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VIA ELECTRONIC SUBMISSION AND HAND DELIVERY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852


Altria Client Services Inc. (“ALCS”), on behalf of U.S. Smokeless Tobacco Company LLC (“USSTC”), submits these comments to the Food and Drug Administration’s ("FDA’s" or the “agency’s”) Proposed Rule for a Tobacco Product Standard for N-Nitrosonornicotine Level in Finished Smokeless Tobacco Products (the “Proposed Product Standard” or “Proposed Rule”).

FDA’s Proposed Rule to limit NNN in smokeless tobacco products to 1 ppm is unlawful because, among other things, it (1) is impossible to achieve and therefore constitutes a prohibited de facto ban and (2) effectively regulates farming practices, which is forbidden by sections 901 and 907 of the Federal Food Drug and Cosmetic Act (“FDCA”). It also fails to “protect the public health” because it would eliminate from the market a reduced harm tobacco product.

(1) NNN levels in tobacco leaves vary widely from plant to plant and year to year. Because the overwhelming factor driving NNN levels is the humidity during the long, slow curing process, the Proposed Rule amounts to an irrational command to control the weather. Despite decades of diligent and innovative efforts by USSTC, working directly with small family farmers, to reduce NNN in tobacco leaves, levels over the past decade have averaged 2 to 5 times, and ranged up to 100 times, FDA’s proposed limit. Neither farmers nor manufacturers can control the weather. For that reason, not a single moist smokeless tobacco (“MST”) or chewing tobacco product – the kind used by 99% of the adults who use smokeless tobacco – could meet the Proposed Product Standard on a consistent, on-going basis. If adopted, the Proposed Rule would effectively, and

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1USSTC is a wholly-owned subsidiary of Altria Group, Inc. (“Altria”). ALCS provides certain services, including regulatory affairs, to the Altria family of companies. “We” and “our” are used throughout these comments to refer to USSTC, except where the context requires otherwise.
impermissibly, ban smokeless tobacco products from the market, taking with them the primary source of income for more than 1,000 family farms, and wreaking havoc on the economies of the small communities in and around Hopkinsville, Kentucky, where the type of tobacco used is grown. Section 907 simply does not permit such a de facto product ban.

(2) Section 907 of the FDCA empowers the FDA to set standards for manufacturers of tobacco products, but it and section 901(c)(2) prohibit the FDA from regulating the practices of tobacco farmers. Yet that is precisely the effect of the Proposed Rule. In 2001, USSTC began modifying its manufacturing processes to reduce NNN levels developed at that stage of production. By 2005, those innovative practices eliminated any increase in NNN during the manufacturing process. In short, the NNN levels in the finished product sold in stores do not exceed the levels in the tobacco purchased from the farm. As of today, USSTC can do no more with respect to its manufacturing processes and any further reduction in NNN levels, if possible, would have to occur on the farm. Thus, the Proposed Rule violates sections 901 and 907, which deny the FDA authority to regulate farming practices.

(3) FDA’s Proposed Product Standard does not protect the public health because it would eliminate from the market a category of tobacco products that are, based on overwhelming scientific, medical and public health consensus, substantially less hazardous than cigarettes. If smokeless tobacco products, such as MST and chewing tobacco, are effectively banned from the market, many of its more than 8 million users would switch to or back to more risky products like combustible cigarettes, thus increasing the risk to public health. FDA’s proposal is contrary to tobacco harm reduction goals.

I. **Background on the Smokeless Tobacco Product Category**

A. Types of Smokeless Tobacco Products Sold in the U.S.

Smokeless tobacco originated in the U.S. in the late 1600s, when colonists would dry the leaves of tobacco plants, pulverize them to a dust and inhale or “snuff” the tobacco dust. Later, users would chew the end of a stick to moisten it, dip it into the dry snuff, and chew the end of the coated stick. Chewing tobacco was often made by wadding tobacco leaf into a hole in a log and adding something like brandy or cane sugar as a flavoring or sweetener. This eventually led to the creation of MST, which is now the choice of about 85% of the U.S. adults who enjoy smokeless tobacco products. A pinch is placed between cheek and gum and kept there for 20-40 minutes. Chewing tobacco, which as the name suggests is chewed to release the flavor of the tobacco, makes up about 14% of the market. A product called “snus” was developed in Scandinavia and is highly popular there but has only about a 1% share of the U.S. market. Finally, dry snuff is still sold but commands less than 0.5% of the market.

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2 Because of this history, MST is still commonly referred to as “dipping” tobacco.
Smokeless tobacco is primarily made of Dark tobacco, which is more robust and richly flavored than the thinner and more bitter Burley and Bright tobaccos primarily used in cigarettes. MST is made of Dark fire-cured and Dark air-cured tobacco. Some MST products also include small amounts of Burley and Flue-Cured tobacco. Chewing tobacco consists primarily of Dark air-cured tobacco, but can also include some Dark fire-cured and Flue-Cured tobaccos. Snus is made of Dark air-cured tobacco, and can also include some Burley tobacco, while dry snuff is primarily made of Dark fire-cured tobacco.

B. Adult Smokeless Tobacco Consumers

Adult consumers mention a variety of reasons for using smokeless tobacco products including relaxation, stimulation, taste, and the convenience of being able to use it where smoking is not allowed. Approximately 8.1 million U.S. adults use smokeless tobacco products. Of those:

- Approximately 5.1 million adults use smokeless tobacco products and do not smoke cigarettes.
  - Of those, approximately 1.3 million adults use both cigars and smokeless tobacco products.
- Approximately 3 million adults use both cigarettes and smokeless tobacco products.
  - Of those, approximately 700,000 adults are poly-users who also use cigarettes and cigars.3

The percentage of U.S. adults who say they have used smokeless tobacco products in the past 30 days has remained roughly stable at between 3% and 4% since regular measurements began in 2002.4

C. Dark Tobacco is the Critical Component of U.S. Smokeless Tobacco Products

The key to the appeal of smokeless tobacco products is Dark tobacco, so called because of its large, dark green leaves. These leaves help keep the product from disintegrating in the mouth and millions of adult consumers expect and enjoy the unique flavor, aroma, taste and color that result from the fire and air curing processes.

Dark tobacco is grown and cured in and around Hopkinsville, Kentucky, including some parts of north central Tennessee, where the nutrient rich soil produces robust leaves with a rich, slightly floral taste.5 Dark tobacco has been grown there on small family farms for well over two centuries and is typically a farmer’s most profitable crop. Some 1,200 farmers, along with their families and farm hands, plant more than 20,000 acres of Dark tobacco and use 8,000 specially

3 Based on ALCS analysis of the 2014 National Survey on Drug Use and Health public use file.
4 Id.
built and maintained barns to cure it using techniques passed down from generation to generation.  

It typically takes up to 300 hours of labor to produce an acre of Dark tobacco, and farmers grow up to 5,000 plants per acre. In 2015, for example, 23,650 acres of Dark tobacco yielded 73 million pounds and a cash value of $190 million.

Dark tobacco is also grown in foreign countries, including Argentina, Bangladesh, Brazil, Canada, Guatemala, India, Indonesia, Italy, Malawi, Mexico, Mozambique, Philippines, Poland, South Africa, Spain and Uganda. Non-U.S. production of Dark tobacco for 2017 is estimated to be about 196 million pounds. USSTC uses only U.S. grown and cured tobacco in its products.

In fire curing Dark tobacco, the farmer builds a smoldering fire fueled by sawdust and slabs of wood obtained from hardwood trees, such as hickory or oak. During this phase, a dark, rich brown color starts to develop on the tobacco leaf. The complete curing process typically takes 35 to 45 days, and yields a leaf dark in color with the unique flavor, aroma and taste that adult smokeless tobacco consumers expect and enjoy.

Some air cured Dark and Burley tobacco is also used in smokeless tobacco products. During this process, the leaf is cured on the stalk using ambient conditions (without fire). The farmer hangs the tobacco in ventilated barns or field structures over 4 to 8 weeks. The metabolizing of sugars and the breakdown of chlorophyll during curing creates flavor, aroma and taste compounds.

Some smokeless tobacco products also contain a small amount of Virginia tobacco, also called Flue-Cured or Bright tobacco. This tobacco is grown along the coastal plain regions in Virginia, North Carolina, South Carolina and Georgia due to the sandy loam and nutrient-deficient soil types found in those regions. Flue-curing usually takes 7 to 9 days. Only small amounts of Flue-Cured are used in smokeless tobacco products because the rapid curing process results in a leaf with a bitter taste.

II. FDA’s Proposed Product Standard is Technically Unachievable and Therefore Unlawful

Dark tobacco is essential to smokeless tobacco products but it is impossible to grow and cure it to meet the proposed 1 ppm NNN ceiling on a consistent, on-going basis. Congress prohibited the FDA from banning certain categories of tobacco products such as smokeless tobacco products, yet that is precisely what the technically unachievable standard set by the Proposed Rule would do – effectively ban smokeless tobacco products from the market. Such a de facto ban violates not only section 907(d)(3)(A), but also the Administrative Procedure Act (“APA”), which forbids impossible standards as arbitrary and capricious.

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6 ALCS internal estimates.
A. A Technically Impossible Standard is an Unlawful De Facto Ban on Smokeless Tobacco Products

In section 907 of the FDCA, Congress authorized FDA to impose tobacco product standards, but expressly prohibited it from banning a category of tobacco products, including “smokeless tobacco products.” This reflects Congress’s dual goals of making tobacco products safer while preserving adults’ right to choose to use them.

While the Proposed Rule is not framed as a ban, because the standard it sets is impossible to meet, it has precisely that effect. The Supreme Court has made clear that courts must look to the substance and practical effect of a regulation, not merely its form, in determining whether it constitutes an illegal ban. Thus, for example, in Granholm v. Heald, the Court compared a New York law that required out-of-state wineries to establish a distribution operation in New York to ship directly to New York consumers to a Michigan law that expressly banned out-of-state wineries from shipping directly to Michigan consumers. The Court found that New York’s law, while not an express ban, was just an “indirect way” of achieving the same result as Michigan’s ban by increasing the out-of-state wineries costs to make it impossible to compete. The Court, therefore, found that both laws violated the dormant Commerce Clause.

Section 907 in particular demands such a practical, substance over form approach. First, section 907’s prohibition on “ban[ning]” tobacco products must be understood as intended to implement Congress’s stated “purpose” “to continue to permit the sale of tobacco products to adults.” Whether a standard is framed as a “ban” or not, if, in practice, it would prevent adult consumers from purchasing a tobacco product, it is unlawful. Because the Proposed Rule would prohibit the sale of smokeless tobacco with more than 1 ppm of NNN, and all MST and chewing tobacco products would fail that test on a consistent, on-going basis, the Proposed Rule would prevent adults from purchasing these products – in other words, a prohibited product ban.

Further, by requiring the FDA to “consider information . . . regarding the technical achievability of compliance” with a proposed product standard, Congress made clear its concern with the effect a product standard would have on the market. Congress likewise instructed the FDA to consider, in setting the effective date for a new standard, “the technical achievability of compliance with the standard; whether, assuming the standard is technically achievable, it is possible to comply in the timeframe proposed; and whether meeting the standard would require manufacturers to demand substantial changes to the methods used by domestic farmers to grow the tobacco used by manufacturers.” Finally, Congress made clear in section 907 that an effective date for a product standard must “be established so as to minimize, consistent with the public health, economic loss to, and disruption or dislocation of, domestic and international trade.”

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8 FDCA § 907(d)(3)(A).
9 Tobacco Control Act § 3(7) (TCA).
11 TCA § 3(7).
12 FDCA § 907(b)(1) (emphasis added).
13 Id. § 907(d)(2).
14 See id.
Congress was sufficiently concerned with the harm a ban would cause to consumer choice and the farm economy that it prohibited the FDA from banning tobacco products even if it would reduce health risks. It expressed the same concerns regarding the effective date of a new standard. It follows that setting a standard that would create the same market mayhem and substantial economic loss as an express ban or premature effective date is likewise inconsistent with Congress’s expression of purpose and of section 907.15

B. A Technically Impossible Standard Violates the Administrative Procedure Act

Independent of the limitations prescribed by section 907, the APA precludes FDA from imposing impossible regulatory requirements. The APA bars agencies from promulgating regulations that are “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.”16 Courts have long recognized that unachievable standards are the epitome of arbitrary and capricious regulation. In Alliance for Cannabis Therapeutics v. DEA, for example, the D.C. Circuit agreed with medical marijuana advocates that the DEA could not make the inclusion of marijuana as a Schedule I drug turn on its “general availability” and use by doctors, when at the same time the DEA made it impossible to meet that standard because it treated marijuana as a Schedule I controlled substance making it effectively unavailable even to doctors.17 “Impossible requirements imposed by an agency are perforce unreasonable,” the Court found.18 Similarly, in Messina v. U.S. Citizenship and Immigration Services, the District Court rejected the defendant agency’s enforcement of a regulation regarding the adoption of non-citizens that was impossible to comply with under the complicated facts of that case. In ruling against the agency, the Court held, “It is arbitrary and capricious to require compliance with a regulation when compliance is impossible.”19 In this regard, the APA simply reflects fairness and common sense.

15 In other respects as well, section 907 reflects Congress’s concern with the practical impact of any product standard. For example, section 907(b)(2) postponed for at least two years the effective date of any standard that would require substantial changes in the method of farming by domestic growers. It also directed FDA to assess the potential that the standard could trigger a significant demand for contraband tobacco products. The apprehension these directives reflect regarding practical consequences far less drastic than the effective ban proposed here highlights that Congress did not intend to authorize such overreaching by FDA.
17 Alliance for Cannabis Therapeutics v. DEA, 930 F.2d 936, 940 (D.C. Cir. 1991).
18 Id.
19 Messina v. U.S. Citizenship and Immigration Services, 2006 WL 374564 (E.D. Mich. 2006), at *6. The parents adopted the child in Italy and brought her back to the U.S. as an infant. When they tried to reaffirm the adoption in Michigan, where they lived, they could not do so until she was 18 because before the age of consent Michigan law required a new consent from her natural parents, who could not be found. The plaintiffs therefore waited until the child was 18 before obtaining an adoption in Michigan, nunc pro tunc to the time of the Italian adoption. The defendant agency refused to recognize the adoption, citing its regulation requiring that non-citizens be adopted before turning 16. The Court found that the regulation set an impossible standard as applied to this case because adoption before 16 required consent of the birth parents, who could not be found. See also, Southwestern Bell Telephone Co. v. F.C.C., 100 F.3d 1004, 1006 (D.C. Cir. 1996) (requiring Bell to demonstrate competitiveness of industry by reference to competitors’ bids that it could not review created an impermissible “Catch-22”); Cont’l Bank v. United States, 517 F. Supp. 918, 924 (E.D. Pa. 1981), aff’d, 688 F.2d 819 (3d Cir. 1982) (“that the regulation, on its face, precluded successful compliance by this plaintiff weighs heavily against penalizing the plaintiff for failing to attempt to comply with the regulation”); Campbell v. Bennett, 212 F.Supp. 2d 1339, 1343 (M.D. Ala. 2002) (“[A]ny law that requires you to do something by a certain date must give you adequate time to do
As discussed below, the proposed standard would impose the kinds of impossible requirements that are proscribed by the APA.

C. FDA’s Proposed NNN Standard Is Technically Unachievable and Therefore a De facto Ban and a Violation of Section 907 and the APA

In violation of the requirement in both section 907 and the APA that a proposed tobacco product standard be technically achievable, FDA has proposed an NNN standard that is impossible to meet. In a nutshell, compliance is not within a farmer’s or manufacturer’s control. Rather, FDA’s proposed standard is unachievable because it fails to account for the environmental factors that increase NNN, for example, relative humidity during curing, which is the largest contributor to NNN in the tobacco used in smokeless tobacco products. Neither farmers nor manufacturers can control the weather, but FDA’s proposal, in essence, puts such a burden on them and results in a de facto ban of smokeless tobacco products.

Although FDA claims its proposed standard is technically achievable for 38% of all smokeless tobacco products registered with FDA, published research from its own scientists shows otherwise. Amman et al. tested 34 smokeless tobacco products sold in the U.S. as of January 2015. Of the 34 products tested, which account for about half the smokeless tobacco products sold, only 3 of those products would meet the 1 ppm limit – two snus products and one chewing tobacco product. Not a single MST product – the kind used by about 14% of adult U.S. smokeless users – met the 1 ppm limit. Further, no chewing tobacco product – the kind used by about 14% of adult U.S. smokeless product consumers – could meet the 1 ppm limit on a consistent, on-going basis. All of USSTC’s products tested by the authors exceeded the 1 ppm limit.

Based on data we collected from batch testing of tobacco purchased from farmers from 2005-2013 and in 2016, if the 1 ppm standard had been in effect, USSTC would have been required to reject 70%-90% of the Dark fire-cured tobacco grown by U.S. farmers and 10%-70% of the Dark air-cured tobacco. See Attachments 1 and 2.

At these rejection rates, manufacturers would not have nearly enough compliant leaf to be able to produce finished product that meets the 1 ppm limit. For example, at the finished product level, average NNN levels for USSTC’s top 20 MST products by volume for 2010-2016 all exceed FDA’s proposed 1ppm standard. And, measured on a batch by batch basis, none could consistently meet the proposed standard. As a result, 100% of USSTC’s top 20 MST products would be banned from the market under FDA’s proposed standard. In fact, none of USSTC’s currently marketed smokeless products could meet the 1ppm standard.

NNN occurs naturally in tobacco and can be formed during growing and curing on the farm, in the manufacturing process, in the downstream distribution chain, and while the product sits on

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21 As of Q4 2016, USSTC’s products make up 55.8% of the U.S. smokeless market and use 100% U.S. grown tobacco.
the retail shelf. Concerted efforts over many years by tobacco farmers and manufacturers have substantially reduced NNN formation. FDA’s standard, however, requires further drastic reductions in NNN levels that cannot be achieved.

FDA’s new standard is drawn from the GothiaTek® standard, which applies to a single, small subcategory of smokeless tobacco products. Over a 20 year period, Swedish Match developed this standard to promote the sale of its snus products in Sweden and Norway. As discussed in detail below, FDA mistakenly asserts that such a product standard is achievable domestically because certain snus products manufactured in Sweden using foreign-sourced Dark tobaccos and sold in the U.S. already meet it. It is important to note that Swedish Match MST products actually manufactured in the U.S., and which use some U.S. sourced tobacco, do not meet the GothiaTek® standard.

FDA’s rationale is fundamentally flawed because it fails to recognize that (1) because Swedish Match snus has such a small U.S. market share – less than 1% – that it can cherry-pick the very limited volume of low NNN tobacco it needs from an international supply nearly three times the size of the U.S. yield to create GothiaTek®-compliant snus products; (2) even if U.S. manufacturers were to start using foreign-grown Dark tobacco, there is not a sufficient global supply of low NNN tobacco available to meet the demand of U.S. manufacturers; and (3) even if a sufficient global supply of low NNN Dark tobacco existed – which it does not – a 1 ppm limit would severely prejudice U.S. tobacco farmers relative to tobacco farmers located elsewhere in the world in violation of section 907’s command that product standards should “not advantage foreign-grown tobacco over domestically grown tobacco.”

Ignoring these facts, the FDA plows ahead with its suggestions about how manufacturers can meet the proposed standard. Its suggestions, though, include steps that are either already implemented or are unworkable. In fact, as will be shown below, USSTC implemented procedures almost a decade ago that prevent the formation of any additional NNN from the time it purchases the tobacco through the end of the product’s retail shelf life. In neglecting the progress made thus far, FDA failed to consider whether or how the NNN levels in the smokeless tobacco products currently sold in the U.S. could be reduced further through available technologies, and the incremental costs that would be associated with those measures. Any additional reduction in NNN levels would have to come from the growing and curing processes, which the FDA is not authorized to regulate. In any event, given the overwhelming contribution

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22 Product Standard for N-nitrosonornicotine Level in Finished Smokeless Tobacco, 82 Fed. Reg. 8004, 8009-10 (proposed Jan. 23, 2017) (“Swedish snus products generally have much lower levels of tobacco-specific nitrosamines (TSNAs) than smokeless tobacco products found in the United States, and, therefore, they were of particular interest in the development of this proposed rule. . . . 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. . . . 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.”) (references omitted) (emphasis added).

23 See 82 Fed. Reg. at 8015 (“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. . . . 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.”)

24 See also Section II(C)(5)(a), below.
of weather to the formation of NNN in the growing and curing process, farmers cannot control NNN formation even if the FDA could require them to do so. The bottom line is that FDA has proposed a product standard that is technically unachievable and will result in a de facto ban of smokeless tobacco products in violation of section 907 and the APA.

1. NNN Arises Primarily from Factors that Farmers and Manufacturers Cannot Control

Since 2005, we have taken thousands of samples of purchased Dark air-cured and Dark fire-cured tobacco leaf to measure tobacco-specific nitrosamines (“TSNA”) levels, including NNN. The results of this testing program show the high variability in average NNN levels resulting from a variety of factors beyond the control of farmers and manufacturers – most prominently, relative humidity levels. For example, for the years 2005-2013 and 2016, average NNN levels for Dark air-cured tobacco range from approximately 0.3 ppm to 5.0 ppm and from approximately 1.9 ppm to 4.4 ppm for Dark fire-cured tobacco. See Figures 1 and 2, below.

![Figure 1. Average NNN levels in American Dark air-cured basket sampling. From 2005 – 2011 we used a non-validated method to measure NNN; for all years, we extrapolated low values beyond the calibration curve. We did not test NNN levels in 2014-2015.](image-url)
FDA acknowledges that “[w]eather is a significant factor in NNN formation.” In fact, not only is the weather the single largest contributor to NNN formation in tobacco, its impact is all the more decisive because, as discussed in detail below, USSTC has implemented processes that prevent NNN formation from the time USSTC purchases leaf from farmers through the end of retail shelf life. Thus, any further reductions in NNN would have to occur in the fields or, more likely, curing barns, where the relative humidity is driven by forces beyond the control of farmers.

The impact of the weather on NNN formation is clearly seen by correlating data from 2005-2013 and 2016 test samples with the average relative humidity near curing locations during the curing season for those same years. Years in which the Dark tobacco crop had higher levels of NNN are correlated with periods of higher average relative humidity during curing. On the other hand, years in which the Dark tobacco crop had lower NNN levels are correlated with periods of lower average relative humidity during curing. See Figures 3 and 4, below.
Figure 3. Correlation between relative humidity and NNN levels in Dark air-cured tobacco.

Figure 4. Correlation between relative humidity and NNN levels in Dark fire-cured tobacco.
We have conducted similar research with Burley tobacco, another important component of smokeless tobacco products, including MST. As with Dark tobacco, Burley tobacco has high NNN variability on the farm which is correlated with relative humidity during curing. Average NNN levels in the U.S. Burley tobacco crop purchased by Philip Morris USA for the years 2010-2015 ranged from approximately 1.7 ppm to 4.6 ppm. The lowest average NNN level (1.7 ppm) occurred in 2010, which correlates to a year with low humidity. Years with higher NNN levels correlate with higher humidity. See Figures 5 and 6, below.

![Domestic Burley Crop Annual NNN Average](image)

**Figure 5.** Average NNN levels in American Burley tobacco.
Collectively, the data above show that average relative humidity during curing is the major factor influencing NNN levels in Dark fire-cured, Dark air-cured, and Burley tobaccos. Furthermore, average relative humidity levels during curing can vary significantly based on geographical location even in and around Hopkinsville, resulting in high variability within the overall crop in a given year.

Plant to plant variability – even when those plants are grown together in the same field and cured together in the same barn – also contributes significantly to differences in NNN levels. In 2016, we conducted a study to understand variations in TSNA formation. We produced 100 TN 90 Burley Low Converter plants from the same seed lot; grew the plants in the same field under identical, idealized conditions; harvested the plants at the same time and then air-cured them in the same well-ventilated barn under identical conditions such as relative humidity and spacing. Curing coincided with low relative humidity levels at the curing barn, which typically leads to lower NNN levels. After curing, we took the 3rd, 4th and 5th leaves from each plant, created a pooled sample for each plant and measured NNN levels. Despite using all available means to produce a uniform crop under ideal conditions, including low ambient humidity during curing, NNN levels for the individual plants differed by over 100-fold from ~0.1 ppm up to ~11 ppm in an unpredictable manner for unknown reasons. These data illustrate that stochastic factors can have a dramatic impact on NNN levels in addition to identified macroclimatic factors, such as average relative humidity during curing.

Even under ideal curing conditions, the NNN levels of individual plants cannot be predicted. Plants sitting right next to each other may have dramatically different NNN levels. Furthermore,
tobacco farmers have no means of measuring NNN levels in tobacco bales, let alone individual leaves. Even if they knew the NNN levels in their cured leaf, which they do not, and knew how to change it, which no one does, it would be too late for them to make any changes to the tobacco they had already planted, grown, cured and baled for market. Thus, under the Proposed Product Standard, farmers would essentially face a kind of Russian Roulette, where they toil for thousands of hours to produce a crop without knowing until after they have invested all that time and money what percentage of a given crop, if any, they will actually be able to sell. With a potential rejection rate as high as 90%, manufacturers could not buy nearly enough compliant tobacco to satisfy the market – if, indeed, any farmers would continue to grow the crop. See Attachments 1 and 2. The practical effect would be the end of Dark tobacco farming and smokeless tobacco products in the U.S.

2. Low Converter Seed Varieties Help Limit, But Cannot Cap or Eliminate NNN Formation

The chemical process by which NNN in tobacco forms is well understood. During plant growth, a small fraction of nicotine in the plant is “converted” to nornicotine by the enzyme Nicotine Demethylase. Additionally, growing plants absorb nitrate fertilizers, and their leaves become colonized by nitrate-reducing bacteria. During curing, these nitrate-reducing bacteria transform the plant-absorbed nitrate to nitrite, and its addition to nornicotine produces NNN. Moreover, NOX gases produced during combustion can lead to the formation of NNN in Dark-fired tobacco. See Figure 7, below.

![Figure 7](image_url)

**Figure 7.** The mechanism of NNN formation in tobacco.

For much of the 2000s, manufacturers and university researchers focused on developing so-called low converter (LC) seed varieties to help reduce NNN formation in tobacco leaf relative to earlier generations of seed varieties. LC seed is derived from tobacco plants screened for low conversion rates of nicotine to nornicotine due to low levels of Nicotine Demethylase. While LC seed varieties diminish nornicotine production to a greater extent than non-LC varieties, they

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remain the same as the original variety with respect to yield, quality, agronomic character and
disease resistance. See Figure 8 for the impact of screening for the LC phenotype on nicotine to
nornicotine conversion.


As early as 2003, some industry buyers of Burley and Dark tobaccos were encouraging their
contract growers to use LC varieties. Thereafter, the Kentucky-Tennessee Burley tobacco
breeding program re-released existing burley varieties as “LC” varieties and began to use this
designation for easier identification. Dark tobacco varieties carrying the “LC” designation soon
followed. In addition, seed companies discontinued production of non-LC varieties and withdrew
existing seed inventories from the market. Since 2005, the use of LC varieties for the production
of Dark and Burley tobacco has been the standard in the U.S. and many other parts of the world.
While LC seed has limited NNN formation, it cannot eliminate or cap it, or control for variability
in NNN levels resulting from the weather. Nor can LC seed produce tobacco that meets FDA’s
proposed 1ppm standard on a consistent basis.28

Building on industry efforts to develop and use LC seed, and with the specific goal of stabilizing
LC seed and preventing it from reverting back to a “converter” status, certain manufacturers and
universities developed ZYVERT™ technology.29 We believe this technology could reduce NNN
levels approximately 70% in finished smokeless tobacco products compared to products with

28 Like many of FDA’s other suggestions about ways to meet the proposed standard, the use of commercially
available LC varieties has already been implemented across the industry and will not produce additional incremental
reductions in NNN levels.
29 Scientists at USSTC, as well as at the University of Kentucky and North Carolina State University (funded by
Philip Morris USA, now an affiliate of USSTC), independently developed low NNN technology and respectively
own several U.S. patents related to these technologies, including U.S. Patent Nos. 8,319,011 and 9,247,706 and
others. The ZYVERT trademark is used to identify tobacco seeds, plants and leaf having low NNN technology.
tobacco leaf grown using LC seed.\textsuperscript{30} While a major stride in reducing NNN levels, ZYVERT\textsuperscript{TM} technology does not lower NNN levels enough to achieve consistent compliance with a 1ppm product standard because NNN levels are still subject to uncontrollable variations in the weather during curing. Leaf containing ZYVERT\textsuperscript{TM} technology has not yet been incorporated into commercially available products.\textsuperscript{31}

Efforts to develop and implement LC seed and to develop ZYVERT\textsuperscript{TM} technology show that, despite many years of work and the expenditure of tens of millions of dollars, FDA’s proposed product standard remains technically unachievable.

Finally, in the PRIA FDA suggests that selection of appropriate seed varieties is one way farmers may be able to produce low NNN tobacco leaves.\textsuperscript{32,33} FDA’s suggestion seems to subvert Congress’s clear intention that FDA not regulate how those farmers produce tobacco leaf.\textsuperscript{34} FDA’s explanation that “[p]reventing NNN levels from increasing during production is possible through changes in farming, harvesting and curing methods, though these changes are not ‘directly’ required by this rule . . .”\textsuperscript{35} rings hollow. FDA has focused directly on driving such changes in agricultural practices. In any event, it is the effect of the rule, not the FDA’s intent, that matters. Given that USSTC has currently eliminated any increased NNN from the time it purchases the leaf, any further reduction in NNN, if possible, would have to come at the farm level. There is simply no escaping that the effect of the rule would be to regulate farming practices.

3. Good Agricultural Practices on the Farm Have Helped Reduce, But Cannot Cap or Eliminate NNN Formation

Beyond research on seed varieties, prior efforts to reduce NNN have focused on fertilizer application rates, barn structure, ventilation (including stick spacing in the barn) and temperatures associated with the curing process. This work identified other steps that farmers could take to limit NNN formation. These steps are included in the Good Agricultural Practice

\textsuperscript{30} ZYVERT\textsuperscript{TM} technology works by mutating the three genes in tobacco that encode for the enzyme Nicotine Demethylase, the principal enzyme involved in the biosynthesis of nornicotine from nicotine. These mutations permanently eliminate production of Nicotine Demethylase, and thus, substantially reduce the biosynthesis of nornicotine from nicotine. Since nornicotine is nitrosated to form NNN, elimination of Nicotine Demethylase results in approximately 70% reduction in nornicotine and subsequent NNN levels.

\textsuperscript{31} We have shared information about this technology with FDA, and have been advised that use of leaf from ZYVERT\textsuperscript{TM} tobacco in any product requires us to obtain market orders for each. See also Section VII, below, regarding our concerns about the current Substantial Equivalence process and its interplay with the Proposed Product Standard, if finalized.

\textsuperscript{32} PRIA at 97 (“…[I]n response to demand for low NNN tobacco leaves, farms may need to select the appropriate tobacco seed variety.”).

\textsuperscript{33} We assume that in referring to “Variety,” FDA intended to use the word “Type.” In the tobacco growing community the term “Type” refers to differences in the major classes of tobacco such as Flue-Cured, Dark, Burley and Oriental. The term “Variety” refers to different genetic lines of the same tobacco type, each line having different performance characteristics such as days to flowering, disease resistance and susceptibility, leaf angle, leaf spacing and the like. For example, for the Dark tobacco Variety NL Madole, Dark tobacco is the tobacco Type and NL Madole is the Variety.

\textsuperscript{34} See FDCA §901(C)(2)(A-C).

\textsuperscript{35} PRIA at 44.
(GAP) protocols that are provided to the farmers to assist them in producing a high quality crop while minimizing undesirable tobacco properties, such as NNN. Since the 2005 crop year, USSTC has included certain harvesting and curing practices requirements in its contracts with farmers, which are based on GAP protocols. These steps help reduce, but cannot cap or eliminate, the formation of NNN on the farm. Specifically, USSTC’s current contract requires farmers to:

- Use LC or screened seed certified by either Kentucky or Tennessee (discussed in Section II(C)(2), above).
- Use fertilizer in amounts appropriate for tobacco and apply in accordance with the application rates and methods recommended by university production guides or similar authorities.
- Cure in barns with adequate ventilation that avoids high relative humidity and prevents house burn. If using outdoor structures, keep the tobacco covered.
- House (in the case of Dark fire-cured tobacco) such that stick spacing is a minimum of 8” in a non-lapped barn and a minimum of 12” in a lapped barn.
- Cure (in the case of Dark fire-cured tobacco) such that interior temperature in each curing structure does not exceed 130°F.
- House (in the case of Dark air-cured tobacco) such that stick spacing is a minimum of 12” in a non-lapped barn and a minimum of 16” in a lapped barn.

GAP protocols and USSTC’s contract requirements have their limitations, but have proven effective in limiting NNN formation. Given that these techniques have been in widespread use by farmers for over 10 years, however, their continued use will not further reduce NNN formation. FDA’s belief that such actions could further reduce NNN from current levels is mistaken.

4. USSTC Has Successfully Prevented NNN Formation From the Time it Purchases Tobacco Leaf From Farmers Through the End of Retail Shelf Life

Since Hoffmann et al.’s 1974 publication that identified NNN in tobacco, USSTC has worked to prevent NNN formation in its products. In addition to the work with farmers and university

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37 See PRIA at 44 (“Preventing NNN levels from increasing during production is possible through changes in farming, harvesting and curing methods, though these changes are not directly required by this rule. We expect that manufacturer interest in purchasing tobacco blends with lower NNN content will result in growers making such changes in response to regular market forces.”).
researchers discussed above, USSTC implemented procedures in the manufacturing process more than a decade ago that prevent NNN formation from the time USSTC purchases tobacco leaf from farmers through the end of retail shelf life of the product.

Much of our work since the mid-70s has focused on trying to identify the steps in the manufacturing process where TSNA formation, including NNN, occurs and develop ways to limit such activity. Our work began to show appreciable results with 75 to 85 percent reduction in TSNA levels from 1980 to 1992, as reported in the scientific literature (Figure 9).³⁹

![Figure 9. Total TSNA levels (NNN represents ~40% of the total) in USSTC products from 1980 – 2006. Blue line indicates data from published literature. Red line indicates USSTC internal data.](image)

We began to understand that certain bacterial cells and spores derived from purchased leaf which remained in our finished products, contributed to increasing NNN levels beyond those found in the tobacco leaf at the time it was purchased directly from farmers. As with wine and cheese, bacteria play a vital role in our almost 200 year-old fermentation process that gives the end product its unique and desired qualities. To reduce NNN levels, we focused on separating and characterizing those essential bacteria from other, nonessential bacteria. We found that these nonessential bacterial increases levels of nitrite, pH and moisture, which resulted in increased NNN levels. To address this, we started to “select” fermentation seed⁴⁰ with significantly reduced levels of nitrate reducing bacteria and saw further NNN reductions in our products. At the same time, we began to develop a cleaning and sanitation program that would further minimize levels of these nitrate reducing bacteria remaining on equipment between manufacturing runs.

In 2001, we started to modify our manufacturing process through a program called Vertically Integrated Process Management (VIPM). One of the goals of VIPM is to prevent NNN formation from the time USSTC purchases tobacco leaf from farmers through the end of retail shelf life.


⁴⁰ The use of a small amount of fermented tobacco provides reproducible initiation of fermentation and also provides competitive microflora (fermentation bacteria) to mitigate potential proliferation of nitrate-reducing bacteria.
Part of the VIPM program involves using production equipment that can be easily sanitized and examining each and every production batch for TSNAs. By 2005, we had achieved our goal of preventing any increase in NNN from the time we purchased the leaf from farmers through the end of the product’s retail shelf life. (See Figure 10, below). In 2012, we published the results of our efforts and concluded that “TSNA levels in MST do not increase beyond levels in cured tobacco when production [manufacturing] practices limit the presence of nitrate reducing bacteria.”

Following implementation of VIPM, we continued looking for additional ways to stabilize NNN levels in our products. This work led to the observation that the addition of low levels of sodium chlorate at the beginning of our fermentation process, along with cleaning and sanitation, prevented increases in nitrate reducing bacterial populations. We believe that sodium chlorate is a competitive inhibitor to nitrate when placed in contact with nitrate reducing bacteria. Maintaining nitrate reducing bacterial cell counts (as is or from germinating spores) below a certain threshold level needed to increase nitrite concentrations, therefore, prevented NNN formation from fermentation through the end of retail shelf life. As a result, we incorporated sodium chlorate across all USSTC’s MST product lines. The result is that, like Swedish Snus, the NNN levels in our products do not increase during manufacturing and retail shelf life from the levels that exist when the leaf is purchased from the farmer. Figure 11 shows the results for Copenhagen® Snuff.

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41 Fisher (2012).
42 U.S. Patent 9,271,524 (issued March 1, 2016).
5. FDA’s Suggested Blend or Curing Changes to Meet the Proposed Product Standard are Simply Unworkable

As explained in detail above, USSTC and its contract farmers have already implemented essentially all of FDA’s suggested methods to meet the proposed product standard. Still, FDA’s proposed standard remains technically unachievable.

FDA acknowledges, correctly, that no cost-effective technologies currently exist to reduce NNN levels at the finished product stage. FDA’s remaining suggestions focus on the sources of tobacco used in smokeless tobacco products and blending and curing changes. These suggestions are either outright unachievable or, even if achievable in theory, would so change the fundamental character – the texture, flavor, aroma and taste – of smokeless tobacco products, like MST, that adult tobacco consumers would not recognize or accept them – creating a de facto ban.

See PRIA at 44 (“FDA’s tobacco subject matter experts have noted that no cost effective technologies currently exist to reduce NNN levels at the finished smokeless tobacco product stage, so we believe that compliance activities will follow techniques for controlling NNN levels earlier in the production process, with the most likely method being the purchase of tobacco varieties and blends which have lower NNN levels. Preventing NNN levels from increasing during production is possible through changes in farming, harvesting and curing methods, though these changes are not directly required by this rule. We expect that manufacturer interest in purchasing tobacco blends with lower NNN content will result in growers making such changes in response to regular market forces.”).
a. FDA Mistakenly Assumes That Because a Small Volume of Snus Products Manufactured by Swedish Match Using Foreign Tobacco Can Meet the 1ppm Limit, All Smokeless Tobacco Products Can Meet It

In multiple provisions of the TCA, Congress charged FDA with achieving a “level playing field between domestic tobacco growers and foreign tobacco growers with regard to the development and implementation of any tobacco product standard.” Given this intent, FDA cannot satisfy the technical achievability requirement by driving manufacturers to foreign growers. It would be particularly unfair to punish U.S. farmers for living and working where the humidity during curing season is higher than in the areas of foreign countries where Dark tobacco is grown. In any event, foreign sources could not produce the necessary volumes of compliant Dark tobacco to meet U.S. demand.

FDA asserts that its proposed standard is technically achievable for all smokeless tobacco products because certain of Swedish Match’s snus products manufactured in Sweden, which are compliant with its own internal GothiaTek® standard, can meet the 1 ppm limit. FDA asserts further that “smokeless tobacco product manufacturers would have flexibility in identifying appropriate methods or processes for reducing the NNN level in their products.” And FDA “assume[s] both that tobacco leaves with lower NNN levels would be generally available and that the practices that result in reducing NNN levels can be readily adopted.”

FDA’s rationale is flawed, however, because it fails to recognize that these Swedish Match snus products constitute such a small part of the overall U.S. smokeless market – less than 1% – that Swedish Match can selectively purchase the very limited volume of low NNN tobacco it needs; that the global supply of low NNN Dark tobacco available cannot meet the demand of the U.S. MST marketplace; and even if such a sufficient global supply of low NNN Dark tobacco existed, implementation of a 1 ppm limit would severely prejudice U.S. tobacco farmers relative to tobacco farmers elsewhere in the world, which is impermissible under section 907.

By relying on the existence of a relatively few snus products with a very small U.S. market share by one manufacturer to justify the technical achievability of its proposed product standard, FDA failed to consider, or even acknowledge, that to comply on a larger scale manufacturers would also need to be highly selective in purchasing tobacco. There is, however, only a very limited amount of available U.S. Dark tobacco leaf that will yield a compliant product in any given year. Therefore, manufacturers would reject a large portion of the crop after it had been financed and grown by small family owned farms. A strategy of such highly selective purchasing would only

45 See 82 Fed. Reg. at 8015 (“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. . . . 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.”).
46 82 Fed. Reg. at 8019 (“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. . . .”).
47 PRIA at 40.
work for niche product manufacturers with limited volumes, not for the manufacturers of 99% of the smokeless tobacco products sold in the U.S. It would also be devastating to farmers, who would not know until after they had invested in growing and curing a crop how much of it, if any, could be sold.

As explained in the background section above, Swedish snus differs significantly from MST and other smokeless tobacco products typically sold in the United States. Swedish Match has not made public its source countries. Nevertheless, Swedish Match purchases all the Dark tobacco it uses to produce its snus from foreign countries such as Guatemala, the Philippines and South Africa where the curing season coincides with extremely low humidity levels. These low humidity levels help limit NNN formation. By contrast, some domestically produced snus have NNN levels above the proposed 1 ppm NNN limit due solely to the source of the tobaccos used.

Using the amounts of Dark tobacco grown in Guatemala, the Philippines, and South Africa as an example can provide some context about sourcing challenges for low NNN Dark tobacco. We estimate that farmers in these three countries will produce about 23 million pounds of Dark tobacco. We also estimate that Swedish Match will purchase about 8-10 million pounds of Dark tobacco for snus production in 2017. If Swedish Match acquired all its 2017 Dark tobacco from these three countries, it would leave about 13-15 million pounds for purchase by others. If the FDA required USSTC and other U.S. manufacturers to abandon U.S. farmers and purchase from these countries, and even assuming the remaining 13-15 million pounds all met a 1 ppm limit – which will not be the case since Swedish Match already selectively purchases the lowest NNN tobacco – the remaining supply still falls far short of replacing the approximately 73 million pounds grown annually in the United States.

It is unrealistic and impractical to base a standard on the assumption that these countries could increase their production four to five fold in three years given limited amounts of available and suitable land and a finite number of farmers with the expertise to grow tobacco.

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48 See 82 Fed. Reg. at 8009 (“Moist snuff is the most popular type of smokeless tobacco in the United States. It is typically made of fire-cured or air-cured tobacco that has been finely ground or shredded and fermented. Moist snuff may contain up to 60 percent moisture and it is often flavored (e.g., wintergreen). . . . Swedish snus is commonly used in Sweden but it is relatively new to the U.S. market. It typically consists of low-nitrosamine tobacco that has been air-cured, moistened, ground, and heat treated. Swedish snus may contain up to 50 percent moisture and some flavoring but no added sugars.”) (references omitted).

49 In Guatemala, for example, Dark air-cured tobacco is grown mainly along the south coastal region and cured during the dry months of December through May. In the Philippines, Dark air-cured tobacco is grown in the Agoo region, which is north of Manila, and cured during the dry months of October through March. Finally, in South Africa, Dark air-cured tobacco is grown in the Rustenburg region and is cured in the dry months of October through March.

50 82 Fed. Reg. at 8010 (“In recent years, some U.S. tobacco manufacturers began introducing snus products . . . in the United States. . . . Studies indicate that early versions of these snus products would not comply with the current GothiaTek standard for NNN and NNK . . .”) (references omitted).

51 Even if one assumes that production could be ramped up in these countries, it would take at least 10 years to build the necessary infrastructure to produce the amount of tobacco needed to meet U.S. demand. Under no circumstances could it happen in the 3 years FDA proposes before the effective date of its proposed 1 ppm standard.
In addition to Guatemala, the Philippines and South Africa, there are a number of other foreign countries where farmers grow Dark tobacco, but most do not have a history of producing Dark tobacco with low NNN levels. Moreover, many of them have not consistently produced the high quality tobacco that U.S. consumers demand and/or have not satisfactorily addressed concerns related to social responsibility. As a result, we made the decision not to source tobacco from those countries for use by Altria tobacco operating companies, such as PM USA, that do use foreign sourced tobacco in their products. Not sourcing tobacco from countries with these issues reduces the Dark tobacco available for purchase by approximately 126 million pounds, leaving only 70 million pounds available for purchase in the remaining foreign countries that grow Dark tobacco. And, there is no evidence that the remaining 70 million pounds could meet the 1 ppm standard.

Importantly, there is no international source that can replace the Dark fire-cured tobacco grown in the U.S. As described earlier, U.S. Dark fire-cured tobacco is cured by fires smoldering hardwoods such as hickory or oak. The smoke compounds from these fires interact with the tobacco leaf to create a unique taste, flavor and aroma. Foreign producers generally do not have access to these hardwoods and often substitute animal fodder, corn cobs and other types of trees, such as eucalyptus, during the firing process. Using substitutes for hardwoods produces much lower leaf quality overall and substantially higher NNN levels than those produced in the U.S.

The bottom line is that there is nothing further U.S. farmers can do to meet the 1 ppm standard, and there is not nearly enough high quality, low NNN Dark tobacco available on the global market to make compliance with a 1 ppm standard achievable at the volumes required by U.S. manufacturers.

b. Using Flue-Cured Tobacco Instead of Dark Tobacco in Smokeless Tobacco Products is Not Commercially Feasible

FDA suggests that changing the type of tobacco varieties and blends used in smokeless products (e.g., from Dark tobacco to Flue tobacco, which generally has lower levels of NNN than Dark tobacco) is one way manufacturers could meet the proposed 1 ppm limit. But the reason Dark tobacco is used is that it gives consumers what they want – texture, aroma and good taste. Substituting Flue-Cured tobacco would so fundamentally – and detrimentally – change smokeless tobacco products that adult consumers would reject them. Allowing manufacturers to

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52 Bangladesh, India, Indonesia, Mexico, Poland, South Africa and Uganda.
53 In addition, most of the foreign countries that grow Dark tobacco (see Section I(C), above) are signatories to the World Health Organization’s Framework Convention on Tobacco Control (FCTC), which has a goal of helping transition tobacco growers and workers to other crops. See World Health Organization Framework Convention on Tobacco Control, arts. 4, 17, 21, May 21, 2003-June 29, 2004, WHA56.1, 2302 U.N.T.S. 166, 42 I.L.M. 518, available at http://www.who.int/fctc/cop/en/ (last visited June 29, 2017).
54 See e.g., 82 Fed. Reg. at 8013, 8018; PRIA at 96-98. FDA also notes that “[i]n response to demand for low NNN tobacco leaves, farms may need to select the appropriate tobacco seed variety and implement production techniques that result in lower NNN levels. Upon implementation of the rule, some farms may shift acreage from growing higher NNN level tobacco to those seed varieties that result in tobacco plants with lower NNN levels, or producing other agricultural products.” PRIA at 98.
make and sell only smokeless products that consumers do not want is no different than banning
the products they do want.

Dark tobacco’s large, thick leaves help maintain the structural integrity of the product when it is
placed in the mouth. Dark tobacco also imparts a unique texture, color, flavor, aroma and taste
that adult tobacco consumers expect and enjoy. Flue-Cured tobacco, on the other hand, lacks the
textural components and structural integrity of Dark tobacco. Flue-Cured tobacco’s thin leaves
would break down and disintegrate in the mouth while imparting a bitter taste – neither of which
would satisfy an adult smokeless tobacco consumer. In addition, replacing Dark tobacco with
Flue-Cured tobacco in MST products results in the formation of texturally non-homogenous
product (the resulting condition is sometimes referred to as “aggregated balls”). This would be
unacceptable to the adult tobacco consumer and also make it difficult to maintain consistency of
the product when manufacturers add ingredients like flavors and salts.

FDA’s suggestion is akin to telling a farmer to substitute field corn for sweet corn in selling to
consumers. Both are corn, but field corn, fed to animals, is fundamentally different in taste and
texture from the sweet corn bought by consumers. Requiring farmers to grow only field corn that
no one would eat effectively bans corn from the consumer market. FDA’s implied suggestion to
substitute Flue-Cured tobacco for Dark tobacco in smokeless tobacco products as a way to meet
the 1 ppm standard is not a solution at all – it is a backdoor ban of MST and chewing tobacco
which have been in use for hundreds of years, are currently used by more than 8 million adult
tobacco consumers, and constitute 99% of the smokeless category.

c. Using Flue-Cured Tobacco Instead of Dark Tobacco in Smokeless
Tobacco Products is Not Feasible Because Farmers in Kentucky
and Tennessee Cannot Grow Flue-Cured Tobacco

Even if smokeless tobacco consumers would accept radically different products made with Flue-
Cured tobacco,55 the FDA ignores the reality that the land and growing seasons in Kentucky and
Tennessee are not conducive to growing Flue-Cured tobacco and that the infrastructure and
knowledge to grow and cure Flue-Cured tobacco in that region does not exist.

The soil in Kentucky and Tennessee, where Dark tobacco production is concentrated, is nutrient
rich – a critical factor in growing Dark tobacco and creating its unique and desired
characteristics. Flue-Cured tobacco, on the other hand, is grown in the sandy loam and nutrient
deficient soil found in places like the coastal regions of Virginia, North and South Carolinas and
Georgia. Due to the differences in soil needs for Dark and Flue tobacco, farmers in Kentucky and
Tennessee could not successfully grow Flue-Cured tobacco on their farms.

In addition, the Dark tobacco growing season in Kentucky and Tennessee, which runs from May
to August, is too short for successful Flue-Cured production. Flue-Cured tobacco requires the
longer growing season of places like Virginia, North and South Carolinas and Georgia, which
runs from April to September, and sometimes as late as early November.

55 See e.g., 82 Fed. Reg. at 8013, 8018; PRIA 96-98.
Skills, knowledge and infrastructure developed over generations by Dark tobacco farmers would not directly or quickly transfer to Flue-Cured production. For example, the approximately 8,000 barns used by farmers in Kentucky and Tennessee to cure Dark tobacco could not be retrofitted to cure Flue-Cured tobacco. Instead, farmers would need to purchase new barns, at a cost of approximately $40,000 – 68,000 per barn. Differences in how Dark and Flue-cured tobacco is harvested also would create economic disincentives for farmers in Kentucky and Tennessee to switch to growing Flue-Cured tobacco. Dark tobacco is harvested by hand while much of Flue-Cured harvesting is mechanized. Farmers would have to purchase new, expensive machinery to harvest Flue-Cured tobacco in an economically efficient way. A typical Flue-Cured tobacco harvester can cost $90,000 – 110,000. On top of that, the yield per acre and price per pound of Flue-Cured tobacco are both about 30% less than for Dark tobacco. The reality is that the massive losses farmers would suffer from the demise of their Dark tobacco business, coupled with the costs of transitioning to Flue-Cured tobacco production would force the approximately 1,200 Dark tobacco farmers in Kentucky and Tennessee to walk away from Dark tobacco production altogether.

d. Changing Curing Techniques for Dark Tobacco is Not Practical and Would So Fundamentally Change Smokeless Tobacco Products That Adult Tobacco Consumers Would Reject Them

FDA suggests, incorrectly, that manufacturers could meet the proposed 1 ppm limit if farmers changed the curing techniques they currently use for the Dark tobacco.\textsuperscript{56} Presumably, FDA is proposing that Dark fire-cured and Dark air-cured tobacco could be cured like Flue tobacco or that Dark tobacco could be air-cured exclusively. Neither suggestion is practical, and, even if they could be implemented, would so fundamentally change current smokeless tobacco products that adult tobacco consumers would reject them.

As described in Section I, above, flue-curing is a rapid curing process that usually takes 7 to 9 days. Tobacco types amenable to flue-curing have thin leaves. To prepare the leaf for curing, the farmer stacks tobacco leaves in racks or boxes and then places them in the barn. The tobacco is then basically heated in the barn in a manner similar to a convection oven. During the relatively short flue-curing process, there is insufficient time for the leaves’ components, like sugars, to break down and the leaf is essentially dried to a point of suspended animation. This process results in a leaf with a bitter taste.

Dark fire-curing and air-curing, on the other hand, are slower curing processes. Dark-fire curing takes approximately 35 to 45 days, and Dark air curing takes approximately 28 to 42 days. In contrast to Flue tobacco, Dark tobacco has large, thick leaves. Stacking these large thick leaves on top of each other in the barn, as is done in flue curing, could actually create microbial “hot spots” that could lead to increased NNN formation. Stacking the leaves could also create scalding of the leaf and uneven curing, which would result in a lower quality leaf. The slower curing process for Dark tobacco allows the leaf to mellow and is a key factor in producing its unique color, texture, aroma and flavor. The shorter flue-curing process would fail to produce these same attributes. Just as consumers who crave a spare rib smoked for hours over a low,

\textsuperscript{56} Id.
hardwood flame would reject one seared for five minutes over blaring heat, leaving it tough and flavorless, adult tobacco consumers would reject smokeless products with flue-cured Dark tobacco.

Air-curing all Dark tobacco is not a practical solution either. First, Dark air-cured tobacco does not always have lower NNN levels than Dark fire-cured tobacco. Air-cured tobacco in smokeless products would dramatically change the flavor, aroma and taste of smokeless tobacco products that are on the market today.

e. FDA’s Other Suggestions for Meeting a 1 ppm Standard are Speculative or Unworkable

Bacterial Control: FDA suggests treating tobacco with a bacteriostatic, bactericidal or heated solution during growing, harvesting or curing to reduce the number of bacteria in the tobacco leaf and thereby reduce the NNN levels. The only bactericide approved by U.S. Environmental Protection Agency (“EPA”) for use on tobacco is streptomycin, which is used to control certain bacterial diseases that are rarely observed during the growing season. The use of streptomycin in tobacco is somewhat limited, however, due to its low efficacy. To our knowledge, the residual carryover and bacterial resistance potential for widespread use of streptomycin have not been studied. Furthermore, Burton et al. examined tobaccos treated with streptomycin and rifampicin and reported no impact on the reduction of nitrate reducing bacteria or nitrosamines. FDA cites no research, and we are aware of none, that supports FDA’s speculation that treating tobacco might lower NNN levels.

Reducing Humidity During Curing: FDA suggests improving air circulation in barns as a means to reduce humidity during curing. What FDA fails to take into account is that many of the approximately 8,000 structures used to cure Dark tobacco in Kentucky and Tennessee are old and often in remote areas without electrical service, precluding the use of electric fans, dehumidifiers and other similar systems. It would be cost prohibitive for farmers to run electricity to these structures. In addition, mechanically reducing humidity in curing structures by use of dehumidifiers is not possible for existing Dark tobacco barns because they are designed to facilitate tobacco drying through natural airflow; they cannot be sealed sufficiently such that mechanical dehumidification would be effective.

Finally, these suggestions, like several others FDA makes, reach down to the farm in a way that impermissibly regulates how farmers grow tobacco. The TCA expressly makes that area off-limits to FDA.

57 See Figures 1 and 2, above.
58 82 Fed. Reg at 8014.
60 82 Fed. Reg. at 8018.
III. In Many Other Respects The Proposed Standard is Arbitrary, Capricious, and Contrary to Law

The APA requires agencies to employ a thorough, reasoned, and balanced process in adopting new regulations. As it stands now, the proposed NNN standard does not reflect such fair and thoughtful consideration. The standard, and FDA’s explanation of it, rest on flawed assumptions and calculations that make it impossible to provide meaningful comments; overlook meaningful distinctions among categories of products; do not adequately consider the interests of tobacco farmers; fail to develop facts critical to the assessment of the likely costs and benefits; and neglect to analyze a practical and incremental alternative approach.

A. FDA’s Use of Flawed Assumptions and Erroneous Calculations to Support the Proposed Standard Fail to Satisfy the Regulatory Flexibility Act, the Administrative Procedure Act, and the Basic Due Process Rights That Drive Notice and Comment Rulemaking

On March 7, 2017, USSTC notified FDA of a critical flaw in FDA’s calculations to support the Proposed Product Standard. Specifically, FDA used two different and conflicting formulas to calculate the dry weight basis of NNN levels in finished smokeless tobacco products in key portions of the Proposed Rule. We pointed out that the two formulas are fundamentally different, and only one can be correct. The question of which formula is correct and should be applied makes a significant difference in assessing the Proposed Product Standard. Depending on which formula is applied, the consequences change dramatically with respect to issues such as technical achievability, the associated percentages of products that FDA posits could meet the Proposed Product Standard, and the resulting economic impact on U.S. tobacco farmers and manufacturers, among others.

On March 22, 2017, the FDA extended the comment period on its Proposed Rule. In granting the extension FDA conceded that it incorporated an incorrect formula for calculating NNN on a dry weight basis from NNN measured in the final product on a wet weight basis. While acknowledging the error, FDA stated that the error did not affect the analyses related to the Proposed Rule.

As explained below, the FDA’s estimated compliance rates with the Proposed Product Standard are implausible. In all likelihood, they resulted either from the use of the erroneous formula or from a misinterpretation of the industry reports of NNN submitted to FDA under Section 904 of the FDCA. Because it appears that FDA’s formula, analysis, and assessment are erroneous, FDA’s decision simply to extend the time for the submission of comments is inadequate. FDA should withdraw the Proposed Rule and use the corrected formula to conduct the required analysis and assessment before issuing any new proposed rule. Only then can the public understand and meaningfully comment on the Proposed Rule.

For example, in its PRIA, FDA does not provide any meaningful information about FDA’s calculations regarding the current level of manufacturer and product compliance with the Proposed Product Standard. This silence on such a critical element of the PRIA makes it impossible to ascertain whether FDA used the incorrect formula in its calculations or misinterpreted the NNN values that were submitted under Section 904 on a wet weight basis as being on a dry weight basis. Based on our knowledge of NNN levels in our products and some information regarding NNN levels in competitor products, we conclude that FDA used the incorrect formula or misinterpreted the submitted values for determining compliance throughout the PRIA, resulting in a fundamentally flawed assessment of achievability and economic impact.

As one illustration, the PRIA estimates that 30% of currently marketed MST products are already in compliance with the proposed product standard and that another 29% of current products are “nearly compliant.”63 These numbers simply cannot be correct. The values submitted by USSTC under Section 904 for its MST products were on a wet weight basis and identified as such. When these values are converted to a dry weight basis, as required under the Proposed Rule, none of these products would be compliant with the Proposed Rule. Since USSTC products represent approximately over 50% of the currently listed MST products, in order for 30% of the total listed products to be compliant, as calculated by FDA, an implausible 60% of the non-USSTC products would have to be compliant with the 1 ppm limit. However, if FDA misinterpreted the NNN values submitted under Section 904 as already on a dry weight basis, then just under half of the USSTC products would appear to be compliant, roughly consistent with the proportion estimated by the FDA for all of the MST products. Had the agency correctly interpreted the submitted values and used the correct formula, the estimated industry compliance rates for MST products would be significantly lower, likely very close to zero.

Because FDA’s cost estimates are predicated on the agency’s flawed compliance calculations, these estimates also appear to be fundamentally inaccurate. For example, the PRIA assumes that it will cost manufacturers between $86.13 million to $314.36 million to reformulate their products to comply with the proposed standard and other proposed requirements.64 These estimates, however, are based on the erroneous assumption that many currently marketed smokeless tobacco products are already in compliance, or “nearly compliant,” with the proposed product standard. FDA’s compliance assumptions are critical to an assessment of the economic impact upon tobacco growers, manufacturers, and others in the distribution chain, as well as on the technical achievability of the rule. FDA’s apparent erroneous cost estimates, therefore, undermine the entire Proposed Rule.

Because the PRIA’s opaque – and now apparently erroneous – calculations make it impossible to assess and comment meaningfully on the regulatory assumptions and conclusions underlying the proposed rulemaking, FDA has not provided stakeholders with the adequate notice and opportunity for comment required by federal law.

Extending the comment period does not help when the problem is that USSTC cannot know on what assumptions and calculations it is commenting. The Proposed Rule is based on a

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63 PRIA at 25-26.
64 PRIA at 53.
fundamental error in calculating dry weight levels of NNN, which drives the FDA’s assessment of current compliance as well as the cost of compliance for those not already there. These are two critical parts of the FDA’s required regulatory assessment, but we simply cannot know what we are responding to until the FDA uses the correct formula to produce accurate assessments.

The need for a meaningful opportunity to comment is all the more important in light of the enormous consequences that the proposed rule, if finalized, will have on the economies and lives of farmers and communities in western Kentucky and Tennessee, manufacturers, and consumers. Before FDA proposes a rule that threatens to destroy industries and companies, to say nothing of family economies, it should make sure that the proposed rule is based on correct formulas and correct interpretation of submitted values, correct analyses, and correct assessments. Nothing less satisfies the Regulatory Flexibility Act, the APA, and the basic due process rights that drive notice and comment rulemaking.

Finally, FDA’s flawed PRIA assumptions would invalidate FDA’s economic analysis and prevent the Office of Information & Regulatory Affairs (“OIRA”) within the Office of Management and Budget (“OMB”) from conducting a meaningful or accurate analysis of the Proposed Rule. Under Executive Order 12866 (Sept. 30, 1993) and Executive Order 13563 (Jan. 18, 2011), FDA is required to submit significant regulatory actions (like this one) to OIRA for review and clearance. To have meaning, that review must be based on a good faith preliminary estimate of the costs that would be imposed by the Proposed Rule.

Rather than simply extending the confusion, the FDA should withdraw the Proposed Rule now and head back to the drawing board armed with the right formula to conduct the necessary calculations and assessments. If it so concludes, it can then propose a new rule based on accurate information that allows stakeholders to understand and meaningfully comment on it. It should

65 See, e.g., 5 U.S.C. § 604(a)(2) (an agency’s final regulatory flexibility analysis must address all “significant issues raised by the public comments in response to the initial regulatory flexibility analysis”); id. § 611(a)(1) (authorizing judicial review); see also, e.g., Associated Fisheries v. Daley, 127 F.3d 104, 114 (1st Cir. 1997) (agency must make “a reasonable, good-faith effort to carry out the mandate” of the Regulatory Flexibility Act); North Carolina Fisheries Ass’n v. Daley, 27 F. Supp. 2d 650, 660 (E.D. Va. 1998) (“contradictory and confounding” economic impact analysis violated 5 U.S.C. § 604); Southern Offshore Fishing Ass’n v. Daley, 995 F. Supp. 1411, 1436 (M.D. Fla. 1998) (agency “could not possibly have complied with § 604” where it failed to provide an opportunity for comment).

66 See, e.g., Allied Local & Reg’l Mfrs. Caucus v. EPA, 215 F.3d 61, 79 (D.C. Cir. 2000) (the agency’s preliminary analysis under the Regulatory Flexibility Act is relevant to determining whether the agency “complied with the overall requirement that [its] decisionmaking be neither arbitrary nor capricious”) (collecting cases); see also, e.g., Doe v. Rumsfeld, 341 F. Supp. 2d 1, 15 (D.D.C. 2004) (final FDA rule vacated where the agency’s post-comment revisions to a proposed rule “deprived the public of a meaningful opportunity to submit comments and participate in the administrative process mandated by law”).


68 In addition, FDA should change its recommended test method from the one proposed in LIB 4623 to ISO/CD 21766 “Tobacco and tobacco products – Determination of tobacco-specific nitrosamines in tobacco products – Method using LC-MS/MS”. Although FDA’s proposed test method was validated by FDA, it lacks long-term stakeholder use and has not been evaluated in collaborative studies. On the other hand, ISO/CD 21766 was developed from CORESTA Recommended Method 72 and has been used in numerous, published collaborative
also prepare a new PRIA to be submitted to OIRA that clearly lays out FDA’s calculations concerning estimated compliance rates and associated implications and, if cleared, published for public comment. Any re-issued proposal must comply with the terms of the Executive Order 13771 on Reducing Regulation and Controlling Regulatory Costs (Jan. 30, 2017).69 If FDA does issue the standard as a final rule, it also must comply with the requirements of Executive Order 13771.

B. FDA Failed to Recognize Distinctions Between Different Tobacco Products that Make it Impossible for Some to Meet the Proposed Standard

An agency acts in an arbitrary and capricious manner when it “fail[s] to consider an important aspect of the problem” and overlooks material differences in regulated products.70 Here, in proposing a single NNN standard for all smokeless products, the FDA failed to consider crucial variations among smokeless tobacco products that make it possible for some to meet that standard at the same time that it is impossible for others, like MST and chewing tobacco, to do so.

FDA recognizes that a “wide range of products” fall under the definition of smokeless tobacco products, and that NNN levels differ substantially within and among the different subcategories.71 “The levels of NNN in smokeless tobacco products on the U.S. market can vary several fold, not only among different subcategories of products, but also among products in the same subcategory.”72

Despite acknowledging these differences, FDA did not propose a product standard tailored for each subcategory of smokeless tobacco products. Nor did FDA focus on the best practices and available technology for achieving reduced NNN levels for the kinds of smokeless tobacco products typically sold in the United States. Had FDA done so, it would have been able to assess the differences in NNN levels between Swedish snus, MST and chewing tobacco, and the costs and benefits of proposing an NNN reduction that can be achieved with reasonably available technology. Instead, FDA imposed a one-size-fits-all standard for smokeless tobacco products sold in the United States, regardless of subcategory. That standard, however, is ill-suited for all

71 See 82 Fed. Reg. at 8009 (“The term ‘smokeless tobacco’ covers a wide range of tobacco products that can be used orally or nasally without combustion . . . This includes moist snuff, snus, dry snuff, chewing tobacco and some dissolvables.”) (references omitted); Id. at 8006. (“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”) (references omitted).
72 82 Fed. Reg. at 8014 (citing studies of TSNA levels).
snus sold in the U.S., much less for all the other U.S. smokeless products it covers. FDA’s indiscriminate approach is arbitrary and capricious, and therefore violates the APA.

C. FDA Did Not Adequately Consider the Interests of Tobacco Growers

FDA acknowledges that “some of the spillover changes in practices resulting from the rule may occur at the tobacco grower level.”73 The Agency recognizes further that these changes could have dramatic consequences for a large number of tobacco growers,74 but FDA did not quantify impact on growers.75 That passing reference was the full extent of FDA’s assessment of an “important aspect of the problem”76 – the congressionally-protected interests of tobacco growers. That inattention fell far short of the meaningful consideration the APA requires.

During the extended legislative deliberations on the TCA, Congress added provisions limiting FDA’s authority to burden tobacco growers. The legislative history of these important protections sheds light on how they should be read together, and identifies the factors FDA should have considered before issuing a product standard harmful to growers.

By the fall of 2007, the Senate Committee on Health, Education, Labor and Pensions had considered and reported out an amended TCA, and the House Health Subcommittee was holding a hearing on it. At the hearing, tobacco growers expressed concern regarding FDA’s authority to adopt product standards jeopardizing their livelihood. For example, at the Subcommittee hearing on October 3, 2007, the Alliance for Health Economic & Agricultural Development (“AHEAD”) worried that the TCA would “allow the FDA to have influences [sic] indirectly over tobacco production through such things as performance standards.” AHEAD urged Congress to draft the TCA “to ensure that FDA does not have excessive and undue influence over tobacco production.”77

By March 2008, as the House authorizing committees marked up the legislation, tobacco growers were seeking specific changes to limit FDA’s product standard authority, beyond the provisions already included to allay the tobacco growers’ concerns. The bill as it stood barred FDA from directly regulating tobacco growers, tobacco warehouses, and tobacco grower cooperatives. It also prohibited FDA from banning a class of tobacco products or achieving a de facto ban by requiring the elimination of nicotine. Further, the bill required FDA to consider the potential that a product standard may trigger “a significant demand for contraband or other

73 PRIA at 97.
74 See id. at 96-98 (“[f]arms growing the tobacco varieties, such as dark air-cured and dark fire-cured, most commonly used in smokeless tobacco blends are concentrated in several counties within the states of Kentucky and Tennessee”). FDA also notes that “the physical and chemical composition of the raw tobacco leaves that are formed into modern snus products fluctuates from year to year, partially due to variations in climate, growing, and curing conditions. In response to demand for low NNN tobacco leaves, farms may need to select the appropriate tobacco seed variety and implement production techniques that result in lower NNN levels. Upon implementation of the rule, some farms may shift acreage from growing higher NNN level tobacco to those seed varieties that result in tobacco plants with lower NNN levels, or producing other agricultural products.” Id.
75 Id. at 97.
76 State Farm Ins., 463 U.S. at 43.
tobacco products that do not meet [FDA standards] and the significance of such demand.”78 The bill also directed that the effective date or dates established for a product standard “minimize, consistent with the public health, economic loss to, and disruption or dislocation of, domestic and international trade.”79 Tobacco growers viewed these safeguards as insufficient.

In the Subcommittee markup on March 6, 2008, Rep. Marsha Blackburn expressed these concerns to the Staff’s Counsel:

> What’s the point of having language in the bill that says the FDA can’t go on the farm if the FDA can put tobacco growers out of business all at one time going at it through a different route if the FDA can regulate the chemicals that are naturally occurring in the leaf and are not required to adhere to a technology standard to do so?80

The Dissenting views section of the Subcommittee’s Report echoed this “concern[] about provisions in H.R. 1256 which will affect our nation’s tobacco growers.”81 Even though “the bill purports to have no effect on tobacco growers,” the legislators believed that the bill made regulation of leaf cultivation and curing inevitable, and “might lead the FDA to require tobacco manufacturers to buy only certain types of tobacco which are grown or cured in specific ways.”82

The Committee accommodated the growers’ concerns by adding or strengthening important limits on FDA’s authority, such as the provision on technical achievability.83 Other provisions also reflect Congress’s intent to deny FDA authority to regulate crops out of existence. For example, the legislation recognizes that in some situations, a product standard may require “substantial changes to the methods of farming the domestically grown tobacco used by the manufacturer.”84 The phrase “substantial changes” modifies “methods of farming,” not “domestically grown tobacco used by the manufacturer.” That language contemplates potential changes in farming techniques, but not changes in the crop used in the production of a tobacco product as FDA acknowledges likely would be necessary for compliance with the Proposed Product Standard.85 Yet, as described above, the impact of the effect of the Proposed Product Standard will be to do just that – change the crop itself or render it valueless.

On the eve of enactment, Representatives from tobacco growing states obtained reassurances from sponsors of the legislation that these provisions would prevent FDA interference with agricultural decisions, like crop selection, as well as other threats to the growers’ businesses.

78 FDCA § 907(b)(2).
79 FDCA § 907(d)(2).
82 Id.
84 FDCA § 907(d)(2) (emphasis added).
85 PRIA at 97-98.
Rep. Etheridge, who “represent[ed] one of the largest tobacco-producing districts in the Nation,” asked whether “th[e] bill in any way authorize[s] the FDA to regulate tobacco farms?” Rep. Waxman, the lead sponsor of the bill, stated “[i]t is not the intent of this bill to allow FDA on the farm. The bill gives FDA the authority to regulate tobacco products but not tobacco leaf.”

FDA’s Proposed Product Standard validates the concerns of growers of Dark tobacco used to make smokeless tobacco products, and upsets the TCA’s carefully-crafted limitations on the agency’s ability to regulate farmers. As discussed above, growers of Dark tobacco leaf could not adapt their practices and continue to supply tobacco inputs for U.S. smokeless tobacco products. The available volume of tobacco leaf (although insufficient to satisfy U.S. demand) would instead come from farms located in other parts of the United States or overseas. This inevitable shift in tobacco leaf production away from current domestic growers would conflict with Congress’s directive to FDA to allow growers adequate time to adapt their practices so that FDA’s requirements do not drive them out of business.

The proposed NNN standard nowhere indicates that FDA even considered this glaring conflict. Thus, in this regard, too, FDA failed to consider an “important aspect of the problem,” and its Proposed Product Standard is therefore arbitrary and capricious.

IV. **FDA Failed to Consider, Let Alone Quantify, the Devastating Economic Impact That Would Result from Implementation of a 1 ppm NNN Limit for Smokeless Tobacco Products**

An agency considering a proposed rule must consider the full range of costs the rule would impose and the benefits it would achieve. FDA expressly limits its preliminary estimate of the costs of the Proposed Rule to those incurred by smokeless tobacco manufacturers to achieve compliance with the proposed rule and by the government to administer the necessary regulatory processes to help facilitate industry compliance.

Before proposing any product standard and especially one as draconian as a 1ppm NNN limit in finished smokeless tobacco products, FDA should have considered the potential economic impact on each component in the supply chain for smokeless tobacco products. Specifically,

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86 Congressional Record (April 1, 2009) at H4339 (emphasis added).
87 *State Farm Ins.*, 463 U.S. at 43.
88 As FDA acknowledges, it must examine the impacts of the proposed rule under the Unfunded Mandates Reform Act of 1995, the Regulatory Flexibility Act, and Executive Orders 12866 and 13563. See 82 Fed. Reg. at 8037. An agency’s cost benefit analysis containing “a serious flaw undermining that analysis can render the rule unreasonable.” Nat’l Ass’n of Home Builders v. E.P.A., 682 F.3d 1032, 1040 (D.C. Cir. 2012). See, e.g., *Business Roundtable*, 647 F.3d at 1152 (holding agency cost-benefit analysis was arbitrary because it “duck[ed] serious evaluation of the costs that could be imposed upon [regulated] companies”); *Competitive Enter. Inst. v. Nat’l Highway Traffic Safety Admin.*, 956 F.2d 321, 323 (D.C. Cir. 1992) (remanding fuel efficiency rule to agency because it failed “to conduct[] a serious analysis of the data and decid[e] whether the associated fuel savings are worth the lives lost”); *State of Texas v. EPA*, 499 F.2d 289, 315-16 (5th Cir. 1974) (remanding rule for agency to offer “satisfying explanations of why . . . some slightly lower target has not been adopted in order to avoid the ‘very high’ incremental costs of complex systems”).
89 PRIA at 40–95.
FDA should have considered and quantified the negative economic impact of its proposed product standard on Dark tobacco farmers and farm workers, workers in the manufacturing facilities, and the communities in which Dark tobacco is grown and manufactured.

A de facto ban of smokeless tobacco products would have a devastating economic impact throughout the smokeless tobacco product supply chain – from tobacco farmers and other farm workers to employees in smokeless tobacco manufacturing facilities to the wholesalers and retailers as well as the budgets of state and federal governments. And, due to the geographic concentration of where Dark tobacco is grown and much MST and chewing tobacco is manufactured, these negative economic impacts would be particularly crippling in the Hopkinsville, Kentucky area. FDA utterly and admittedly ignored the devastating economic impact that would result from implementation of its unachievable product standard.90

Had FDA conducted such an analysis, it would have learned that a large number of small, family owned farms will lose a stable and highly productive crop, which supports about 1,200 farm owners as well as a large number of field workers; that the shutdown of manufacturing facilities will lead to the loss of as many as 5,700 stable, well-paying jobs – some through direct effect and some through ripple effects and that hundreds of suppliers of intermediate goods serving the smokeless tobacco industry will lose a key client.

A. The Proposed Product Standard Would Decimate Dark Tobacco Farmers

Because it is impossible to meet, the FDA’s proposed product standard would decimate Dark tobacco farmers, who would no longer have a market for their most profitable crop. This loss of income could threaten the viability of many of these family owned farms because the profits from selling Dark tobacco help subsidize and sustain other crops and operations on these farms. The economic effects would reverberate throughout the farmers’ communities. Unfortunately, FDA made only a glancing reference to the potential burdens on growers, and concedes that it did not attempt to quantify them.91 The farmers, their families and communities deserve better.

Dark tobacco production in the U.S. is concentrated within about a 50-mile radius of Hopkinsville, Kentucky, including some northern counties of central Tennessee. In 2015, 24,000 acres of Dark tobacco yielded 73 million pounds and a cash value of $190 million.92 Some 1,200 farmers grow Dark tobacco in this region using about 8,000 barns each curing season.93 Many Dark tobacco farmers learned the skills and know-how growing and curing Dark tobacco from their parents and grandparents on farms that have grown Dark tobacco for more than a century. For many, Dark tobacco represents the largest cash-valued crop grown on their farms. As noted by one farmer in comments submitted to FDA, the “farm has been in my family for generations,

90 See, e.g., PRIA at 97.
91 Id. at 97.
93 ALCS internal estimates.
and I intend to pass on the legacy to my own son someday, who would be the fifth generation to raise tobacco on this land.” FDA’s proposed product standard directly threatens this legacy.

Farms that grow tobacco tend to be small, family owned operations that rely on tobacco for the majority of their income. In fact, 87% of tobacco farms nationwide are family or individually owned; 79% of tobacco farmers consider the farm their primary place of residence; and 83% of tobacco farmers had been at their farm for 10 years or more. Nationwide, of the farmers who grow tobacco along with other crops, 72% consider tobacco farming as their primary occupation.

Three key characteristics make the Dark tobacco grown in Kentucky and Tennessee such a valuable crop for the farmers who grow it, for their workers, and for the communities where it is grown. First, Dark tobacco is a **highly productive** crop, both in terms of revenue per acre and in terms of profits per acre. Second, it is an **economically stable** crop, and a large majority of the farms that grow it are profitable in any given year. Third, it is a **labor-intensive** crop, as it pays a large share of its total revenues in wages to farm workers.

First, Dark tobacco is a **highly productive** crop. Data from the U.S. Department of Agriculture show that revenue per acre for Dark tobacco ranges from $3,975 to $6,361 – between 6 and 21 times higher than other crops commonly grown in Kentucky and Tennessee such as soybean, cotton, and hay. Tobacco also has higher profit margin than most other crops, making it highly productive in terms of profits per acre. For example, profit margins for tobacco are 26%, compared to 27%, 14%, and 5% for soybean, cotton, and hay farming, respectively. Comments submitted by Dark tobacco farmers align with this data. One farmer states, “Even with just the small number of acres devoted to dark tobacco, it accounts for 30% of [my] business.” Another farmer reported that he “make[s] as much money off 20 acres of dark tobacco as [he does] from 1,000 acres of grain.”

Second, Dark tobacco is an **economically stable** crop. Data from the Census of Agriculture show that the share of tobacco farms that are profitable in a given year is higher than for other crops. Every year, 81% of tobacco farms are profitable compared to 77% of oil seed and grain farms.

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(including soybean farming), 73% of cotton farms, and 48% of sugarcane, hay and all other crop farms. Over the course of a few years, the differences between tobacco and other crops are compounded: the probability that a tobacco farm is not profitable for three consecutive years is less than 1%. For a hay farm, this probability is roughly 15 times higher.\footnote{This calculation assumes that profitability in one year is independent of profitability in the previous year. 2012 Census of Agriculture United States, Issued May 2014. Available at \url{https://www.agcensus.usda.gov/Publications/2012/Full_Report/Volume_1,_Chapter_1_US/usv1.pdf} (last visited June 29, 2017). See table 68 on p. 182-183.} For a small, family owned farm – and the majority of tobacco farms are just that – the stability offered by growing Dark tobacco is extremely valuable. The real life experiences of tobacco farmers confirm this data. As one farmer explained, “The other operations on the farm would not be enough to sustain the family business…. Over the years, when my grandfather and father were running the farm, they had other crops. If it was a bad season for corn or beans, they always had tobacco to help make ends meet.”\footnote{Comment from Bob Lawrence, \url{https://www.regulations.gov/document?D=FDA-2016-N-2527-0282} (last visited June 29, 2017).}

Third, it is a \textit{labor-intensive} crop. According to the Census of Agriculture, on an average tobacco farm 18\% of total revenue, which represent 24\% of total expenses, are paid out in wages to workers. Labor share of revenue in other crops that are common in the area range from only 3\% in the case of soybean to 13\% for hay. Thus, the labor share of revenue in tobacco is between roughly 1.5 and 6 times greater than other common crops in the region.\footnote{2012 Census of Agriculture United States, Issued May 2014. Available at \url{https://www.agcensus.usda.gov/Publications/2012/Full_Report/Volume_1,_Chapter_1_US/usv1.pdf} (last visited June 29, 2017). Labor expenses includes “hired farm labor expense” and “contract labor value expense.” See table 68 on p. 174-181.} Combined with the fact that Dark tobacco farms also have larger total revenue than other crops, this means that an acre of a tobacco farm can provide jobs to a substantially larger number of workers than an acre of land used for other crops.

In addition, Dark tobacco farmers have experienced less mechanization in harvesting processes compared to other types of tobacco farmers, as Dark tobacco harvesting requires additional care to ensure a quality crop.\footnote{“Quantitative Comparison of Mechanical Harvesting Methods and Conventional Harvesting Methods of Burley Tobacco in the Southeast,” Robert Baily Elliott, University of Tennessee, Knoxville, 12 -2008, pp.4. Available at \url{http://trace.tennessee.edu/cgi/viewcontent.cgi?article=1407&amp;context=utk_gradtheses} (last visited June 29, 2017).} In fact, the Houston Chronicle reported that Dark tobacco is especially labor intensive, requiring about 300 hours of labor per acre of production.\footnote{Rudy Miller, \textit{Seasonal Tobacco Worker Job Description}, \url{http://work.chron.com/seasonal-tobacco-worker-job-description-27169.html} (last visited June 29, 2017).} For example, a farmer noted that his farm, which “grows 67 acres of dark tobacco […] requires an extensive amount of labor to raise that crop.” He further describes that he hires “11 full-time H-2A workers to perform the work. They are well-paid, and their dollars do a lot to drive the economy where we live.”\footnote{Comment from Donald Hobgood, \url{https://www.regulations.gov/document?D=FDA-2016-N-2527-0272} (last visited June 29, 2017).} This is especially important since many farm workers are also migrant farm workers, a vulnerable segment of the population.
The key to a farmer maintaining financial stability is generating enough cash flow from year-to-year to be able to manage long-term debt, such as payments for equipment and land, as well as short-term debt for daily operating expenses. Farmers typically carry relatively high levels of debt due to land and equipment purchases that take decades to pay off. For example, the average farmer, with a 100-acre farm that grows 20 acres of Dark tobacco, can easily be carrying long-term debt of up to $1 million.

At the beginning of each year, farmers typically obtain an operating loan that allows them to purchase seed, fertilizers, chemicals and other items so they can plant crops, including Dark tobacco. In many cases, farmers obtain these loans by pledging their land and homes as collateral. Given its high profitability, Dark tobacco plays a key role in enabling farmers to pay back these loans. This revenue is a critical part of making the farmer’s overall operation financially viable.

FDA’s Proposed Product Standard poses a profound threat to this business model and the farmer’s livelihood. For example, if a farmer’s crop was rejected by a manufacturer because it failed to meet an unachievable 1 ppm NNN limit, the farmer would lose not only the entirety of the investment in the Dark tobacco crop, but the relatively high profit that helps to service debt and support other less profitable operations on the farm. Land and homes pledged as collateral would be at risk, as would the ability of the farmer to continue financing other, less profitable farming operations. Yet, the FDA, by its own admission, considered none of this.

If finalized, the standard would create unmanageable financial uncertainty and strain for a Dark tobacco farmer because of the inevitability that manufacturers will reject the farmer’s tobacco because it does not meet an unachievable 1ppm NNN limit. Faced with that risk, farmers are unlikely to invest their money into a Dark tobacco crop and lenders would be even more unlikely to provide financing to farmers to grow it or fund other farm operations.

As a result, farmers would lose the high profits from the sale of Dark tobacco, along with the subsidy it provides for other, less profitable operations on the farm. Take, for example, how one farmer explained how the growth and investment in his farm would not have been possible without Dark tobacco. “You have to have the tobacco income in order to do the rest. Most farms unless all the ground and equipment is paid for, can’t be sustained with only grain.”107 Another farmer noted, “Commodities are down right now. Many farmers are losing money on their grains. They rely on dark tobacco to make any sort of profit at the end of the year.”108

Farmers, ranchers, and other agricultural managers have an average hourly wage of $37.75 in Kentucky and $25.57 in Tennessee, which is an annual average wage of $79,000 and $53,000 respectively.109 For farmers that grow Dark tobacco, FDA’s Proposed Rule puts these salaries at

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109 Bureau of Labor Statistics as of May 2016. Available at https://data.bls.gov/oes/#/home (last visited June 29, 2017). These hourly and annual mean wages are listed under the Standard Occupational Classification codes,
risk. A farmer noted that FDA’s proposed regulation “would ruin [him] as an American tobacco farmer which is [his] sole income.” He also noted without tobacco farming “I would not be able to support my family. It would take away income from my employees and the local businesses in my area that I purchase supplies, equipment, plants, chemicals, etc. from.”

Beyond their salaries, farmers stand to lose considerable value in their farms’ property, plant, and equipment assets. The average estimated market value of the land and buildings of a primary tobacco farm is $1.2 million. In addition, the average market value of the machinery and equipment used is $171,000. Multiplying these figures by 1,200 dark tobacco farmers yields aggregate land and buildings value of approximately $1.4 billion and equipment of $205 million, respectively. If FDA implements its Proposed Product Standard, these investments would lose much of their value, and some would lose all of their value.

Other Dark tobacco farmers have raised these same concerns. One farmer explained that he has “a lot of money invested in the infrastructure on my farm. The tobacco barns alone are major assets, and they are built for the sole purpose of housing tobacco. They would not be of much use for anything other than curing tobacco. It is not as easy as simply growing something else instead of tobacco.” Another notes that this loss would not only affect the farmers but also the “significant amount of revenue for the mills that sell sawdust and slabs to the tobacco farmers,” and that the regulation “would also be detrimental to carpenters in the area who help to build the barns for growers in the area. Growers are often building more barns to house tobacco. Everywhere you look, there are potential economic impacts […].” A farmer who has loans on his land, explained that FDA’s proposal would put him out of business since “land values will inevitably drop, and family farms would all be in jeopardy.” Another said that if the Proposed Rule is implemented, “I would have to sell my farm and get a job as a laborer on somebody else’s farm. Tobacco is the lifeblood of this part of Tennessee and Kentucky. Passing this rule would mean the end of many of the farms in this region.”

Farm workers, many of whom are vulnerable migrant workers, would also be hurt by FDA’s Proposed Product Standard. According to the U.S. Department of Labor, 21% of U.S. field crop
workers are migrant workers. Farm workers in general struggle with limited job security, which results from a number of external variables, including seasonality, weather, and/or crop conditions. Having more stable crop farms to work on, such as tobacco farms, provides some of these workers job security. In many cases, farm workers return to the same farm year after year to harvest Dark tobacco. This consistent work helps workers to earn more money than going to a different farm each season. Field crop workers work on average 50 hours per week, 38 weeks a year, and earn on average an hourly wage of $9.35 per hour, or around $18,000 per year. Research has shown, however, that wages in agriculture depend heavily on whether the worker has worked for the same employer for multiple years, with workers making on average 19% more if they have been with the same employer for at least 6 years. The stability provided by a tobacco crop benefits the farm workers who help harvest Dark tobacco on the same farm year after year.

Jobs for farm workers harvesting Dark tobacco would disappear if the FDA implements its proposed 1 ppm NNN limit. In Kentucky and Tennessee, it takes more than 2,000 hired farm workers to harvest Dark tobacco each year. For example, one Dark tobacco farmer employs six-full time workers and hires an additional 20 migrant workers during the growing season. If the regulation were imposed, his farm would “immediately be forced to eliminate 2 to 4 full-time jobs, and there would be no need to hire the migrant workers at all. In total, our one farm would eliminate anywhere from 22-24 good-paying jobs.” Another farmer worries about his migrant workers “some [of] whom have been working with [him] for nearly 20 years” and who as a result can participate in their local economy. Even if those laid off farm workers find work at a different farm, they stand to lose a significant part of their income because they are starting over with a new employer.

119 USDA – NASS. Available at https://www.nass.usda.gov/ (last visited June 29, 2017); 2012 Census of Agriculture United States, Issued May 2014. Available at https://www.agcensus.usda.gov/Publications/2012/ (last visited June 29, 2017). This is a conservative estimate of workers on Dark tobacco farms, inasmuch as it assumes that Dark tobacco and other tobacco have the same labor intensity per acre, when in fact Dark tobacco is more labor intensive.
B. The Proposed Standard Would Force the Shut Down of Manufacturing Facilities, Eliminate Thousands of Jobs, and Hurt Local Economies, Especially Hopkinsville, Kentucky

A de facto ban of smokeless tobacco product category would force the shutdown of numerous manufacturing facilities, including USSTC’s facilities in Hopkinsville, Kentucky and Nashville, Tennessee and result in the elimination of about 500 jobs at these facilities. Other communities with similar manufacturing facilities would suffer the same fate. For example, the American Snuff Company, the second largest MST producer in the U.S., employs an estimated 50 –100 workers in Clarksville, Tennessee, a facility about 30 miles south of Hopkinsville, Kentucky and another 400 – 600 workers in facilities in Winston-Salem, North Carolina and Memphis, Tennessee. Other manufacturers employ an estimated 450 – 700 workers in their facilities in Owensboro, Kentucky (Swedish Match), Wheeling, West Virginia (Swisher International), and Dresden, Tennessee (Turning Point Brands). In total, 1,400 – 1,900 good paying manufacturing jobs are at serious risk if FDA implements its proposed product standard.

Of course, the economic activity associated with these 1,900 jobs indirectly supports an even larger number of jobs in the community. A recent study by MIT and UCSD economists of the effect of Chinese imports on job losses in the U.S. found that taking into account the jobs lost through ripple effects “more than triples the estimated direct employment effects for manufacturing alone.” A de facto ban of smokeless tobacco products would likely have a similar ripple effect, resulting in the elimination of between 4,200 to 5,700 jobs. The economic impact of these job losses would be particularly painful because many of the lost jobs would be in small communities that are economically vulnerable.

To get a conservative estimate of the lost economic activity that would result from the loss of these jobs, we assume that the jobs lost as a result of the ripple effect paid the average wages in the service sector in Kentucky of about $39,000 per year and that the share of labor in the added value of these activities is the national average (55%). Based on these assumptions, the loss of 4,200 – 5,700 jobs translates into a loss of between $340 million – $450 million in economic impact. Each of these sums would be split about equally across workers, business owners, and tax revenue.

Consider the example of USSTC’s Hopkinsville facility. Job losses would be devastating to the workers and their families. The average salary of an employee at the USSTC Hopkinsville plant is $60,461, or about 25% higher than the average pay of $48,634 for a manufacturing job in the area, Christian County. In 2015, the average pay for a private industry service job in Christian

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County was $34,313 and $39,721 in Kentucky. If the average USSTC worker who lost her job moved into an average paying service industry job in Christian County, she would lose $26,148, or 43% of her USSTC income. To quantify the potential loss, consider a family’s housing expenses. This lost income is equivalent to a typical household’s budget for housing, food, and healthcare combined, and would constitute a drastic drop in the family’s standard of living.

Making matters worse, USSTC just announced the opening of a second facility in Hopkinsville called Eagle One. The hope and excitement in the community over this investment and opportunity for more good jobs would be dashed by the Proposed Rule.

Many of the USSTC employees who would lose their jobs as a result of a de facto ban on smokeless tobacco product face limited alternative job prospects. The average hourly wages for private sector employees in the Clarksville Metropolitan Statistical Area (which includes the city of Hopkinsville) is about 30% lower than the national average and 36% lower than the average salary for hourly workers at USSTC’s Hopkinsville facilities.

The USSTC facility in Hopkinsville is also a major source for the city’s tax revenue. In the fiscal years 2014 and 2015, USSTC was the second or third largest property taxpayer in Hopkinsville, with $21 million in taxable assessed property value (before the completion of the new Eagle One facility), accounting for about 1.1% of total city taxable assessed property value. In 2014-2015, USSTC was one of the ten largest employers in Hopkinsville, and it directly employed about 1.4% of workers in the city.

The importance of USSTC’s manufacturing activity for the area was recognized in 2014 by then-Governor of Kentucky Steve Beshear. Following the announcement that USSTC would expand its activity in the state, Beshear stated, “U.S. Smokeless Tobacco’s investment will make a significant economic impact on the state and bring more jobs to the region.” The current Governor of Kentucky, Matt Bevin, signaled his support for USSTC’s manufacturing activity in Hopkinsville by attending a ribbon cutting ceremony to celebrate the opening of the new Eagle One facility. He recognized the generational importance

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127 A household consisting of a married couple with at least one child spends, on average, 10.5% of its income on food, 25.1% on housing, 14.1% on transportation, 5.5% on healthcare, and 10.7% on personal insurance and pensions. “Consumer Expenditures – 2015,” U.S. Bureau of Labor Statistics. August 30, 2016. Available at https://www.bls.gov/news.release/cesan.nr0.htm (last visited June 29, 2017).


of smokeless tobacco manufacturing in the area, stating, “This is where the recipe starts...some of you have been doing this for generations. The people are the ingredient, the work ethic is the ingredient, the attitude is the ingredient.”132

Direct purchases by the facilities in Hopkinsville are responsible for further economic activity and employment in Hopkinsville and its surrounding communities. It is well-documented that in the U.S. businesses tend to transact locally.133 Monies that manufacturers spend on non-leaf constituents, packaging materials, processing costs, etc. are all direct economic activity that would no longer occur if the Proposed Rule is finalized.

USSTC alone spent $107 million in 2016 with farmers and suppliers in Kentucky and Tennessee. These expenditures, the bulk of which were to farmers within a 50-mile radius of Hopkinsville, were made to approximately 700 growers and 300 other suppliers. The ripple effects from the elimination of USSTC’s activity in Hopkinsville would affect not only USSTC’s suppliers but also business activity more generally. The workers who lose their jobs (workers at USSTC and at its suppliers), would suffer a loss of income, and would consequently reduce their consumption. Americans direct on average about 66% of their total spending to services, which are generally local.134 The loss of income for the workers laid off would result directly in a decline in local spending. The decline in local spending would in turn lead to losses by local businesses, reduced job opportunities for local workers, and a decline in local tax revenues.

Another aspect of USSTC’s local economic impact is its capital expenditures in the Hopkinsville area. USSTC recently spent approximately $140 million on its new Eagle One facility in Hopkinsville. An expenditure of that magnitude is uncommon, but USSTC’s regular capital expenditure on its first Hopkinsville facility is between $5 million and $7 million per year, on average over the last 7 years. This sum is expected to grow by $1-2 million per year as the new Eagle One facility comes online. These substantial, recurring investments add to the economic vitality of Hopkinsville. If the Propose Rule is implemented, however, that plant will be shuttered and further investments lost.

While the Nashville economy is substantially larger than that of Hopkinsville, USSTC is still an important contributor to the Nashville economy and business landscape.135 USSTC’s Nashville plant had 44 salaried employees and 268 hourly employees as of December 2016. Total spending

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135 Nashville has a population of more than 20 times that of Hopkinsville (more than 56 times if including the Nashville metropolitan area). As of 2014, the manufacturing industry employs an estimated 77,900 workers in the Nashville MSA as a major industry in the regional economy. “Regional Stats,” Nashville Chamber of Commerce. Available at https://www.nashvillechamber.com/economic-development/data-reports/regional-stats (last visited June 29, 2017).
on labor and salaries in 2016 was $30.9 million.\textsuperscript{136} Since its peak in 1979, manufacturing jobs have steadily declined across the U.S. and in Tennessee, although the Nashville MSA has experienced a small increase in recent years.\textsuperscript{137} In 2016, USSTC expanded its smokeless tobacco operations in the Nashville facility, increasing the importance of the Nashville plant in the manufacturing of smokeless tobacco products.\textsuperscript{138} A de facto ban of the smokeless tobacco products manufactured in Nashville would eliminate hundreds of jobs at the facility and have other negative ripple effects with suppliers and others throughout the Nashville economy.

FDA owes it to the farmers and the local communities to quantify the economic impact of its proposed standard, give notice of its assessment, and allow stakeholders an opportunity to comment on the analysis that FDA admits it has not done.

C. FDA Failed to Assess the Loss of Consumer Surplus that Would Result from the Proposed Standard

FDA acknowledges that consumers may face increased prices and potentially a loss in consumer welfare due to inferior product or lack of product availability. But FDA does not quantify nor effectively account for this dramatic loss in consumer choice, which necessarily would accompany implementation of the product standard. It is axiomatic in economic analysis that consumers value the products they purchase. A de facto ban would deprive consumers of their surplus. Given that Congress expressly protected adult consumers’ right to purchase tobacco products, this loss in consumer choice should be quantified and considered by FDA in its rulemaking and made open to comment by stakeholders.

In addition, faced with the loss of such smokeless tobacco options, consumers might opt to consume higher-risk products, including cigarettes. Notwithstanding the TCA’s directive that tobacco product standards must be appropriate for the protection of the public health, FDA failed to consider this possibility. Neglecting such obvious and significant potential costs renders the product standard arbitrary and capricious.

V. FDA’s Proposed Product Standard is Contrary to Tobacco Harm Reduction Goals

The overarching goal of the TCA is to “protect the public health.” Yet FDA’s proposed product standard risks doing precisely the opposite in a way FDA did not even consider.

As set forth above, the proposed standard would effectively eliminate from the market a category of tobacco products that are, based on overwhelming scientific, medical and public health consensus, substantially less hazardous than cigarettes. If MST and chewing tobacco are effectively banned from the market, as they will be under the Proposed Product Standard, many of their more than 8 million users will look for alternative tobacco products. Because many of

\textsuperscript{136} USSTC internal data.
\textsuperscript{138} Altria Group, Inc. Form 10-K filed February 27, 2017, at 10.
them would switch to or return to smoking, the proposed standard would actually increase the risk to public health. In fact, we estimate that, using FDA’s own substitution rate, removing smokeless tobacco from the market would result in approximately 700,000 current smokeless tobacco consumers who do not now smoke cigarettes becoming cigarette smokers.

Notwithstanding the TCA’s directive that tobacco product standards must be appropriate for the protection of the public health, FDA failed to consider this possibility. Neglecting such obvious and significant potential costs renders the product standard arbitrary and capricious.\footnote{In addition, FDA’s analyses and estimates of the health benefits of its Proposed Product Standard suffer numerous deficiencies. See Appendix 1.}

A. Smokeless Tobacco Products Are Substantially Less Hazardous Than Cigarettes

Despite massive, long-standing public health campaigns against using tobacco products, millions of adults continue using tobacco products and more use cigarettes than any other tobacco product. For these adult consumers, products with lower health risks than cigarettes offer a promising opportunity to reduce their risk of harm. Making sure that products with lower reduced harm potential are available to these consumers should be a critical part of protecting the public health.\footnote{Discouraging initiation and promoting cessation, particularly among those not legally permitted to buy tobacco products because they are underage, are and should remain core strategies to reduce tobacco-related harm. While prevention and cessation efforts can successfully reduce harm, however, it is highly unlikely that they will eliminate tobacco use altogether. There is growing consensus that public health policies based solely on prevention and cessation are not sufficient in the real world. Indeed, a regulatory approach that forces cigarette smokers to choose between smoking, on the one hand, and not using tobacco at all, on the other, could have the consequence of preserving cigarette smoking as the dominant form of tobacco use in the U.S.}

There is an overwhelming scientific, medical, and public health consensus that smokeless tobacco products available in the U.S. are substantially less hazardous than cigarettes. This consensus is based on extensive and compelling scientific evidence, including epidemiological disease risk data in human populations from the U.S. and other countries. As early as 2001, the Institute of Medicine observed that smokeless tobacco products posed a lower overall risk than cigarettes.\footnote{Institute of Medicine, Committee to Assess the Science Base for Tobacco Harm Reduction, \textit{Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction} (K. Stratton et al., Washington D.C.: National Academies Press 2001) at 167, available at \url{http://books.nap.edu/openbook.php?record_id=10029} (last visited June 29, 2017).} Since that time, panel after panel of experts have critically and thoroughly examined the evidence and reached the same conclusion: using smokeless tobacco products is undeniably far less hazardous than smoking cigarettes.

A 2009 article entitled “The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the United States” (“Strategic Dialogue”) critically examines the role that smokeless tobacco products could play in harm reduction.\footnote{See M. Zeller et al., \textit{The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the United States}, Tob. Control J.; vol. 18: 324-332 (2009).} The Strategic Dialogue is the outcome of more than two years of dialogue by a group of twenty-six scientists and researchers, including the current Director of FDA’s Center for Tobacco Products, which convened to
develop guidance for future efforts to reduce the harm caused by tobacco products. It confirms that there is a “very pronounced” continuum of risk among different tobacco and nicotine-containing products.

The Strategic Dialogue concludes that cigarette smoking is “undoubtedly” more hazardous than smokeless (“non-combustible”) tobacco:

There is a very pronounced continuum of risk depending upon how toxicants and nicotine, the major addictive substance in tobacco, are delivered. Cigarette smoking is undoubtedly a more hazardous nicotine delivery system than various forms of non-combustible tobacco products for those who continue to use tobacco, which in turn are more hazardous than pharmaceutical nicotine products.

Others have similarly confirmed the continuum of risk concept, which can be represented as follows:

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143 The Strategic Dialogue participants were: Cathy Backinger (National Cancer Institute, Bethesda, Maryland, USA); Neal Benowitz (University of California, San Francisco, California, USA); Lois Biener (University of Massachusetts, Boston, Massachusetts, USA); David Burns (University of California, San Diego, California, USA); Pamela Clark (University of Maryland, College Park, Maryland, USA); Greg Connolly (Harvard School of Public Health, Boston, Massachusetts, USA); Mirjana Djordjevic (National Cancer Institute, Bethesda, Maryland, USA); Thomas Eissenberg (Virginia Commonwealth University, Richmond, Virginia, USA); Gary Giovino (University at Buffalo, SUNY, Buffalo, New York, USA); Dorothy Hatsukami (University of Minnesota, Minneapolis, Minnesota (co-chair)); Cheryl Healton (American Legacy Foundation, Washington, DC, USA); Stephen Hecht (University of Minnesota, Minneapolis, Minnesota, USA); Jack Hemmingfield (Pinney Associates, Bethesda, Maryland, USA); Corinne Husten (Partnership for Prevention, Washington, DC); Kimberly Kobus (University of Illinois, Chicago, Illinois, USA); Scott Leischow (University of Arizona, Tucson, Arizona, USA); David Levy (Pacific Institute for Research & Evaluation, Calverton, Maryland, USA); Stephen Marcus (National Cancer Institute, Rockville, Maryland, USA); Matthew Myers (Campaign for Tobacco-Free Kids, Washington, DC, USA); Mark Parascandola (National Cancer Institute, Rockville, Maryland, USA); Prabhu Ponkshe (HealthMatrix Inc., McLean, Virginia, USA); Peter Shields (Georgetown University, Washington, DC, USA); Paul Slovic (Decision Research, Eugene, Oregon, USA); David Sweanor (University of Ottawa, Ottawa, Ontario, Canada); Kenneth Warner (University of Michigan, Ann Arbor, Michigan, USA); and Mitchell Zeller, (Pinney Associates, Bethesda, Maryland (co-chair)). Id. at 331.

144 Id. at 325.

145 Id. (emphasis added). See also id. at 327 (“On the continuum of risk, non-combustible tobacco products are more likely to reduce harm than a smoked form of tobacco for individuals who would otherwise be using conventional cigarettes.”).

146 See e.g., D.K. Hatsukami et al., Developing the science base for reducing tobacco harm, Nic. & Tob. Res.; val. 0: S537-S553 (2007) at S546 (“Hatsukami et al. (2007)”; see also Zeller, M. Reflections on the ‘endgame’ for tobacco control, Tob. Control 2013; 22:i40-i41. (if a new approach to reduce consumption of cigarettes “is to succeed, it will be because policy makers and tobacco control advocates have overcome their reluctance and finally embraced a concept known as the ‘continuum of risk’.”); Zeller, M. Three years later: an assessment of the implementation of the Family Smoking Prevention and Tobacco Control Act, Tob. Control 2013, 21:453-54 (“Experts agree that there is a distinct ‘continuum of risk’ when it comes to products that deliver nicotine.”).
Smoking conventional cigarettes is at one end of the continuum, presenting the highest health risk to the individual tobacco consumer due to the combustion and inhalation of tobacco smoke. Smoking cessation is at the opposite end. Noncombustible tobacco products, such as smokeless tobacco products, are substantially lower on the risk continuum than cigarettes – closer, in fact, to medicinal nicotine and smoking cessation than to continued smoking.147

The Scientific Committee on Emerging and Newly Identified Health Risks (“SCENIHR”) advises the European Commission’s Health & Consumer Protection Directorate-General, which is responsible for updating various European Union laws relating to the safety of food and other products, consumer rights, and the protection of public health. In 2008, after examining the scientific evidence, SCENIHR issued a final report concluding that the overall health risks of smokeless tobacco products of the types found in Sweden and North America are “clearly” and “substantially” less than the overall health risks of cigarettes:

Overall therefore, in relation to the risks of the above major smoking-related diseases, and with the exception of use in pregnancy, [smokeless tobacco products] are clearly less hazardous, and in relation to respiratory and cardiovascular disease substantially less hazardous, than cigarette smoking. The magnitude of the overall reduction in hazard is difficult to estimate, but as outlined above, for cardiovascular disease is at least 50%, for oral and GI cancer probably also at least 50%, and for respiratory disease close to 100%.148

147 Strategic Dialogue at 325; see also Hatsukami et al. (2007) at S546.
SCENIHR found the body of evidence so compelling that it described its finding regarding the relative risks of cigarettes and smokeless tobacco as “undeniable”:

It is *undeniable* that for an individual substitution of tobacco smoking by the use of moist snuff would decrease the incidence of tobacco related diseases.\(^{149}\)

In addition to those noted above, many other medical and scientific organizations have examined the relative health risks of smokeless tobacco products and cigarettes and reached similar conclusions. In a 2002 report, the Royal College of Physicians (“RCP”), the oldest medical organization in England, concluded that “the consumption of non-combustible tobacco is of the order of 10-1,000 times less hazardous than smoking, depending on the product,” and that “[s]ome smokeless tobacco products . . . may offer substantial reductions in harm compared to smoking.”\(^{150}\) The RCP followed up with a second study in 2007,\(^{151}\) again concluding that the overall health risks of using smokeless tobacco are “considerably” and “substantially” less than those of cigarette smoking:

The health risks of smokeless tobacco are considerably lower than those associated with combustible tobacco products as *it is largely the combustion process that makes tobacco use so deadly.*\(^{152}\)

In 2008, an international group of experts that provides scientific and technical advice on tobacco products to the World Health Organization (“WHO”) similarly recognized that smokeless tobacco products are less hazardous than cigarettes. The WHO Study Group on Tobacco Product Regulation (“TobReg”) concluded, “[u]sers of smokeless tobacco products generally have lower risks for tobacco-related morbidity and mortality than users of combustible tobacco products such as cigarettes.”\(^{153}\)

The American Council on Science and Health (“ACSH”) has also weighed in, issuing a number of reports and statements about smokeless tobacco over the last several years. ACSH is a public health-oriented consumer education consortium with a board comprised of 350 physicians, scientists, and policy advisors.\(^{154}\) In a report released in 2006, ACSH concluded that, “[o]verall, the use of smokeless tobacco confers only about 2% of the health risks of smoking,” emphasizing that in contrast to cigarette smoking, smokeless tobacco poses no risk of lung cancer or chronic pulmonary diseases and little risk, if any, of other cancers.\(^{155}\) In a subsequent publication, ACSH

\(^{149}\) *Id.* at 14 (emphasis added).


\(^{152}\) *Id.* at 18 (emphasis added).


noted that almost 80% of peer-reviewed scientific and medical articles have acknowledged the differential risks between smokeless tobacco and cigarettes and concluded that the “health risks associated with ST [smokeless tobacco] use are vastly lower than those of smoking.”\textsuperscript{156}

A close examination of data from the American Cancer Society Cancer Prevention Study II (CPS II) supports the same conclusion.\textsuperscript{157} This study is among the largest known prospective cohort studies to compare mortality among former U.S. cigarette smokers who substituted using smokeless tobacco for cigarette smoking with those who quit using tobacco entirely. Although all-cause mortality after twenty years follow-up for smokers who switched to smokeless tobacco was higher than quitting altogether, this result was marginal and, as the authors discuss, may simply be the result of residual confounding.\textsuperscript{158}

In addition, ALCS conducted an extensive analysis of the comparative health risks of smokeless tobacco and cigarettes using two large, nationally representative linked mortality data sets: The National Health Interview Survey (NHIS) mortality linkage and the National Longitudinal Mortality Study (NLMS).\textsuperscript{159} Both data sets are more recent than CPS II and contain similar numbers of smokeless tobacco users. Among smokeless tobacco users in these data sets, the all cause and all cancer mortality risks were not elevated while mortality risks were significantly elevated among cigarette smokers (Figure 12). These data directly demonstrate the significant risk differential between smokeless tobacco use and cigarettes.

The NLMS mortality linkage includes survey years 1993 through 2005 linked to National Death Index. The data have five years of mortality follow-up for all survey years, with each decedent’s underlying cause of death assigned to one of 113 aggregate causes. The analyses were limited to respondents at least 18 years old at survey who are never users of both pipe tobacco and cigars, and for whom analysis weight, follow-up time, vital status, and model covariates are known. This data set included 210,090 total observations including 3,492 current smokeless tobacco users.

\textsuperscript{156} See American Council on Science and Health, *Smokeless Tobacco as Harm Reduction for Smokers* (2007), available at http://www.acsh.org/news/2007/04/30/smokeless-tobacco-as-harm-reduction-for-smokers (last visited June 29, 2017). (emphasis added). In February 2007, ACSH President Elizabeth Whelan and Executive and Medical Director Dr. Gilbert Ross released a statement on behalf of the ACSH for a Senate hearing on the then-proposed FDA regulation of tobacco. See American Council on Science and Health, *Statement for Senate Hearing on FDA Regulation of Tobacco* (Feb. 27, 2007), available at https://www.gpo.gov/fdsys/pkg/CHRG-110shrg33769/pdf/CHRG-110shrg33769.pdf. In its statement, the ACSH addressed what it termed the “fallacy that all tobacco products are equally harmful to public health” and pointed out that “[s]cientific studies have proven that they are not, and a rapidly-growing body of evidence confirms that they are not.” Id. at 174. In October 2008, ACSH Executive and Medical Director Dr. Ross stated in a letter to the medical journal Lancet that “the health risks of smokeless tobacco are at least an order of magnitude less than those of cigarettes.” G. Ross, *Smokeless Tobacco for Cigarette Cessation*, Lancet; vol. 372: 1271 (2008).

\textsuperscript{157} Cancer Prevention Study II, sponsored by the American Cancer Society, is a large, ongoing prospective cohort study of 1.2 million U.S. adults that began in the fall of 1982. It was designed to examine the effect of tobacco use on death rates from cancer and other tobacco-related diseases.


\textsuperscript{159} The results of this analysis are also discussed in Section IV and are incorporated by reference in this section.
NHIS mortality linkage includes survey years 1987, 1991-1992, 1998, 2000, and 2005 because these surveys identified smokeless tobacco use, pipe use, and cigar use.\textsuperscript{160} ALCS’s research analyzed both the publicly available data (includes 10 most common underlying causes of death) and the restricted access data (includes 113 underlying causes of death). The data are linked to the 2011 National Death Index update\textsuperscript{161} and therefore include between six and 24 years of mortality follow-up.\textsuperscript{162} Restrictions were the same as for the NLMS. This data set included 154,391 total observations including 3,006 current smokeless tobacco users.

Mortality hazard ratios were estimated using Cox proportional hazards regression analyses for leading causes of mortality, and other selected mortality causes attributed to tobacco use. The following covariates were used: gender, race (white, non-white), age, BMI (not available in the NLMS data), education, family income, health status, tobacco use, and cigarettes per day (limited to current or former smokers in NHIS).

As shown in Figure 12, ALCS detected statistically significant excess risks among current cigarette smokers for mortality from all causes, all cancers, diseases of the heart and chronic lower respiratory diseases. The magnitudes of these excess risks among cigarette smokers are entirely consistent with prior studies,\textsuperscript{163} supporting the reliability of ALCS’s analyses. Among current smokeless tobacco users, however, ALCS detected no excess risks for mortality from all causes, all cancers, diseases of the heart or chronic lower respiratory disease. These analyses of two large, independent, nationally representative data sets in which ALCS directly compared the mortality risks of smokeless tobacco use and cigarette smoking clearly demonstrate that smokeless tobacco is associated with vastly lower mortality risks than cigarette smoking.

<table>
<thead>
<tr>
<th>Mortality outcome</th>
<th>Current SLT users</th>
<th>Current cigarette smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NLMS</td>
<td>NHIS</td>
</tr>
<tr>
<td>All causes</td>
<td>0.88 (0.67-1.15)</td>
<td>1.08 (0.95-1.22)</td>
</tr>
<tr>
<td>All cancers</td>
<td>1.01 (0.57-1.79)</td>
<td>1.04 (0.82-1.31)</td>
</tr>
<tr>
<td>Diseases of the heart</td>
<td>1.07 (0.69-1.67)</td>
<td>0.79 (0.60-1.04)</td>
</tr>
<tr>
<td>Chronic lower respiratory diseases</td>
<td>0 deaths</td>
<td>0.43 (0.20-0.94)</td>
</tr>
</tbody>
</table>

Bold numbers are statistically elevated.

**Figure 12.** Comparison of the hazards for select mortality outcomes between current smokeless tobacco users and current cigarette smokers.

In sum, these and many other scientific reports demonstrate beyond credible dispute that the health risks of moist smokeless tobacco products are substantially less than cigarettes.\textsuperscript{164}

\textsuperscript{160} Pipe and cigar users were excluded from our analyses.


\textsuperscript{162} Results from our analyses of the NHIS mortality linkage shown in Table 1 are based on a 10-year follow up.

\textsuperscript{163} Rostron, B. 2013. ‘Smoking-attributable mortality by cause in the United States: revising the CDC’s data and estimates’, *Nicotine Tob Res*, 15: 238-46.

B. A De facto Ban of Smokeless Tobacco Products Will Lead to a Negative Public Health Outcome Because Current Smokeless Tobacco Users Could Switch to or Back to Cigarettes

FDA’s proposed product standard would essentially remove smokeless tobacco products from the market. Its own estimates of the substitution rate of cigarettes for smokeless tobacco indicate that approximately 700,000 current smokeless tobacco consumers who do not currently smoke cigarettes will become cigarette smokers. Clearly, given the reduced risk of smokeless tobacco products relative to cigarettes, this would result in a net negative impact on public health.

A de facto ban on smokeless tobacco products would likely result in significant substitution from smokeless products to cigarettes because there is significant overlap of users between the categories in the U.S. market. According to the 2015 National Survey on Drug Use and Health (NSDUH), there are 8.9 million current adult smokeless tobacco users in the U.S., of whom 3 million (34%) are also current cigarette smokers (dual users). Dual users present a significant harm reduction opportunity because they already use smokeless tobacco which is far less harmful than cigarettes. Given appropriate information regarding the health risk differential between smokeless tobacco and cigarettes, these dual users may be persuaded to quit smoking cigarettes and become exclusive smokeless tobacco users, thereby significantly reducing their individual health risk and improving public health. Removing smokeless tobacco from the market will almost certainly cause these individuals to become exclusive cigarette smokers, resulting in no health benefit or even a detrimental effect.

More troubling from a public health perspective are the implications of the proposed tobacco product standard to the 2.5 million (28%) of current smokeless tobacco users who are former cigarette smokers. In the PRIA, FDA cites data from Finland where smokeless tobacco was banned after Finland’s entry into the European Union. After the ban went into effect, there was a 3.5% increase in the smoking rate in Finland compared to Sweden where snus remained on the market. FDA calculates that, based on the Finnish smoking rate of 31.6% prior to the ban,

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165 In this instance, we reference the 2015 NSDUH for smokeless tobacco prevalence data because it allows us to estimate the number of former cigarette smokers among current smokeless tobacco users. We recognize that the prevalence estimates we use here differ from data referenced elsewhere in this document.

166 PRIA at 112-13

167 Id.
the smoking rate increased by 11% after the ban. FDA then assumes that 11% “is the upper bound of smokeless tobacco initiation from combustible tobacco smokers.” FDA further assumes that the substitution rate of cigarettes for smokeless tobacco products in Finland is identical to the projected substitution rate of smokeless tobacco products for cigarettes in the U.S.

However, FDA conducts no analysis of the effect of removing smokeless tobacco products from the market on cigarette smoking, which is what the Maki et al. study cited by FDA actually assessed. If we apply FDA’s 11% substitution rate, which we believe is too conservative, to the 2.5 million former smokers who now use smokeless tobacco, this suggests that 275,000 current exclusive smokeless tobacco consumers would become cigarette smokers. This estimate, however, is likely to be significantly low because the majority of smokeless tobacco consumers do not know that smokeless tobacco poses a substantially lower risk to health than do cigarettes.

Finally, 3.5 million current smokeless tobacco users were never cigarette smokers. It is likely that a proportion of these individuals would also become cigarette smokers if smokeless tobacco products are eliminated from the market. Applying the 11% substitution rate FDA cites in the PRIA, results in 385,000 current exclusive smokeless tobacco users becoming cigarette smokers.

**Figure 13. Substitution patterns assuming FDA’s 11% substitution rate.**

- Approximately 700,000 current non-smokers to begin smoking cigarettes, thereby increasing their individual health risks.
- 3 million current dual users would likely continue smoking cigarettes, thereby not changing their individual health risks.

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168 Id. at 113.

169 Id.

• 5.3 million current smokeless tobacco users would become former users, thereby slightly reducing their individual health risks.

Given the vast risk differential between smokeless tobacco and cigarette smoking, however, removal of smokeless tobacco products from the U.S. market would have a negative impact on public health. For example, ACSH estimates that smokeless tobacco carries only 2% of the risks of smoking. To be conservative, if we assume that smokeless tobacco carries 10% of the individual health risk as cigarettes, ten times as many current users would have to cease using smokeless tobacco as begin using smoking cigarettes. Even using FDA’s very conservative assumptions of 11% substitution, the ratio of former smokeless users to new cigarettes smokers is only 8:1 (5.3 million former smokeless users / 0.7 million new smokers = 8.0) and results in a negative public health impact by increasing the number of cigarette smokers. The public health impact becomes even worse if you apply more realistic, higher substitution rates than FDA assumes.

The TCA gave FDA the authority to regulate tobacco products to “protect the public health.” Harm reduction based on the continuum of risk should be a cornerstone of FDA’s regulatory policy to achieve the greatest and most sustainable benefit to the public health. A de facto ban of smokeless tobacco products does not demonstrate regulation based on the continuum of risk and would cause more tobacco related harm than keeping smokeless tobacco products on the market. Accordingly, FDA should withdraw its proposed standard, and, should it choose to propose a different standard, do so in a way that regulates based on the continuum of risk and advances tobacco harm reduction.

VI. FDA Ignored a Practical and Incremental Alternative of Low-NNN Yield Tobacco Seed

A particularly glaring omission in FDA’s development and analysis of the proposal is its failure to explore a more practical, incremental, and cost-effective alternative. That omission renders the proposed standard arbitrary and capricious.171

FDA should have considered whether and how NNN levels in smokeless tobacco products could be lowered – beyond the substantial reductions some manufacturers have already achieved – using the same types of U.S. grown tobacco used in existing smokeless tobacco products. For example, ZYVERT™ technology could reduce NNN levels with minimal economic disruption to growers and manufacturers. FDA could adopt effective dates allowing ample time for growers to adapt their practices and for manufacturers to clear their new products through the FDA review process.

Such an incremental standard would limit the costs imposed on farmers, consumers (from a consumer choice perspective), and manufacturers. For example, MST consumers in the U.S. would not suffer any loss in consumer value if the proposed standard could be met by making

171 See, e.g., Nat’l Black Media Coal. v. FCC, 775 F.2d 342, 357 (D.C. Cir. 1985) (agency action held arbitrary and capricious for failure to explain why other options were unavailable); Public Citizen v. Steed, 733 F.2d 93, 103 (D.C. Cir. 1984) (similar); Natural Res. Def. Council, Inc. v. SEC, 606 F.2d 1031, 1053 (D.C. Cir. 1979) (an agency must consider and explain its rejection of “reasonably obvious alternative[s]”).
reasonable and cost-effective changes in the way that traditional MST is produced. Farmers would not be put out of business. And manufacturers would avoid the potential loss of the largest category of smokeless tobacco products.

VII. The Proposed Standard Would Force Smokeless Tobacco Products Off the Market En Masse By Requiring Substantial Equivalence Reports

FDA should ensure that implementation of the required changes to meet the NNN tobacco product standard (assuming that it could be met) does not force provisional products off the market. FDA states that “[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.” 82 Fed. Reg. at 8009.

Nearly all of the smokeless tobacco products that would be subject to the new NNN standard are provisional, with pending reports that demonstrate substantial equivalence to a grandfathered product. 173 To comply with the NNN standard regarding these provisional products, the manufacturer in the normal course would be required to submit a new SE report.

If FDA is able to rule on the new SE application in its entirety—including the original changes to the grandfathered product and the NNN modifications—prior to the effective date of the NNN standard, a manufacturer receiving an SE finding could continue to sell its product without interruption. Given the number of SE applications pending, it is unlikely that FDA could accomplish that objective for a substantial number of the applications. If FDA could not, many provisional products could be forced off the market unless and until FDA determines that they are substantially equivalent to the grandfathered products identified in the new SE submissions.

In the preamble to the proposed rule, FDA appears to recognize this conundrum and seek ways to avoid it. FDA notes that with respect to products eligible for the SE process, the Agency:

| 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)). |

172 82 Fed. Reg. at 8009.
FDA asks for comments “regarding the type of modifications that may allow a reduced amount of information to proceed through the SE pathway,” and the types of information necessary to demonstrate that the changes do not raise different questions of public health.\textsuperscript{175}

Previously, in dealing with what it regards as limited modifications to a provisional product, \textit{e.g.}, changes in product quantity, FDA has allowed the continued sale of the products while the Agency reviews the filings regarding those discrete changes.\textsuperscript{176} FDA should follow a similar approach here. Any change to a provisional product mandated by the new NNN standard should be reviewed on a standalone basis, while the product remains on the market pending that review as well as FDA’s review of the provisional SE report. It would be inconsistent with Congress’s intent in creating provisional status if FDA were able to terminate it by mandating a product change. In addition, requiring removal of those products pending FDA’s determination would amount to a de facto ban prohibited under section 907.\textsuperscript{177}

In reviewing these modifications to lawfully marketed tobacco products solely for the purpose of complying with the tobacco product standard and to achieve parity from an adult consumer perspective with the pre-modified products, FDA should issue expedited market orders if a manufacturer demonstrates that other HPHC levels, besides NNN, remain in the range of agronomic variability and/or the addition of GRAS ingredients/approved food additives at or below the average daily intake.

\textbf{VIII. Conclusion}

FDA’s Proposed Rule to limit NNN in smokeless tobacco products to 1 ppm is unlawful because it is impossible to achieve and constitutes a prohibited de facto ban and effectively regulates farming practices, which is forbidden by sections 901 and 907 of the FDCA, and it violates the APA. It also fails to “protect the public health” because it would eliminate from the market a reduced harm tobacco product. If smokeless tobacco products are effectively banned from the market, many of its users would switch to or back to more risky products like combustible cigarettes, thus increasing the risk to public health. Accordingly, FDA should withdraw its Proposed Rule.

Sincerely,

\textsuperscript{175} \textit{Id.}
\textsuperscript{177} FDCA § 907(d)(2).
**Attachment 1.** Rejection rates for Dark fire-cured tobacco based on proposed 1 ppm NNN standard.

<table>
<thead>
<tr>
<th>Crop Year</th>
<th>Rejection Rate Based on Proposed 1ppm NNN Standard (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>88%</td>
</tr>
<tr>
<td>2006</td>
<td>83%</td>
</tr>
<tr>
<td>2007</td>
<td>90%</td>
</tr>
<tr>
<td>2008</td>
<td>84%</td>
</tr>
<tr>
<td>2009</td>
<td>88%</td>
</tr>
<tr>
<td>2010</td>
<td>84%</td>
</tr>
<tr>
<td>2011</td>
<td>70%</td>
</tr>
<tr>
<td>2012</td>
<td>88%</td>
</tr>
<tr>
<td>2013</td>
<td>80%</td>
</tr>
<tr>
<td>2016</td>
<td>85%</td>
</tr>
</tbody>
</table>
Attachment 2. Rejection rates for Dark air-cured tobacco based on proposed 1 ppm NNN standard.

<table>
<thead>
<tr>
<th>Crop Year</th>
<th>Rejection Rate Based on Proposed 1ppm NNN Standard (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>69%</td>
</tr>
<tr>
<td>2006</td>
<td>54%</td>
</tr>
<tr>
<td>2007</td>
<td>20%</td>
</tr>
<tr>
<td>2008</td>
<td>24%</td>
</tr>
<tr>
<td>2009</td>
<td>68%</td>
</tr>
<tr>
<td>2010</td>
<td>10%</td>
</tr>
<tr>
<td>2011</td>
<td>15%</td>
</tr>
<tr>
<td>2012</td>
<td>34%</td>
</tr>
<tr>
<td>2013</td>
<td>67%</td>
</tr>
<tr>
<td>2016</td>
<td>35%</td>
</tr>
</tbody>
</table>
Appendix 1. Scientific Deficiencies in FDA’s Estimate of the Benefit of its Proposed Product Standard

FDA overestimates both avoided oral cancer cases and deaths attributable to smokeless tobacco products178 for two reasons:

- FDA’s estimate of the oral cancer risk associated with use of smokeless tobacco products is too high and ignores significant published scientific literature contrary to FDA’s chosen risk estimates; and

- FDA’s estimate of the oral cancer risk reduction associated with lowering NNN to 1.0 ppm in smokeless tobacco products uses a cancer slope factor that is not based on science rigorous enough to support regulatory action.

In addition, FDA does not provide sufficient evidence linking NNN exposure from smokeless tobacco products to human disease because FDA relies on a study of cigarette smokers, not smokeless tobacco product users, to link NNN and human cancer risk.

FDA should withdraw its proposed product standard to correct these errors and recalculate the possible health benefits associated with its proposed standard.

A. FDA’s Estimate of Oral Cancer Risk Associated with the Use of Smokeless Tobacco Products Ignores Significant Published Scientific Literature

FDA estimates of oral cancer risks179 are flawed for two significant reasons. First, FDA relies upon studies conducted more than 30 years ago, before the changes in farming and manufacturing described above that have dramatically reduced NNN levels in MST products, while not considering far more recent data that show dramatically fewer cases of oral cancer and oral cancer deaths associated with smokeless tobacco use. Second, FDA chose risk estimates which did not adjust for significant, non-tobacco causes of oral cancer.

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178 See 82 Fed. Reg. at 8006 (FDA estimates that the proposed standard will prevent approximately 12,700 oral cancer cases and approximately 2,200 oral cancer deaths in the 20 years following implementation of the 1 ppm NNN limit.)

179 See PRIA at 28-20 (FDA estimates that the proposed NNN product standard would reduce oral cancer by between 475 and 1,553 cases each year and oral cancer deaths by between 102 and 335 each year.) FDA derives this estimate by first calculating the population attributable risk (PAR) to determine the number of oral cancer cases and deaths attributable to smokeless tobacco use using low, primary and high oral cancer risk estimates and then scales these risk estimates down by 65% based on FDA’s estimate of the cancer risk reduction associated with implementing the proposed NNN standard. Id. at 27. We note that in its calculation of the excess lifetime cancer risk associated with NNN exposure from smokeless tobacco use, FDA assumed an NNN absorption rate of 60%. The study FDA cites to support this assumption (Hecht, S. S., S. G. Carmella, I. Stepanov, J. Jensen, A. Anderson, and D. K. Hatsukami. 2008. 'Metabolism of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanolone to its biomarker total NNAL in smokeless tobacco users', Cancer Epidemiol Biomarkers Prev, 17: 732-5) estimated NNK absorption, not NNN and did not account for the NNK expectorated by users. Two well conducted studies (Caraway, J. W., and P. X. Chen. 2013. 'Assessment of mouth-level exposure to tobacco constituents in U.S. snus consumers', Nicotine Tob Res, 15: 670-7; Digard, H., N. Gale, G. Errington, N. Peters, and K. McAdam. 2013. 'Multi-analyte approach for determining the extraction of tobacco constituents from pouch snus by consumers during use', Chem Cent J, 7: 55) actually estimated NNN absorption and reported it to be 23.1 and 25.6% respectively.
1. FDA Should Have Relied on the Most Recent Published Data and Used Gender Specific Estimates to Calculate Risk Estimates

FDA derives its primary estimate of the oral cancer risk (RR=2.16, 95% CI: 1.55-3.02) associated with smokeless tobacco product use from a reanalysis of a published meta-analysis. This meta-analysis includes seven studies whose conduct periods span 1959-2000, but which were predominantly conducted between approximately 1970 and 1985. These data do not represent the most recent assessment of the oral cancer risks associated with smokeless tobacco use in the U.S., nor do they account for the dramatic reduction in NNN that has taken place in the past 30 years.

In October of 2016, Wyss, with the National Institute of Environmental Health Sciences (NIEHS), published a combined analysis of eleven large studies evaluating the relationship between smokeless tobacco use and oral cancer risk. The conduct periods for studies included in this analysis ranged from 1981-2005, with four conducted during the 2000s, five conducted during the 1990s and only two conducted during the 1980s. These data, therefore, provide a much more recent and more pertinent evaluation of the oral cancer risk associated with smokeless tobacco use in comparison to the studies included in FDA’s meta-analysis (Figure 1).

![Figure 1. Conduct periods for studies included in FDA’s meta-analysis and in Wyss et al., 2016.](image)

FDA should have considered the Wyss data, which were available in the published literature when FDA developed its proposed product standard, in its calculation of the population risk for estimating the oral cancers attributable to smokeless tobacco use. Doing so would have accounted for any changes in smokeless tobacco products or the smokeless tobacco user.

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population during the approximately 20 years between the conduct of the studies FDA relied upon and the studies included by Wyss et al. In addition, low converter seed, which significantly reduces the level of NNN in tobacco, was fully implemented for Dark tobacco in 2005. None of the available epidemiology for smokeless tobacco and oral cancer reflects this important change, so the oral cancer risk associated with current products may be lower than that reported in the Wyss et al. study. As FDA recognizes throughout its proposed rule, this decline in TSNAs has implications for oral cancer risk and, therefore, renders older studies less relevant to current smokeless tobacco products.

Another reason that FDA should use the Wyss estimates is that it includes gender-specific risk estimates and oral cancer risk estimates for males and females are quite different. Wyss et al. report that the odds ratio for head and neck cancer among never smoking female smokeless tobacco users is 8.89 (95% CI, 3.59-22.0) while among never smoking male smokeless tobacco users it is 0.86 (95% CI, 0.49-1.51). The observation that female smokeless tobacco users demonstrate higher oral cancer risks compared to males is not unique to Wyss. Vogler et al. reported that male smokeless tobacco users had an oral cancer relative risk of 7.38 (95% CI, 4.31-12.62) while female smokeless tobacco users had a significantly higher relative risk of 38.27 (95% CI, 21.49-68.15).\(^{183}\) Blot et al. also found that female smokeless tobacco users had higher relative risks for oral cancer relative to males (relative risks of 3.44 (95% CI, 1.09-10.91) and 0.86 (95% CI, 0.57-1.26) respectively).\(^{184}\) It is inappropriate, therefore, for FDA to use the combined male and female risk estimate it derived from its meta-analysis. Rather, FDA should apply gender-specific risk estimates in recognition of the apparent risk differential.

It seems biologically implausible that females would be differentially susceptible to oral cancer following smokeless tobacco use compared to males. Following Occam’s Razor, a straightforward hypothesis is that the apparent risk differential results from use of different smokeless tobacco product types. Men predominantly use moist snuff while women have historically used dry, powdered snuff. Dry snuff may have a different risk profile compared to moist smokeless tobacco because TSNA levels in dry snuff have historically been very high. For example, Rodu et al. reported TSNA levels of 1,219 and 1,096 ppm (NNN levels were 287 and 210 ppm) in two dry snuff products.\(^{185}\) In contrast, in the same publication, total TSNA levels in moist snuff were approximately two orders of magnitude lower. Other authors have also observed the use of dry snuff among females in studies with high oral cancer risk estimates.\(^{186}\) Wyss’s analysis, stratified by gender and smoking status, reported no excess oropharyngeal cancer risk for male never-smoking smokeless tobacco users (OR 0.61, 95% CI: 0.61-1.07), male ever-smoking smokeless tobacco users (OR 0.81, 95% CI: 0.49-1.51) or female ever-smoking smokeless tobacco users (OR 0.92, 95% CI: 0.35-2.43). The authors did report a significantly

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elevated oral cancer risk among never-smoking female smokeless tobacco users (OR 8.89, 95% CI: 3.59-22.0).

Overall, the Wyss et al. study provides a much more recent and accurate assessment of the oral cancer risks associated with smokeless tobacco use today than the older data FDA relied upon. In addition, the Wyss data includes gender specific risk estimates. For these reasons, FDA should have considered the results published by Wyss et al. in estimating the potential health impact of the proposed product standard. Its failure to do so means that FDA has overestimated the oral cancer risk associated with the use of smokeless tobacco products.

2. FDA Selected Risk Estimates Which Do Not Adjust for Significant Known Causes of Oral Cancer

FDA also failed to use an appropriate oral cancer risk estimate because it failed to adjust for alcohol consumption. In calculating the range of avoided oral cancer cases and deaths that would result from implementation of its proposed standard, FDA used what it defined as “Low” and “High” estimates of the oral cancer risk associated with smokeless tobacco use. For its “Low” estimate, FDA selected the U.S. specific smoking-adjusted relative risk (1.65, 95% CI: 1.22-2.25) from Lee and Hamling. This estimate includes studies which do not adjust for alcohol consumption despite the fact that alcohol consumption is independently associated with risk for oral cancer.

In their meta-analysis, however, Lee and Hamling provide a pooled risk estimate for the oral cancer risk associated with smokeless tobacco use using only studies which adjust for smoking and alcohol consumption (1.04, 95% CI: 0.80-1.35). FDA should have used this fully adjusted oral cancer risk estimate as its “low” estimate. Instead, FDA incorrectly relied on an estimate which does not consider the independent, and possibly synergistic, effects of smoking and alcohol, which again, led the Agency to overestimate the benefits of its proposed standard.

B. FDA’s Estimate of the Oral Cancer Risk Reduction Associated With Lowering NNN to 1.0 ppm Uses a Cancer Slope Factor That is Not Based on Science Rigorous Enough to Support Regulatory Action

FDA relies on a cancer slope factor (CSF) for NNN to estimate the impact of its proposed product standard on oral cancer. This CSF is central to FDA’s analysis of the public health impact of the proposed rule. The CSF upon which FDA relies, however, is based on a study that

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189 Lee and Hamling (2009).
does not meet internationally recognized standards for studies of carcinogenicity assessment. Consequently, the study is insufficient to support regulatory action for the reasons stated below. And, without a robust and valid CSF, FDA cannot determine what impact, if any, the proposed product standard may have on oral cancer incidence and mortality. Furthermore, no NNN cancer bioassay has been published which meets the Organization for Economic Co-operation and Development’s (OECD) and the U.S. Environmental Protection Agency’s (EPA) recommendations for carcinogenicity studies. The CSF on which FDA relies was derived by the California Environmental Protection Agency (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA) using data from a drinking water NNN exposure study conducted in Syrian Golden hamsters. Hecht et al., however, does not meet testing guidelines established by the OECD for conducting carcinogenicity studies.

The OECD testing guidelines for carcinogenicity studies (Testing Guideline 451) recommend that a study should include at least 50 animals of each sex in order to achieve a thorough biological and statistical evaluation. Also, these guidelines recommend inclusion of multiple doses to develop a data based dose response curve. The Hecht study includes only 12 animals of each sex per group and includes only one dose.

In addition, according to EPA, the types of tumors observed in carcinogenicity studies should be considered in extrapolating from the animal data to the human situation. For example, a greater proportion of malignant tumors is “weighed more heavily” than a response consisting of a higher proportion of benign tumors, and benign tumors that are not expected to progress to malignancy should be assessed on a case-by-case basis. Benign tumors may be considered alone in a carcinogenicity risk assessment if they pose a significant health risk by altering the function of the target tissue. In addition, when reviewing these studies, treatment-related effects considered for estimation of a CSF should be those results reported to be statistically significantly different in treated groups, compared to untreated controls. The tumors reported in the Hecht study were benign nasal and tracheal papillomas, not malignancies, and the incidence of these benign tumors was not statistically different between treated and control groups. These results provide a questionable basis for calculation of a human CSF.

Because the CSF is meant to be predictive for lifetime exposures, carcinogenicity studies involving chronic exposure over the majority of the lifespan of the animal are considered top priority when choosing a dataset for the derivation of the CSF. The Hecht study exposed animals for 31 weeks only, not lifetime. Overall, the non-significant occurrence of benign tumors at sites other than the oral cavity, coupled with the lack of sufficient treatment group size or

194 USEPA 2005
exposure period, do not provide a sufficiently robust study to derive a CSF that can support FDA’s proposed product standard.

Since the study supporting FDA’s CSF is insufficient to support regulatory action, we investigated whether any sufficient study exists to derive a CSF which FDA can use to estimate the effect of its proposed product standard on oral cancer risk among smokeless tobacco users. Our literature search identified 21 publications potentially containing in vivo NNN oral administration data, which we both scored for study quality using Klimisch criteria and critically reviewed.\(^{195}\) The Klimisch criteria used to score the studies are shown in Attachment A1 and the studies are described briefly below and in Attachment A2. None of the studies listed below received the highest scores of a one or two out of four, because, among others reasons, they were not conducted according to Good Laboratory Practices (GLP) and included only one dose group. Overall, the available NNN cancer bioassay studies are not of sufficient quality to support FDA’s proposed regulatory action because none of them meet OECD and EPA guidelines for carcinogenicity assessment.

- Nine of the studies received a score of three out of four.\(^{196}\) These studies received a quality score of three because, among other reasons, each study used only one dose group. Therefore, these nine studies lack the information needed to understand the relationship between dose, or concentration, and response, which would increase the reliability for conducting a quantitative assessment.

- Five studies\(^{197}\) received a score of four out of four. These studies received a quality score of four because the route of exposure (i.e. intraperitoneal or subcutaneous injections) was


not comparable to the route of exposure (oral) expected in human populations. These studies were retained for review, however, because two of the studies had multiple dose groups which may provide information concerning the relationship between NNN dose (i.e. concentration) and carcinogenic responses. Singer and Taylor received a score of four because the study did not include a negative control group.

- Seven studies received a score of four because they were review articles and, therefore, did not contain original data.

FDA states that “[s]tudies 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.” FDA cites 17 studies in support of this statement. However, only two of the 17 studies detected oral tumors following NNN exposure. The first study which detected oral tumors involved ethanol co-administration, a known cause of oral cancer; and the second study included enantiomers of NNN, but no control group. These two studies, therefore, are of little value in determining the carcinogenic effects of NNN per se. Tumors in the remaining 15 studies were most commonly detected in the esophagus, lung and nasal cavity, but not the oral cavity. Overall, these studies do not provide convincing evidence that NNN is a potent oral carcinogen in these animal models.

None of the published in vivo cancer bioassays is sufficiently well conducted to support a CSF robust enough to support regulatory decision making. The CSF is central to FDA’s analysis of the public health impact of the proposed rule because FDA uses the CSF to estimate the magnitude of the oral cancer risk reduction it believes will result from its proposed product standard. Without a robust and valid CSF, FDA is unable to determine what impact, if any, the proposed rule will have on oral cancer incidence and mortality.
C. FDA Does Not Provide Sufficient Evidence to Link NNN Exposure from Smokeless Tobacco Products to Human Disease

FDA inappropriately extrapolates NNN data from studies involving smokers to smokeless tobacco users. Specifically, FDA cites evidence from studies conducted in China among cigarette smokers indicating that TSNA and NNN exposure are linked with cancer in humans. In one of these studies, total urinary NNAL (a biomarker for NNK and recognized as a biomarker for TSNA exposure) was significantly associated with risk of developing lung cancer. In the second study, mean NNN levels were significantly associated with head and neck cancers. FDA suggests that, although these studies were conducted in smokers and not in smokeless tobacco users, the results support the importance of NNN in human cancer development. FDA also notes that smokeless tobacco users are exposed to similar levels of TSNA, including NNN, as cigarette smokers. However, the routes of exposure for cigarette smoke and smokeless tobacco are very different – inhaled versus oral. Therefore, it is inappropriate to extrapolate data on the association between TSNAs, including NNN, in cigarette smokers to smokeless tobacco users. In fact, smokeless tobacco users demonstrate TSNA exposure levels as high as or higher than those of cigarette smokers, but have demonstrably lower cancer risks, including oral cancer risk. Elsewhere in its proposed rule, FDA recognized the deficiencies in relying on studies of smokers as support for a smokeless tobacco carcinogenicity assessment, yet FDA relied on studies of cigarette smokers in formulating this proposed product standard.

Published data indicates that smokeless tobacco users are exposed to similar levels of TSNA, based on urinary levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides

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204 Yuan et al. (2011).
205 Stepanov et al. (2014).
207 “Different measures are required to evaluate the contribution of 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.’” 82 Fed. Reg. 8006. FDA is certainly aware that route of administration is important when considering the toxicological implications of exposure to substances. For example, in its response to a comment to the proposed deeming rule suggesting that Generally Recognized as Safe for use in foods (GRAS) status be used to approve ingredients for use in e-vapor products, FDA notes that the GRAS determination for food ingredients “does not take inhalation toxicity into account” and should not be applied to e-vapor product ingredients. See 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. 28973, 29002 (May 10, 2016) (to be codified at 21 C.F.R. pts. 1100, 1140 and 1143).
We have conducted an analysis of TSNA exposure among current exclusive smokeless tobacco product users and current exclusive cigarette smokers using the National Health and Examination Survey (NHANES) dataset, which includes bioanalytical measures including total NNAL. Our analysis indicates that current exclusive smokeless tobacco users have higher average TSNA exposure than current exclusive cigarette smokers, but as shown below, far lower cancer risk.

We have directly compared the mortality risks associated with smokeless tobacco use and cigarette smoking using two independent, large, nationally representative public health surveys with prospective mortality follow-up available through linkage to the National Death Index. The two surveys are the National Health Interview Survey (NHIS) and the National Longitudinal Mortality Study (NLMS), which is based on the Current Population Survey. Our results, in Figure 2 below, clearly show that the overall mortality risks and cancer mortality risks associated with smokeless tobacco use are vastly lower than those associated with cigarette smoking. These data do not support FDA’s hypothesis that the link between NNN exposure and cancer risk in cigarette smokers is relevant to smokeless tobacco users.

<table>
<thead>
<tr>
<th>Mortality Outcome</th>
<th>Current Smokeless Tobacco Users</th>
<th>Current Cigarette Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NHIS (95% CI)</td>
<td>NLMS (95% CI)</td>
</tr>
<tr>
<td>All causes</td>
<td>1.10 (0.97-1.25)</td>
<td>0.88 (0.67-1.15)</td>
</tr>
<tr>
<td>All cancers</td>
<td>1.04 (0.82-1.31)</td>
<td>1.01 (0.57-1.79)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.34 (0.79-2.27)</td>
<td>1.83 (0.75-4.46)</td>
</tr>
<tr>
<td>Oral Cancer</td>
<td>suppressed*</td>
<td>no deaths</td>
</tr>
<tr>
<td>Esophageal Cancer</td>
<td>suppressed*</td>
<td>1.56 (0.20-12.18)</td>
</tr>
</tbody>
</table>

* These oral and esophageal cancer mortality risks were derived from our analyses of the NHIS restricted access file. The National Center for Healthcare statistics suppresses cell sizes of less than five to protect respondent confidentiality.

Figure 2. Select mortality hazards for current smokeless tobacco users and current cigarette smokers from two large, nationally representative linked mortality data sets.

Compared to never tobacco users, current cigarette smokers have a statistically significantly elevated risk of mortality from all cancers. In both the NHIS and NLMS linked mortality analyses, the all cancer mortality hazard ratios (HR) for current cigarette smokers were 3.04 and 2.90, respectively. In contrast, current smokeless tobacco use was not associated with excess risk for all cancer mortality in either linked mortality data set. The current smokeless tobacco users all cancer mortality HRs were 1.04 and 1.01 in the NHIS and NLMS analyses, respectively.


Figure 3 below compares the NNAL levels and cancer mortality risks between cigarette smokers and smokeless tobacco users.

![Mortality Risk and Average Urinary NNAL](image)

**Figure 3.** Mortality Risk and Average Urinary NNAL All Cancer Mortality, Males Only.

The lung cancer mortality risks among cigarette smokers are also significantly elevated in both the NLMS and NHIS mortality linkages (HRs of 11.84 and 18.06, respectively). Current smokeless tobacco users, however, do not demonstrate significantly elevated lung cancer mortality risks in either mortality linkage (HRs of 1.34 in the NLMS and 1.83 in the NHIS), despite higher levels of NNAL compared to cigarette smokers (Figure 4, below).
We were not able to derive a HR for oral cancer mortality among smokeless tobacco users in either the NLMS or NHIS mortality linkages because there were insufficient numbers of oral cancer deaths among smokeless tobacco users to support an HR calculation.\(^{210}\) However, based on data from the American Cancer Society’s Cancer Prevention Study II, among males, the oral cancer risk associated with cigarette smoking is 10.89.\(^{211}\) In its proposed product standard, FDA posits that the oral cancer risk associated with smokeless tobacco use is 2.16 or approximately five-fold lower than the oral cancer risk associated with cigarette smoking. This risk differential also does not support FDA’s contention that the linkage between NNN exposure and cancer risk in cigarette smokers is relevant to smokeless tobacco users.

In sum, the science FDA cites to support its proposed product standard is subject to significant criticisms which call into question the rigor of FDA’s analysis. FDA has overestimated the potential impact of its proposed standard on oral cancer rates because it relies on older epidemiological data that, in some cases, does not include proper adjustment for known confounders. In addition, FDA’s cancer slope factor analysis, from which it estimates the risk reduction associated with its proposed standard, is not sufficiently well-conducted to support regulatory action. Finally, FDA has not provided sufficient evidence that NNN exposure is

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\(^{210}\) 0 smokeless tobacco user OC deaths in NLMS, <5 in NHIS resulting in suppression of the estimate consistent with NCHS policy.

linked with disease in smokeless tobacco users. As a result, FDA has significantly overestimated the public health benefits of the proposed standard and should withdraw it until FDA fully addresses these significant scientific deficiencies.
### Attachment A1. Klimisch Criteria

<table>
<thead>
<tr>
<th>Quality Score</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Studies or data from the literature or reports that are carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to Good Laboratory Practices [GLP]), or studies in which the test parameters documented are based on a specific (national) testing guideline (preferably performed under GLP), or studies in which all parameters described are closely related/comparable to a guideline method.</td>
</tr>
</tbody>
</table>
| 2             | Studies that are not performed according to GLP or specific testing guidelines but are well documented and scientifically acceptable with the following information reported:  
For in vivo animal studies this includes the following criteria:  
- Data on the test animals including species, sex, and strain  
- The purity/composition/origin of the test substance  
- The number of animals evaluated  
- The scope of the investigation per animal (e.g. clinical chemistry, hematology, organ weights, pathology or histopathology) and description of the methods  
- Description of the changes observed  
- Control group or historical control data of the laboratory  
- Description of the test conditions  
- Description of the route and doses of administration  
- Dose/concentration relationship is possible  
For in vitro studies this includes the following criteria:  
- Description of the test system and test method in details  
- Purity/composition/origin of the test substance  
- Data on the dose/concentration differentiated according to the toxicity of the test substance on the test system; information on volatility  
- Data on secondary effects which may influence a result (solubility, impurities, pH shifts, influence on the osmolality, etc.)  
- Appropriate negative/positive controls as integral parts of the test  
- References on adequacy of the method should be given or generally known |
| 3             | Studies or data from the literature which do not meet the criteria for a quality score of 2. These include studies for which the methods were not clearly defined or specified in the study, in which a lack of dose-response information was available (only one dose was administered), or small numbers of animals per group were tested. The appropriate number of animals per group was determined based on recommendations from OECD guidelines for comparable study types. |
| 4             | Studies or data from the literature which do not provide sufficient experiment details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).  
Additional criteria for in vivo animal studies:  
- Single exposure  
- Inappropriate or irrelevant species tested  
- Route of exposure not relevant to humans  
- If the animals tested underwent any type of alteration or injury prior to testing |
### Attachment A2. Results of the Study Quality Analysis Applying Klimisch Criteria to Studies Potentially Relevant to Calculating a CSF.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Quality Score</th>
<th>Rationale for study quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balbo et al. 2013</td>
<td>3</td>
<td>No information was reported indicating the study was performed according to GLP. The study was not performed according to any specific published testing guidelines. Only one dose group was utilized in the study; therefore dose response could not be determined.</td>
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<tr>
<td>Castonguay et al. 1984</td>
<td>3</td>
<td>No information was reported indicating the study was performed according to GLP. The study was not performed according to any specific published testing guidelines. Only one dose group was utilized in the study; therefore dose response could not be determined. Only one gender was tested. Statistical analysis was not conducted.</td>
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<td>Chen et al. 1994</td>
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<td>Hecht et al. 1983</td>
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<td>Nachiappan et al. 1994</td>
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<td>Padma et al. 1989a</td>
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<td>Hilfrich et al. 1977</td>
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<td>No information was reported indicating the study was performed according to GLP. The study was not performed according to any specific published testing guidelines. Only one dose group was utilized in the study; therefore dose response could not be determined. No statistical analyses were performed. Purity of the test substance was not specified. Route of exposure was not comparable to expected routes of exposure in humans.</td>
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<table>
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<tr>
<th>Study</th>
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<th>Rationale for study quality score</th>
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<td>Hecht 1999</td>
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<td>This is a review article and not a carcinogenicity study.</td>
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<td>Singer and Taylor 1976</td>
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<td>No information was reported indicating the study was performed according to GLP. The study was not performed according to any specific published testing guidelines. Purity of the test substance was not specified. Only one dose group was utilized in the study; therefore dose response could not be determined. The study did not include a negative control group.</td>
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<td>Gijare et al. 1989</td>
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<td>Study was conducted in an inappropriate cell line (i.e. embryonal cells).</td>
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<td>Study was not a toxicity study, nor was it a MOA study.</td>
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<td>Prins and Wang 2013</td>
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<td>Saito et al. 2005</td>
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