.

Product name (NDA #; holder)	OTC or Rx (date approved; date Rx→OTC)	Route (doses)	Indication	Labeled treatment duration and schedule
Commit lozenge (nicotine polacrilex) (NDA 021330; GSK).	OTC (10/3/02; N/A)	Oral (2, 4 mg) ...	Reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking (under Directions: If you are under 18 years of age ask a doctor before use).	12 weeks: • Wk 1–6: 1 per 1–2 hr. • Wk 7–9: 1 per 2–4 hr. • Wk 10–12: 1 per 4–8 hr. If smoke 1st cigarette within 30 min of waking up, use 4 mg; if more than 30 min, use 2 mg.
Nicorette mini lozenge (nicotine polacrilex) (NDA 022366; GSK).	OTC (5/18/09; N/A)	Oral (2, 4 mg) ...	Same use as above	12 weeks; same schedule as Commit lozenge.

Dated: November 22, 2017.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2017–25671 Filed 11–29–17; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 878

[Docket No. FDA–2017–N–4919]

Medical Devices; Exemption From Premarket Notification: Class II Devices; Surgical Apparel; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order; request for comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing its intention to exempt certain subtypes of surgical apparel from premarket notification requirements, subject to conditions and limitations. FDA intends to limit the proposed exemption to single-use, disposable respiratory protective devices (RPD) used in a healthcare setting and worn by healthcare personnel during procedures to protect both the patient and the healthcare personnel from the transfer of microorganisms, body fluids, and particulate material. These devices, commonly referred to as N95 filtering facepiece respirators (FFRs) and surgical N95 respirators (herein collectively referred to as N95s) are currently regulated by FDA under product code MSH. All other class II devices classified under FDA's surgical apparel classification regulation would continue to be subject to premarket notification requirements. FDA is publishing this document to obtain comments regarding this proposed exemption, in accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

DATES: Submit either electronic or written comments by January 29, 2018.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 29, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of January 29, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

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

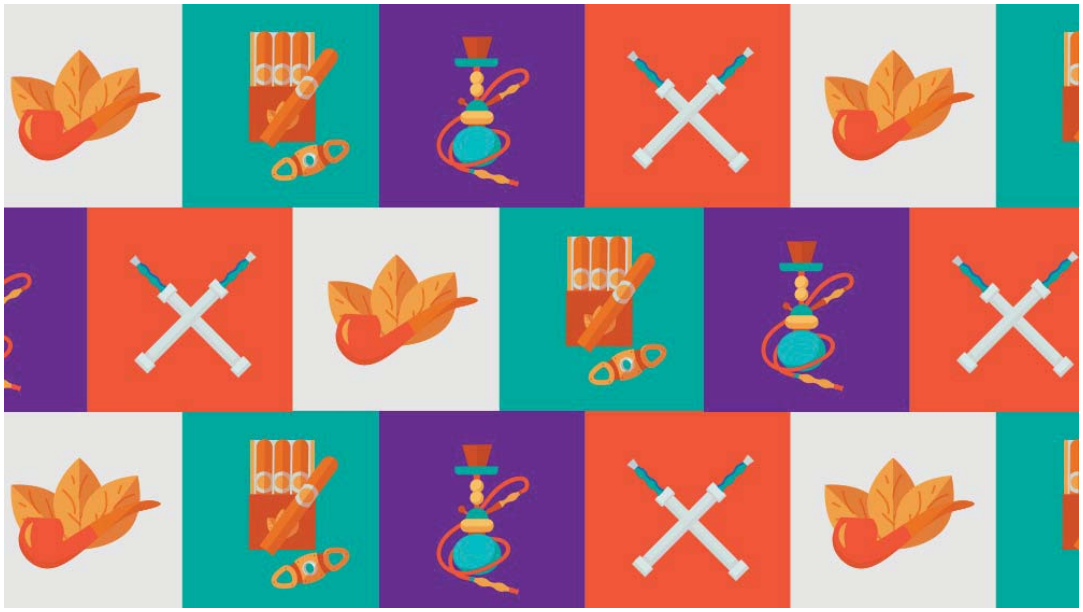
Written/Paper Submissions

Submit written/paper submissions as follows:

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

Instructions: All submissions received must include the Docket No. FDA–2017–N–4919 for ''Medical Devices; Exemption From Premarket Notification: Class II Devices; Surgical Apparel; Request for Comments.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- *Confidential Submissions*—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and



FDA's Comprehensive Approach to Nicotine and Tobacco

by Anne Allen and Caitlyn Ozier

On July 28, 2017, Commissioner of Food and Drugs Scott Gottlieb, announced the U.S. Food and Drug Administration's (FDA's) multi-year comprehensive plan for tobacco and nicotine regulation as the agency intends to take on a new and comprehensive approach to nicotine. Commissioner Gottlieb acknowledged that there is a continuum of risk for nicotine delivery and a potential for innovation to lead to less harmful products as well as confront and alter cigarette addiction. FDA's new policy represents a step forward in its tobacco regulation policy and will likely bring significant change in the coming years for regulated parties.

As a

Anne Allen is an associate in King & Spalding's FDA & Life Sciences Practice. She has worked on a variety of tobacco matters during her time at the firm and in her prior capacity as a counselor to the Center for Tobacco Products at FDA's Office of Chief Counsel.

Update Magazine
September/October 2017

Compounding the Off-Label Promotion Debate: How FDA Could Regulate the Promotion of Unapproved Drugs

Intellectual Property for the Food and Drug Law Professional: Issues that Arise in the Product Development Process

The "New" NDC: Are You Aware of FDA's Rollout of the New Unique Medical Device Identifier (UDI)

Caitlyn Ozier is an associate in King & Spalding's Atlanta, GA office. She is a member of the firm's FDA and Life Sciences practice and has worked on a variety of tobacco matters during her time at the firm.

general matter, FDA's initial actions involve delaying current regulatory deadlines and conducting outreach and research to better inform the agency's intended actions. Key parts of the comprehensive plan include FDA's intention to delay certain deadlines regarding tobacco product applications for newly deemed products, as described in the May 2016 final Deeming Rule, 81 Fed. Reg. 28,974 (May 10, 2016), the agency's plan to issue an advance notice of proposed rulemaking (ANPRM) regarding lowering nicotine in cigarettes, and efforts to obtain public input regarding the role of flavors in tobacco products. Below we analyze the key components of FDA's comprehensive plan, as described in Commissioner Gottlieb's speech and other communications with FDA.

A Delay to Provide Greater Clarity in Premarket Submission Requirements

Since 2009, FDA has worked to develop and implement a consistent premarket review process for tobacco products. With additional time to develop regulations, FDA hopes to establish a clear and reliable premarket review process.

In its announcement, FDA noted that it would publish a new guidance that would extend the timeline to submit tobacco product review applications for newly-regulated tobacco products that were on the market as of August 8, 2016. On August 10, 2017, FDA issued the aforementioned guidance detailing the new enforcement policy,

and Its Potential Future Impact on Payer Claims Forms?

FDA's Comprehensive Approach to Nicotine and Tobacco

Regulatory Update on Acrylamide—State, Federal, and International Oversight

The Changing Face of Marijuana Regulation: Current Federal Status

Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule. 82 Fed. Reg. 37,459. Under the revised timeline, the application deadlines for newly-regulated products are as follows: August 8, 2021 for combustible products, such as cigars and hookah tobacco; and August 8, 2022 for non-combustible products, such as electronic nicotine delivery systems (ENDS) or e-cigarettes. While the agency reviews these product applications, it intends to permit manufacturers to continue marketing the underlying products. FDA stated that it plans to use the intervening period from the extended deadlines to develop product standards that will protect against known public health risks, such as ENDS battery issues and children's exposure to liquid nicotine.

FDA noted that it will also take steps to provide manufacturers with greater clarity on the premarket review process. Specifically, the agency plans to finalize the draft guidance, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS), that was issued concurrently with the final Deeming Rule. Additionally, FDA announced that it intends to issue regulations outlining the information applicants must include in premarket tobacco product applications (PMTAs), modified risk tobacco product applications, and substantial equivalence (SE) reports. FDA anticipates that, with additional time, guidance, and the implementation of a detailed regulatory framework regarding the content of premarket submissions, the submission process will be more efficient, predictable, and transparent, and manufacturers will be able to develop higher quality applications. To the extent that any product standard becomes effective before the new deadline to submit these applications, FDA expects that those product standards will be incorporated in the review of any submissions submitted after the effective date.

Manufacturers will be closely monitoring this process, as they have been awaiting concrete, detailed regulations on these submissions since Congress conferred tobacco regulatory authority on FDA in

India: Pharmaceutical Legal & Regulatory Environment

Japan: A Better Environment

2009. In the context of the current SE submission process, companies have relied on non-binding guidance and individualized feedback.

By promulgating regulations for premarket review applications, FDA stated that it hopes to bring clarity and consistency to the format, structure, and content of these applications, while upholding the agency's public health mission. The rulemaking process will provide stakeholders with a chance to help shape submission requirements and the review process for premarket review applications. We therefore expect to see plenty of interaction and communication between FDA and stakeholders as the agency works to develop and finalize these rules before the delayed application deadlines arise in four and five years, respectively.

Stakeholder Engagement on Key Issues in Public Health

In addition to rulemaking and issuing guidance, FDA intends to issue ANPRMs on a number of topics to seek stakeholder input as it further hones its thinking. One of the proposed ANPRMs regards lowering nicotine in cigarettes to non-addictive levels. FDA stated that it will seek input on the potential public health benefits and any possible adverse effects of lowering nicotine in cigarettes, such as the potential for a black market for higher nicotine cigarettes. Ultimately, FDA said that it hopes to catalyze public dialogue about lowering nicotine levels in combustible cigarettes to minimally or non-addictive levels through achievable product standards. FDA noted that it is only considering nicotine reduction in combustible cigarettes and not in other tobacco products because combustible cigarettes are considered the primary cause of tobacco-related death and disease. See e.g., Scott Gottlieb and Mitchell Zeller, Perspective: A Nicotine-Focused Framework for Public Health, JAMA (Aug. 16, 2017).

The agency also plans to investigate flavors (including menthol) in tobacco products through an ANPRM. FDA intends to seek public

input on the role that flavors in tobacco products play in attracting youth, as well as the role they may play in helping some smokers switch to potentially less harmful forms of nicotine delivery. In promulgating the final Deeming Rule, FDA chose not to issue a ban on all tobacco products with characterizing flavors at that time. 81 Fed. Reg. at 29,055. Rather, the agency stated that, based on available information regarding the growth of the flavored cigar market and its impact on youth and young adult initiation, it intended to issue a proposed product standard to prohibit characterizing flavors in cigars in the future. With regard to ENDS and other products, however, FDA cited a lack of adequate information regarding the potential public health benefits for adults looking to substitute non-combustible products for combustibles, and noted that it would seek additional data on the potential advantages of such characterizing flavors. *Id*.

In a potential reversal of its 2016 final Deeming Rule, FDA intends to seek public comment via ANPRM on the patterns of use and resulting public health impacts from premium cigars, which were included in FDA's 2016 final Deeming Rule. FDA said that it seeks to determine whether and how it would exempt premium cigars from regulation. This matter was a major subject of debate surrounding promulgation of the initial deeming rule, and FDA ultimately chose to regulate premium cigars, stating, "[a]fter thorough review of the comments and the scientific evidence, FDA has concluded that deeming all cigars, rather than a subset, more completely protects public health." 81 Fed. Reg. at 29,020. The agency went on to support its reasoning, suggesting that "all cigars pose serious negative health risks" and "the available evidence does not provide a basis for FDA to conclude that the patterns of premium cigar use sufficiently reduce the health risks to warrant exclusion." Id. In rolling out its comprehensive plan, however, FDA includes this proposed ANPRM in the category of efforts to balance regulation and encourage the development of innovative tobacco products that might be less dangerous than cigarettes. Opponents of premium cigar regulation have suggested that

the products should not be regulated because they are too expensive to appeal to youths, they are not consumed in the same way or at the same rate as other tobacco products, and their production process (typically handrolling) is fundamentally incompatible with FDA's premarket review requirements given the lack of standardization in the resulting product. 81 Fed. Reg. at 29,020-27.

These ANPRMs are indicative of the agency's priorities in the coming years. Stakeholders should use them to identify opportunities for research and to educate the agency on these issues in order to shape future regulatory policy.

Reassessment of Current Policies

Commissioner Gottlieb asked CTP to consider the Center's current plan to review all provisional SE products, including whether this is an effective use of its resources. He asked CTP to determine whether the Center should continue to pursue the current approach to these reviews or (1) whether there is a more appropriate approach for provisional SE reports, (2) if the Center's resources could be freed up for other purposes, and (3) whether greater clarity could be provided to the market. Director Zeller clarified that FDA is not, at this time, announcing any change in policy regarding provisional SE reports, but rather, will be reviewing those provisional SE reports that remain in the queue to determine from a public health and policy perspective whether they should remain in the queue or be removed. With the agency's new focus on promulgating regulations for premarket review applications and potentially lowering nicotine in cigarettes via product standards, it remains an open question as to how pending provisional SE reports will fit into the new regulatory plan.

Concluding Thoughts

FDA's new comprehensive tobacco and nicotine policy is dependent upon engaging industry stakeholders from all sides to assist in

developing regulations and standards that are achievable and appropriate for the protection of public health. This comprehensive plan serves as a roadmap for stakeholders to understand FDA's priorities and begin to develop and refine research to support their positions for each of these issues.

We note that FDA's comprehensive nicotine compliance policy does not affect current requirements for cigarettes and smokeless tobacco products, provisions of the final Deeming Rule that are already in effect, and certain future deadlines for other provisions of the final Deeming Rule, including required warning statements, ingredient listing, health document submissions, harmful and potentially harmful constituent reports, and the removal of modified risk claims (i.e., "light," "low," or "mild," or similar descriptors).

FOOD AND DRUG LAW INSTITUTE
1155 15th Street NW, Suite 910
Washington, DC 20005
Contact Us

en Español (http://esp.fda.gov/TobaccoProducts/default.htm)

FDA's Plan for Tobacco and Nicotine Regulation

Embedded Video

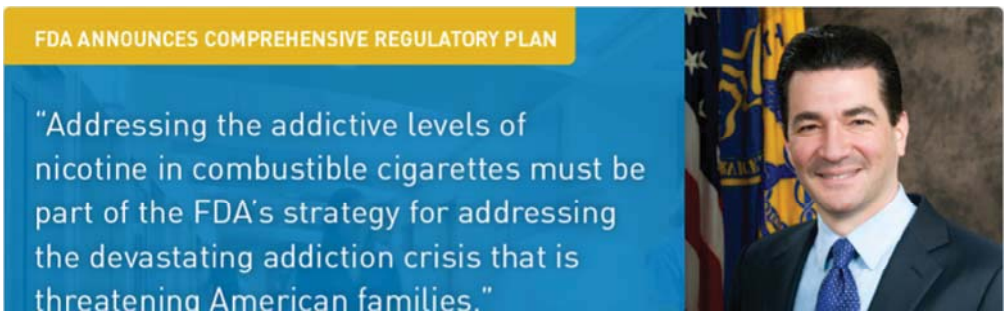
On July 28, the **FDA announced a new comprehensive plan (/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm)** that places nicotine, and the issue of addiction, at the center of the agency's tobacco regulation efforts. This plan will serve as a multi-year roadmap to better protect kids and significantly reduce tobacco-related disease and death in the U.S.

A key piece of the approach is demonstrating a greater awareness that nicotine—while highly addictive—is delivered through products that represent a continuum of risk and is most harmful when delivered through smoke particles in combustible cigarettes. Accordingly, the FDA is announcing several efforts to shift the trajectory of tobacco-related disease and death.

Lowering Nicotine in Cigarettes to Non-Addictive Levels

Almost 90% of adult smokers started smoking before the age of 18[1] and nearly 2,500 youth smoke their first cigarette every day in the U.S.[2] By lowering nicotine levels in cigarettes to non-addictive levels, we could decrease the likelihood that future generations become addicted to cigarettes and allow more currently addicted smokers to quit.

- **FDA plans to begin a public dialogue** about lowering nicotine levels in combustible cigarettes to non-addictive levels through achievable product standards.
- **FDA intends to issue an Advance Notice of Proposed Rulemaking (ANPRM)** to seek input on the potential public health benefits and any possible adverse effects of lowering nicotine in cigarettes.



Public Comment and other Opportunities to Communicate with FDA

The FDA seeks to strike an appropriate balance between regulation and encouraging development of innovative tobacco products that could reduce the public health harms caused by cigarette smoking. Public input on these complex issues will help ensure the agency has the proper science-based policies in place to meaningfully reduce the harms caused by tobacco use.

- **FDA intends to issue an Advance Notice of Proposed Rulemaking (ANPRM)** to seek public comment on the role that **flavors in tobacco products—including menthol**—play in attracting youth, as well as the role they may play in helping some smokers switch to potentially less harmful forms of nicotine delivery.
- **FDA intends to issue an Advance Notice of Proposed Rulemaking (ANPRM)** to solicit additional comments and scientific data related to the patterns of use and resulting public health impacts from **premium cigars**.
- **FDA plans to examine actions** to increase access and use of FDA-approved **medicinal nicotine products**, and work with sponsors to consider what steps can be taken under the safety and efficacy standard for products intended to help smokers quit.
    - **January 2018: Nicotine Steering Committee Public Hearing—Evaluating Safety and Efficacy of Nicotine Replacement Therapies (NRTs) (https://www.federalregister.gov/documents/2017/11/30/2017-25671/approach-to-evaluating-nicotine-replacement-therapies-public-hearing-request-for-comments)**

Extending Timelines to Encourage Innovations

In order to allow the FDA to encourage innovation that has the potential to make a notable public health difference—and to inform future policies and efforts that will protect kids and help smokers quit cigarettes—the agency **extended timelines to submit tobacco product review applications (/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm557714.htm)** for newly-regulated products that were on the market as of August 8, 2016. Under the revised timelines:

- **Applications to market newly-regulated *combustible* products**, such as cigars, pipe tobacco, and hookah tobacco, must be submitted by **August 8, 2021**.
- **Applications to market newly-regulated *non-combustible* products**, such as electronic nicotine delivery systems (ENDS) or e-cigarettes, must be submitted by **August 8, 2022**.

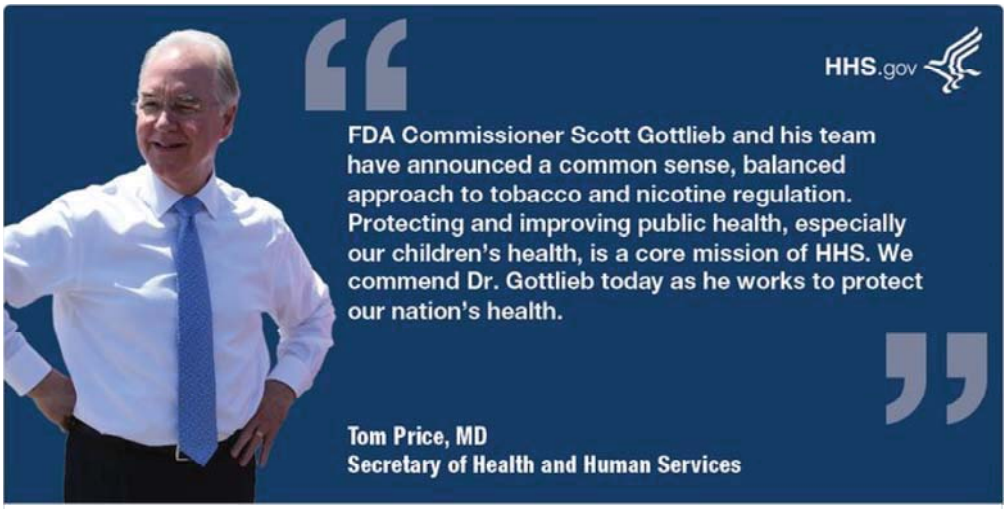
All other **compliance deadlines for manufacturers (/TobaccoProducts/GuidanceComplianceRegulatoryInformation/Manufacturing/default.htm)** will remain the same. Importantly, the new enforcement policy does not affect any current requirements from **the deeming rule (/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm394909.htm)** that have already passed. For example, mandatory age and photo-ID checks to prevent illegal sales to minors remain in effect and subject to enforcement by the FDA.

These revised timelines will afford the agency time to explore clear and meaningful measures to make tobacco products less toxic, appealing, and addictive, such as:

- **FDA intends to develop product standards** to protect against known public health risks such as electronic nicotine delivery systems (ENDS) **battery issues**.
- **FDA intends to develop product standards** around concerns about **children's exposure to liquid nicotine**.

Among other things, the FDA intends to issue regulations outlining what information the agency expects to be included in Premarket Tobacco Applications (PMTAs), Modified Risk Tobacco Product (MRTP) applications, and reports to demonstrate Substantial Equivalence (SE). The FDA also plans to finalize guidance on how it intends to review PMTAs for ENDS.

The agency also will continue efforts to assist industry in complying with federal tobacco regulations through online information, meetings, webinars, and guidance documents.



Tom Price, M.D.
@SecPriceMD

We commend @SGottliebFDA & @US_FDA for adopting a common sense, balanced approach to tobacco & nicotine regulation. go.usa.gov/xRU4U

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References

Additional Resources

- **A Nicotine-Focused Framework for Public Health, by FDA Commissioner Scott Gottlieb and CTP Director Mitchell Zeller in the New England Journal of Medicine (http://www.nejm.org/doi/full/10.1056/NEJMp1707409?query=featured_home) (/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)**
- **Press Release: FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm)**
- **Speech: Protecting American Families: Comprehensive Approach to Nicotine and Tobacco (/NewsEvents/Speeches/ucm569024.htm)**
- **Guidance: Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule (Revised) (/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm557714.htm)**

More in Newsroom (/TobaccoProducts/NewsEvents/default.htm)

Protecting American Families: Comprehensive Approach to Nicotine and Tobacco

Remarks by Scott Gottlieb, M.D.
Commissioner of Food and Drug Administration
July 28, 2017
White Oak, MD

(Remarks as prepared for delivery)

Tobacco use remains the leading cause of preventable disease and death in the United States. But much has changed in the landscape of tobacco product regulation and FDA's ability to address this public health crisis.

For one, FDA has significant new regulatory authorities. When I last served, FDA lacked the authority to regulate tobacco products as traditionally marketed. Since that time, our statute has been amended to include an entire chapter of new authorities. And FDA has stood up a new Center for Tobacco Products that already has a number of important accomplishments.

There's also been enormous change in the marketplace for tobacco products since I was last at FDA. In just the last few years, we've seen the advent and adoption of new product categories that may be able to deliver nicotine without having to burn tobacco.

As a physician who cared for hospitalized cancer patients, and as a cancer survivor myself, I saw first-hand the impact of tobacco. And I know all too well that it's cigarettes that are the primary cause of tobacco-related disease and death. What's now clear is that FDA is at a unique moment in history, with profound new tools to address this devastating impact.

Addressing the addiction crises that are claiming young lives and hurting American families is our most pressing mandate at FDA. In particular, examining the presence of nicotine in combustible cigarettes has to be part of a much broader strategy. I've pledged a deep commitment to taking aggressive steps to address the epidemic of addiction to opioids. I view our opportunity to confront addiction to nicotine with the same obligation. I'll pursue efforts to reduce addiction to nicotine with the same vigor.

Yes, there's been progress since the landmark 1964 Surgeon General's Report on Smoking and Health, including significant reductions in adult and youth tobacco use. But the 50th Anniversary Surgeon General's Report in 2014 indicated that the death toll from cigarette smoking was 480,000 every year. So at this rate, from the release of the 2014 Surgeon General's Report just through the mid-21st century, 17,280,000 Americans will die avoidable premature deaths because of cigarette smoking.

The magnitude of these numbers is hard to fathom. But I'm sure that every person in this room has had a friend or loved one made ill or worse because of tobacco use. And as a doctor I can tell you that tobacco-caused diseases -- especially cancer and lung disease -- are extremely painful.

In addition to the devastating human toll of tobacco use, cigarette smoking also causes direct health care and lost productivity costs totaling nearly $300 billion a year. So there are substantial financial costs to society as well.

There are two key facts about tobacco use that must be front and center in our thinking if we're going to be serious about altering the current trajectory of preventable tobacco-related deaths.

Fact One: The overwhelming amount of the death and disease attributable to tobacco is caused by addiction to cigarettes. Addiction causes long-term sustained use. But it's exposure to the harmful chemicals that cause disease. Cigarettes are the only legal consumer product that, when used as intended, will kill half of all long-term users.

And Fact Two: Almost all adult smokers started smoking when they were kids. Nearly 90 percent started smoking before the age of 18, and 95 percent by age 21. If you make it to age 26 without smoking, the odds are overwhelmingly in your favor that you won't become a smoker. Only about 1 percent of cigarette smokers start at that point or later in their lives.

Congress gave FDA powerful tools to help reduce the harms caused by tobacco use when it passed the Family Smoking Prevention and Tobacco Control Act in 2009. And it sent a strong signal by calling it the Family Smoking Prevention and Tobacco Control Act. To put it simply: it's all about kids and families. Congress made that clear in the law. And we take that responsibility very seriously.

FDA has made great progress protecting those who are the most vulnerable -- our children -- from tobacco's harms. The Agency produces public education campaigns that have kept nearly 350,000 kids who would otherwise have started to smoke from smoking. We vigorously enforce the law that makes it illegal to sell tobacco products to kids.

But too many children still experiment with tobacco products. Too many of these children will make the progression to regular smoking, and end up being addicted to cigarettes. And too many people who are addicted to cigarettes today and want to quit are unable to do so.

We must do more to help these Americans and their families to lead healthier lives, and to avoid or break free from harmful cigarette addiction.

The key lies in taking a new and comprehensive approach to the regulation of nicotine.

Why nicotine?

Because nicotine lives at the core of both the problem and, ultimately, the solution to the question of addiction, and the harm caused by combustible forms of tobacco.

Nicotine is astonishingly addictive. And when nicotine is attached to cigarette smoke particles, it's not only highly addictive, but an addictive chemical mix of disease and death. One feature critical to cigarettes is the efficiency by which they deliver

nicotine. And inhalation is the key. A cigarette can deliver the inhaled nicotine through the lungs and to the brain in less than 10 seconds, adding to its addictive potential.

But the nicotine in cigarettes is not directly responsible for the cancer, lung disease, and heart disease that kill hundreds of thousands of Americans each year. Yes, it got them all addicted and kept them addicted for the long term. And it got most of them addicted when they were still teenagers. But it's the other chemical compounds in tobacco, and in the smoke created by setting tobacco on fire, that directly and primarily cause the illness and death, not the nicotine.

So we need to take a fresh look at nicotine itself, and how the addiction that it causes relates to the potential harm of its delivery mechanism.

Nicotine is by no means a completely safe and benign compound. But a family and population-focused approach to reducing tobacco-caused disease and death must start from the premise that, as far as nicotine is concerned, the problem isn't just the nicotine. The bigger problem is the delivery mechanism -- how the nicotine gets delivered. Attach it to smoke particles created by burning cigarettes and the mechanism is deadly. But attach the very same nicotine to a medicinal product without the other chemicals found in tobacco products and these therapeutic products have been found to be safe and effective by FDA in helping smokers quit. In fact, for nicotine replacement products such as gum, lozenges and patches, FDA doesn't even require a doctor's prescription for them.

So how can we take a new and comprehensive approach to nicotine?

For starters, given everything I just said about the vital role of the delivery mechanism, we must acknowledge that there's a continuum of risk for nicotine delivery. That continuum ranges from combustible cigarettes at one end, to medicinal nicotine products at the other.

We must also acknowledge the evidence that shows the majority of cigarette smokers are concerned about their health and about two-thirds of adult smokers have stated they want to quit. They know it's hard, and they've probably tried many times to quit with over half of adult smokers making an attempt to quit each year.

And we must recognize the potential for innovation to lead to less harmful products, which, under FDA's oversight, could be part of a solution. While there's still much research to be done on these products and the risks that they may pose, they may also present benefits that we must consider. FDA's investment in regulatory science will eventually answer many of those benefit and risk questions.

Armed with the recognition of the risk continuum, and the reality that all roads lead back to cigarettes as the primary cause of the current problem, we need to envision a world where cigarettes lose their addictive potential through reduced nicotine levels. And a world where less harmful alternative forms, efficiently delivering satisfying levels of nicotine, are available for those adults who need or want them.

And that's why today I'm directing our Center for Tobacco Products to develop a comprehensive nicotine regulatory plan premised on the need to confront and alter cigarette addiction. I've followed the compelling discussion—both the public discourse and within the Agency—of FDA's potential to render cigarettes minimally addictive or non-addictive by regulating their nicotine levels. I've seen the science in this area and believe it holds much promise. We intend to take a hard look at the existing published literature on this important topic and hear from stakeholders, which

could provide the basis for regulatory action. To begin this process, we will develop an Advance Notice of Proposed Rulemaking to identify the issues FDA would need to address to use our clear authority under the product standard provisions in the Tobacco Control Act to regulate nicotine in combustible cigarettes and render them minimally or non-addictive.

Cigarettes will likely remain incredibly toxic, what with the presence of over 7,000 chemicals in cigarette smoke. But with a balanced regulatory approach, we may be able to reach a day when the most harmful products are no longer capable of addicting our kids.

I can tell you that FDA and others have done some preliminary analysis of the potential public health impacts if cigarettes could no longer create or sustain addiction. The public health benefits at a population level kick in over time, as future generations of kids who may experiment with cigarettes find it far less likely to ever become addicted to nicotine, and to suffer the chronic diseases that they are at great risk of experiencing once addicted to combustible cigarettes. And those potential generational public health benefits could be staggering in terms of life years gained, and economic costs avoided.

I've also asked CTP to explore the potential for any adverse effects from reducing nicotine levels, especially the possibility of a black market for higher nicotine products. And we need to understand what role, if any, the availability of newer forms of nicotine delivery may play in reducing those adverse effects.

We intend to consider these and other relevant questions as part of our public process. That process will be one of a series of new rulemakings that we will begin working on immediately. These rulemakings will address foundational regulatory elements for a modern and sustainable effort to regulate tobacco products. Our approach to making nicotine the center of our regulatory efforts needs to be accompanied by a firm foundation of rules and standards for newly-deemed products.

Among other things, we will advance rules that will lay out what needs to be in applications for Substantial Equivalence, Modified Risk Tobacco Product, and Pre-Market Tobacco Product applications; whether and how we would exempt premium cigars from regulation; how to possibly regulate kid-appealing flavors in products like Electronic Nicotine Delivery Systems, or ENDS; and whether we should ban menthol in cigarettes and flavors in cigarillos – factors that we know are a leading driver of youth smoking.

But the most substantial new undertaking is the one aimed at nicotine, and to start, an Advance Notice of Proposed Rulemaking to explore how we could reduce nicotine in combustible cigarettes. Looking at ways to reduce nicotine levels in cigarettes so that they are minimally or non-addictive, while not altering the nicotine content of noncombustible products such as e-cigarettes, is a cornerstone of our new and more comprehensive approach to effective tobacco regulation. And Congress has made clear that FDA has this authority. As I see it, taking the next step and addressing nicotine is not just within our authority; it's an enormous public health opportunity and falls squarely within FDA's mission.

But, as we move forward with this approach, we must also take a new and fresh look at the noncombustible side of the house. And that is why part of CTP's task is to reconsider aspects of the implementation of the final deeming rule with an eye towards fostering innovation where innovation could truly make a public health difference, and making sure we have the foundational regulations we need in place to make the entire program transparent, predictable, and sustainable for the long run.

One area of emphasis will be to make sure we have the foundational regulatory architecture to ensure proper oversight of ENDS. This firm foundation will establish a series of proper regulatory gates. Part of this will be developing regulations that we have not yet pursued because the Agency's tobacco program itself is so new. To take one example, I have real concerns about kids' use of e-cigarettes, and I know many others share those concerns, especially those products marketed with obviously kid-appealing flavors. As soon as the FDA deeming rule went into effect last summer that extended our authority to include ENDS, cigars, and all other tobacco products, FDA started enforcing provisions that, for the first time under federal law, made it illegal to sell all those products to kids.

We will re-double our efforts to protect kids from all nicotine-containing products. This has to include looking at the role of kid-appealing flavors, because kids shouldn't be using any of these products. So going forward I am asking the Center for Tobacco Products to develop an Advance Notice of Proposed Rulemaking to address the issue of flavored tobacco products and kids. This will be just one of the new proposed rulemakings and policy actions we are committing to today, in order to start the process for defining how we intend to properly regulate the deemed products.

As we move forward, I also hope that we can all see the potential benefits to addicted cigarette smokers, in a properly regulated marketplace, of products capable of delivering nicotine without having to set tobacco on fire. The prospective benefit may be even greater for the subset of current cigarette smokers who find themselves unable or unwilling to quit.

It's incumbent upon us as regulators to explore both the potential public health benefits and the risks of this new technology with an open mind. And I can assure you, from my discussions with the leadership of the Center for Tobacco Products, that FDA is bringing just that mindset to the task at hand.

To give ourselves time to implement this framework, including through notice and comment rulemaking, I'm directing CTP to reconsider the various compliance policies associated with the deeming regulation. This includes the policies relating to the compliance periods for premarket submissions for products on the market at the time the deeming rule took effect and for FDA's review of those submissions. Specifically, CTP will consider the language in the preamble that set forth timelines for submissions and raised concerns about products coming off the market before FDA had reached a decision. Reconsideration of these policies is within FDA's discretion, and we are exercising that discretion in a targeted way in order to lay the groundwork for a more strategic long-term approach to regulating tobacco products.

The question is this: If we lean in on nicotine regulation wholeheartedly, how do these compliance policies fit into our overall goal? In a world where FDA is pursuing how to regulate nicotine levels in cigarettes, and combustible cigarettes are one day far less addictive, we can take the time to make sure we have in place the foundational elements of a robust and sustainable framework for regulating the non-combustible forms of nicotine delivery. That means extending further some of the current compliance deadlines for newly deemed products, primarily electronic cigarettes and cigars, that were previously extended. All of the requirements for newly deemed products that have already gone into effect will continue to stay in force. In a world where there is no mandated reduction in the levels of nicotine in noncombustible products, our compliance policies should account for changes that will move addicted smokers down that continuum of risk to these less harmful products.

We need to make sure we strike the right balance between FDA fulfilling its vital consumer protection role while also fostering innovation when it comes to potentially less harmful forms of nicotine delivery. This becomes especially true in a world where cigarettes are no longer capable of creating or sustaining addiction.

These are questions that FDA must confront.

I am also directing CTP to explore other aspects of the current application review process. In particular, I have asked CTP to consider whether its current plan, which is to review all of the so-called Provisional Substantial Equivalence products, is an effective use of its resources and whether it should continue to pursue the current approach to these reviews. I have asked CTP to consider whether there is an approach that makes more sense, and whether by not reviewing some of those products, those review resources could be freed up for other purposes and greater clarity could be provided to the market.

In addition, we'll also be revising the so-called "sunset policy" through additional guidance so that existing products under review remain on the market. The current policy could have forced existing products off the market. We'll also be working to put in place a more comprehensive, transparent, and vigorous regulatory framework that will make our regulatory efforts more sustainable.

Finally, as I've noted, I'm also asking the Tobacco Center leadership to explore a process by which it could ask for new information related to the patterns of use and resulting public health impacts from so-called premium cigars. The final deeming rule covers all cigars. But I want the Center to consider opportunities it could provide to interested parties to develop and submit new information or data on this issue. This will take the form of a new Advance Notice of Proposed Rulemaking, to develop a new administrative record to explore these questions. We will explore any new and different questions raised, and seriously consider any additional data submitted relevant to the appropriate regulatory status of premium cigars.

The comprehensive framework for nicotine regulation I've laid out here is an FDA-wide imperative. This means we must also work to have medicinal nicotine and other therapeutic products play a greater role in helping more smokers try to quit with help, to quit successfully, and to stay quit. That's why I'm also asking our Center for Drug Evaluation and Research to examine possible steps we can take to address the performance of medicinal nicotine products, including the speed with which the nicotine is delivered, and other possible innovations in treatments that could help more smokers use FDA-approved products to quit smoking.

The potential to improve product performance here is a significant public health opportunity. And I hope sponsors will come in and talk with us about steps that can be considered under the safety and efficacy standard for products that are intended to help smokers quit.

I want to emphasize that all of the steps I've outlined today are intended to work together as a package deal. One federal court recently upheld the Agency's authority over newly deemed products. Each component of this broader plan builds on the deeming rule and is part of an overall effort to reduce the adverse effects of cigarettes, create clearer guideposts for the regulation of all products, and account for the role of all noncombustible products.

As a comprehensive public health package, it's really all or nothing. For example, we cannot make certain accommodations on compliance deadlines or give ourselves the time to put in place foundational rules, or take a different approach to the sunset

policy or the provisional applications, if we're not also pursuing the regulation of nicotine in combustible cigarettes. It's only in a world where we will work to eventually render cigarettes minimally addictive that we can take on some of the other challenges or provide the greater flexibility outlined here when it comes to e-cigarettes and any other noncombustible products. And we cannot pursue a plan to minimize the addictiveness and attractiveness of cigarettes if we can't simultaneously take the time to adopt additional procedural and foundational policies and regulations that are critically important to achieving our goals. That's why it's a package. And it's why we need to pursue all of these measures together.

I've formalized this comprehensive plan in close collaboration with the leadership of FDA's Center for Tobacco Products. I'm moving forward with their full support and the support of my senior team.

In closing, we truly find ourselves at a crossroads when it comes to efforts to reduce tobacco use. We have the potential to improve the lives of tens of millions of currently addicted cigarette smokers, and future generations of kids. But if we're going to meaningfully improve the public health, we need to be willing to take a hard look at our entire approach to tobacco, to make sure we have the right regulatory gates in place to evaluate products, and to focus more squarely on the nicotine. On the one hand, there's the ongoing divisive debate around the pros and cons of e-cigarettes. Precious little progress has been made as competing camps dig in on the benefits and risks of a harm reductionist approach to this new technology. Both sides are convinced that they're right, but we've seen little progress, and virtually no common ground. On the other hand, there's a pathway forward that reframes the debate around nicotine.

Three things have changed more recently that together provide an extraordinary opportunity to use the tools of product regulation so that tobacco use, and principally cigarettes, will no longer be the leading killer of Americans.

First, the entire spectrum of nicotine-delivering products is now regulated, from the most to the least harmful. Second, regulatory science is providing an evidence-base to inform policy for regulating the addictiveness of the deadliest form of nicotine delivery. And third, even with unanswered questions about benefits and risks, there are now different technologies to deliver nicotine, for those who need it, that doesn't bring with it the deadly consequences of burning tobacco and inhaling the resulting smoke.

I see a way to maximize the positive impact from these three more recent developments by taking the steps I've outlined here today to reduce or eliminate the ability of combustible cigarettes to be addictive while putting in place the foundational regulatory elements for a comprehensive and sustainable framework for properly regulating products that may pose less risk. I see a pathway towards successfully altering the current trajectory I mentioned at the outset that, unchecked, will continue to destroy families by claiming the lives of tens of millions of Americans by century's end.

To succeed, FDA must be strategic about how it uses its tobacco and drug authorities. To succeed, participants from all sectors in the ongoing harm reduction debate need to take a step back and work together to reach greater common ground. And that common ground is worth pursuing around the ultimate harm reduction policy where cigarettes may be no longer addictive.

Reframing shared objectives around the need to rethink nicotine is a start. It could help all of us achieve the one public health goal I know we all share, and that's to save the lives of current and future cigarette smokers.

On a personal note, I started my remarks by describing all that's changed regarding tobacco product regulation since I last served at FDA. In the three months since my return, I see an extraordinary public health opportunity to take the bold and far-reaching actions I've laid out here today. To miss the opportunity to build on everything that FDA has accomplished since the enactment of the Tobacco Control Act would be irresponsible. We have it within our grasp to use the tools of product regulation to dramatically reduce tobacco-caused disease and death. I can think of no more impactful action FDA could possibly take on my watch to help American families.

Unless we change course, 5.6 million children alive today will die prematurely later in life from tobacco use. A renewed focus on nicotine can help us to achieve a world where cigarettes no longer addict future generations of our kids; and where adults who still need or want nicotine can get it from alternative and less harmful sources. FDA stands ready to do its share.

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