The responses in this submission address the U.S. Food and Drug Administration (FDA) Deficiency Letter dated March 26, 2021 and are submitted by Altria Client Services LLC (ALCS) on behalf of U.S. Smokeless Tobacco Company LLC (USSTC).[1]

The proposed MRTP provides an opportunity to motivate a subset of adult smokers to reduce their health risks.

The proposed modified risk tobacco product (MRTP) is a grandfathered moist smokeless tobacco (MST) product, commercially marketed in the U.S. as of February 15, 2007 (FDA Grandfather Status # GF1200194). Because it is not a new tobacco product as defined by Section 910(a)(1) of the Food, Drug and Cosmetic Act (FDCA), it does not require premarket review and authorization. USSTC requests that FDA designate this product as a MRTP authorized to be marketed with the following proposed modified risk claim:

> "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer."

The proposed MRTP, like similar MST products, presents both a dilemma and an opportunity. The dilemma arises from three indisputable facts:

- First, although the proposed MRTP and other smokeless tobacco (ST) products are not risk free, they are substantially less hazardous than combustible cigarettes – not only for lung cancer, but for other tobacco-related diseases. This is the overwhelming consensus of the scientific, medical, and public health communities.[2]
- Second, adult tobacco consumers (ATCs) have preexisting and deeply rooted misperceptions about the health risks of ST products relative to cigarettes. Our research, FDA's research, and more than a dozen published studies establish that a vast majority of adult smokers (AS) still believe that using ST is at least as hazardous as cigarette smoking, if not more so. For example, more than 90% of AS in FDA's Population Assessment of Tobacco and Health (PATH) survey state that ST products are just as harmful or even more harmful than cigarettes.
- Third, evidence from the PATH survey shows that approximately 23 million AS would consider using a tobacco product if they believed it offered a reduced risk of harm.[3] Accurate information can motivate AS, including many of the about 2.3 million adults who currently use both cigarettes and ST, to quit smoking and convert completely to ST products. Indeed, AS who understand that ST products are less

[1] USSTC is a wholly owned subsidiary of Altria Group, Inc. (Altria). ALCS provides certain services, including regulatory affairs, research and development, and regulatory sciences to the Altria family of companies. "We" or similar pronouns are used throughout to refer to USSTC.

[2] *See, e.g.,* Hatsukami, D., Joseph, A. M., Lesage, M., Jensen, J., Murphy, S. E., Pentel, P. R., . . . Hecht, S. S. (2007). Developing the science base for reducing tobacco harm. *Nicotine & Tobacco Research, 9* (Suppl 4), S537-S553. https://doi.org/10.1080/14622200701679040; Zeller, M., & Hatsukami, D. (2009). The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. *Tobacco control, 18*(4), 324-332. https://doi.org/10.1136/tc.2008.027318

[3] Based on ALCS analysis of PATH Wave 1 data Sept. 12, 2013 - Dec. 14, 2014: Response to question – "If a tobacco product made a claim that it was less harmful to health than other tobacco products, how likely would you be to use that product?"

harmful than cigarettes are approximately four times more likely to quit combustible tobacco products and switch to ST.[4]

This dilemma gives rise to the opportunity: To motivate AS and dual users to transition completely from cigarettes to the proposed MRTP by providing them with accurate, non-misleading information, based on compelling scientific evidence, about the relative lung cancer risk of these products.

The scientific evidence submitted satisfies the requirements under section 911.

To that end, we seek a risk modification order under FDCA Section 911(g)(1), which requires FDA to authorize a proposed modified risk claim when a product, as it is actually used by consumers, will – "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products."

The scientific evidence presented in our application satisfies both of those requirements. We have shown that:

- The proposed MRTP is significantly less harmful than cigarettes and switching completely from cigarettes to this product reduces the risk of lung cancer;
- The proposed MRTP claim is truthful, accurate, and substantiated by unequivocal scientific evidence, including the most current epidemiology data;
- The proposed MRTP claim is not misleading: Tobacco users and nonusers understand that the proposed MRTP poses health risks, and the claim does not diminish their perceptions of either its overall harmfulness or its risks for other diseases and conditions, such as mouth cancer, heart disease, and nicotine addiction;
- AS not planning to quit, particularly adult male smokers, are more likely to use this product, and dual users are another logical audience; and
- A net benefit to the health of the population as a whole is expected upon market authorization of the proposed claim.

Moreover, FDA has stated that the proposed claim is "scientifically accurate"[5] and not misleading to consumers.[6] The Tobacco Products Scientific Advisory Committee (TPSAC) overwhelmingly concurred with both of those assessments. With a total of 9 votes (8 yes, 0 no,

[4] Noggle, B.; Sarkar, M.; Rosner, J.; Black, R., "Smokeless Tobacco and Smoking Relative Harm: Beliefs and the Association between Risk Perception and Tobacco Use Transitions". Poster presented at the 25th Annual Meeting of the Society for Research on Nicotine and Tobacco (SRNT), San Francisco, CA, February 20-23, 2019 (analyzing perceptions and transitions among AS from PATH Wave 1 to Wave 2), Beliefs and the Association between Risk Perception and Tobacco Use Transitions (altria.com).

[5] FDA Briefing Document: February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, https://www.fda.gov/media/121996/download, at 21 ("Based on the evidence described above, the proposed modified risk claim "IF YOU SMOKE: CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer" appears to be scientifically accurate.").

[6] *Id*. at 29 (finding that a majority of consumers who viewed the claim correctly comprehended its meaning and that viewing it did not affect consumers' perceptions that using the proposed MRTP poses risks to health). *See also* FDA Presentation: February 6-7, 2019 TPSAC Meeting re USSTC Modified Risk Tobacco Product Application, https://www.fda.gov/media/122007/download, slides 33-34, 49 (same).

and 1 abstaining), the TPSAC agreed that the proposed claim is "scientifically accurate."[7] Similarly, the TPSAC Chair expressed the members' "consensus" that the proposed claim is "clear," "understandable," and does not mislead consumers into believing that the proposed MRTP is "risk-free."[8]

By authorizing the proposed MRTP, FDA can fulfill its duty under the law, make progress on its stated goal of reducing harm through advancement of reduced risk products, and take a first step towards correcting a misperception held by millions of ATCs.

Additional considerations for FDA as it fulfills its duty.

As its evaluation continues, we urge FDA to consider three additional points.

First, FDA should apply the statutory MRTP provisions to this MRTP application in a manner consistent with the First Amendment. Section 911 restricts protected speech – namely, tobacco manufacturers' truthful communications to ATCs about lawful tobacco products. These restrictions discriminate based on both the content of the speech and the identity of the speaker. With regard to content-based discrimination, tobacco product manufacturers can freely convey other messages about their products but cannot make modified risk claims without first obtaining FDA's permission.[9] With regard to speaker-based discrimination, doctors, insurers, government officials, and almost anyone else can speak freely about the comparative risks of tobacco products, but here again, manufacturers cannot speak without first obtaining FDA's permission.

In *Sorrell v. IMS Health Inc.*, the Supreme Court held that content- and speaker-based restrictions on speech are subject to "heightened judicial scrutiny" under the First Amendment – a burden the Court described as ordinarily "all but dispositive."[10] Speech restrictions are especially problematic when, as here, they censor accurate information in the realm of public health. Indeed, the Supreme Court has shown it will readily strike down speech restrictions, especially "in the fields of . . . public health, where information can save lives."[11]

Accordingly, once an applicant has demonstrated that a proposed MRTP claim is accurate and non-misleading, that should be the end of the matter, and FDA should authorize the application.

Such is the case here. As noted above, the record for this MRTP application establishes that the proposed claim is both accurate and non-misleading. FDA should therefore authorize the proposed claim.

To be sure, FDCA Section 911 also requires applicants to demonstrate that marketing a MRTP would "benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products."[12] This requirement can be at odds with the First Amendment when applied to a situation where, as here, the proposed claim has been shown to be accurate and non-misleading. Under both the First Amendment and

[7] Transcript: February 7, 2019 TPSAC Meeting re USSTC Modified Risk Tobacco Product Application, https://www.fda.gov/media/122003/download, at 330-32.
[8] *Id.* at 348-49, 354-55.
[9] FDCA § 911(b)(2)(A)(i).
[10] *Sorrell v. IMS Health, Inc.*, 564 U.S. 552, 565, 571 (2011).
[11] *Nat'l Inst. Of Family & Life Advocates v. Becerra ("NIFLA")*, 138 S. Ct. 2361, 2374 (2018) (quoting *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 566 (2011)).
[12] FDCA § 911(g)(1)(B).

applicable caselaw, FDA should not deny this MRTP application because of how the claim might affect decisions of other ATCs – specifically, decisions by those who use "other smokeless tobacco products" to switch to the proposed MRTP or to dual use it with their current product. *See* Deficiency Letter at 5 (Question 8).

The Supreme Court has long "rejected the notion that the Government has an interest in preventing dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information."[13] The First Amendment guarantees both the right of AS to receive such information and the right of manufacturers to provide it.

Second, FDA should act expeditiously to resolve this MRTP application. Because Section 911 operates as a prior restraint, the First Amendment requires adequate procedural and substantive safeguards to ensure that government does not suppress protected speech. Such prior restraint is permissible only where: (1) the government meets its burden of proving the speech is not protected by the First Amendment; (2) the period of suppression is the shortest period necessary to review an application and a decision is made by a deadline specified in advance; and (3) judicial review is promptly available.[14] Any prior restraint scheme must also employ "narrow, objective, and definite standards to guide the licensing authority."[15]

FDA should therefore establish and adhere to a binding deadline for completing its review of MRTP applications. We (and others) have long urged FDA to take that step,[16] but it has not yet done so. Notably, the Supreme Court has held that even a 57-day delay in reviewing an application is unconstitutional.[17]

FDA's timeline for resolving this MRTP application has not been short. USSTC submitted this application approximately 3½ years ago, on March 19, 2018. More than 2½ years have elapsed since February 7-8, 2019, when the TPSAC convened to respond to FDA's questions. And far more time has passed than the 360 days that FDA described in draft guidance as its intended timeline for acting on MRTP applications.[18] We appreciate FDA's attention to this application and acknowledge the challenges posed by the coronavirus epidemic and the influx of PMTAs for ENDS and other deemed new tobacco products. But the time for authorizing this MRTP application is, respectfully, overdue.

Finally, FDA's review of this MRTP application should conform with the scope of FDCA Section 911. A number of questions in the Deficiency Letter seek information related to

[13] *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002).
[14] *Southeastern Promotions, Ltd. v. Conrad*, 420 U.S. 546, 560 (1975).
[15] *Forsyth Cty. v. Nationalist Movement*, 505 U.S. 123, 131 (1992).
[16] *See, e.g.*, ALCS Comments on "Tobacco Product Application Review; Public Meeting; Request for Comments," Docket No. FDA-2018-N-3504 (83 Fed. Reg. 48,268, September 26, 2018), submitted December 7, 2018; ACLS Comments on "Modified Risk Tobacco Product Applications: Applications for Six Camel Snus Smokeless Tobacco Products Submitted by R.J. Reynolds Tobacco Company," Docket No. FDA-2017-N-4678, submitted August 8, 2018; ALCS Comments on the "Draft Guidance for Industry: Modified Risk Tobacco Product Applications," Docket No. FDA-2012-D-0071 (77 Fed. Reg. 20,026, April 3, 2012), submitted June 4, 2012; ACLS Comments on "Draft Guidance on Preliminary Timetable for the Review of Applications for Modified Risk Tobacco Products under the Federal Food, Drug, and Cosmetic Act," Docket No. FDA-2009-D-0563, submitted February 25, 2010.
[17] *See Teitel Film Corp. v. Cusak*, 390 U.S. 139, 141-42 (1968) (per curiam).
[18] FDA Draft Guidance, Modified Risk Tobacco Product Applications, March 2012, at 42 ("FDA intends to act upon your MRTPA no later than 360 days after the receipt of an application that contains the information required by section 911 of the FD&C Act.").

manufacturing, processing and quality control. We provide this information below. That said, Congress did not intend for FDA to consider such information when determining whether to authorize a modified risk claim. If it had so intended, it would have said so expressly – as it did in FDCA Section 910.[19]

FDA lacks the authority to import Section 910 requirements into Section 911. The statute does not link Section 910 and 911, but instead unambiguously identifies two independent but non-exclusive classes of tobacco products, each with its own authorization process. Section 910 governs the process for statutorily defined "new tobacco products."[20] Section 911 is limited to the review of proposed modified risk claims. Hypothetically, a proposed MRTP could also be a "new tobacco product" subject to Section 910. But such is not the case here. The proposed MRTP is a grandfathered tobacco product. As such, it is not subject to premarket review and authorization, making the requirements of Section 910 inapplicable.

Nor can FDA use Section 911 as a vehicle to apply the equivalent of a tobacco product manufacturing practice regulation indirectly. Some questions in the Deficiency Letter suggest that FDA might issue a risk modification denial order if the responses do not adequately satisfy its expectations regarding manufacturing and processing. To date, however, FDA has not even disclosed these unstated and unknown expectations outside its walls, let alone subjected them to public rulemaking. The law does not permit FDA to covertly establish or enforce such requirements in an ad hoc manner through product applications processes. Tobacco product manufacturing practice requirements must be adopted in accordance with, not apart from, the process mandated by FDCA Section 906(3)(1)(B).

Without waiving these concerns, the responses below address each numerated question and provide the information requested by FDA.

[19] FDA Section 910 requires PMTA applicants to submit "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product." Section 911, by contrast, contains no requirement whatsoever for manufacturing or processing information It is well-established that "[where] Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." *Russello v. United States,* 464 U.S. 16, 23 (1983) (internal quotation marks omitted)); *see also Nat'l Ass'n of Broadcasters v. FCC,* 569 F.3d 416, 421 (D.C. Cir. 2009) (there is a "general presumption that an omission is intentional where Congress has referred to something in one section but not in another").

[20] The term "new tobacco product" is defined by FDCA Section 910(a)(1).

Question 1

Your MRTPA identifies a grandfathered product (GF1200194) as the product subject of the application. (b) (4)

Response

In response to this question, if FDA authorizes the proposed MRTP, we state that we will follow the marketing plan described in our *MRTPA, Section 4*. Additionally, we will:

(b) (4)

In our MRTPA, we provided evidence that:

- the proposed MRTP, as actually used, is significantly less harmful than cigarettes;
- the proposed modified risk claim is accurate, non-misleading, and supported by the scientific evidence; and
- a net benefit to the health of the population as a whole is expected upon market authorization of the proposed modified risk claim.

This evidence provided in the MRTPA remains applicable to the (b) (4), as the tobacco product inside the can will still be the same grandfathered product (GF1200194) and the proposed claim will remain the same.

To confirm that conclusions drawn from the Claim Comprehension and Intentions Study (CCIS)[22] and associated assessments regarding risk perceptions and behavioral intentions[23] remain applicable to the (b) (4), we conducted a two-way randomized crossover design quantitative bridging study among adult tobacco users and nonusers. The purpose of this bridging study was to compare risk perceptions and behavioral intentions between the originally named and (b) (4). The results demonstrate that renaming the proposed MRTP has little impact on adult tobacco users' and nonusers' behavioral

[21] In the *MRTPA, Section 4*, USSTC provided samples of promotional materials that may be used to market the proposed MRTP if authorized. When used, we will use images of the (b) (4) with adjusted labels like the image in *Appendix 1.1*.
[22] See *MRTPA, Section 7.3*.
[23] We did not assess claim comprehension in this study since claim language remains the same.

intentions and risk perceptions. Therefore, the conclusions from CCIS and assessments using the CCIS results remain applicable to the (b) (4). See *Appendix 1.2*.

Briefly, in this study design, adult tobacco users and non-users age 21+ viewed promotional material for the proposed MRTP (b) (4). The promotional material included the modified risk claim from the CCIS (*Figure 1.1*) in an online survey, with two rotations to control for order effect.

Figure 1.1: **Promotional Materials Used in Bridging Study**

Originally Named Proposed MRTP

(b) (4)

Note: All four warnings (per section 3 of the Comprehensive Smokeless Tobacco Health Education Act (CSTHEA), as amended by section 204 of the Tobacco Control Act, in accordance with an FDA approved warning plan) were used during the evaluation, but each participant was exposed to only one of the warnings during testing, randomly assigned by participant. Warnings were randomized within subgroups.

The study included 827 participants, with 301 adult smokers, 225 moist smokeless tobacco (MST) users, and 301 non-users of tobacco, recruited online by (b) (4) via their probability-based (b) (4).[24] Participants answered questions regarding their intentions to try and use the products based on the promotional material as well as their risk perception of general harm. The survey items were taken from the CCIS questionnaire. Questions included specific reference to "Copenhagen Snuff" for the originally named proposed MRTP and (b) (4) for the (b) (4). Intentions to try or use were measured with three or four items, respectively, on a 6-point scale, and a composite score of

[24] The total unique participant population in this study was designed to be approximately 900, with approximately 300 participants in each of three groups. However, the total sample included 827 participants, with only 225 participants in the MST Users group (Group 2), due to lower than expected qualification of MST Users.

intention to try or use was created by taking the average of those items. Risk perception of general harm was based on response to one item using a three-point scale. The proportion of those rating the originally named or (b) (4) as "moderately harmful" or "very harmful" were combined to indicate those participants rating either as "harmful" versus those rating either as "not at all harmful." See *Appendix 1.2* for the final study report with detailed study procedures and results.

We observed no statistically significant differences ($p>0.05$) for intentions to try or use the product among adult smokers and non-users of tobacco products, after viewing the promotional materials for the originally named and the (b) (4).[25] MST users, the vast majority of whom were exclusive users,[26] showed statistically significantly ($p<0.05$) lower intentions to try and use the (b) (4) compared to the originally named proposed MRTP. Nonetheless, the magnitude of the differences was small and within the same response category.[27] Additionally, adult smokers are the intended audience of the proposed MRTP, not exclusive MST users. There were no differences in perceptions of general harm among adult smokers, MST users and non-users of tobacco products. This study demonstrates that behavioral intentions and risk perceptions were similar for promotional materials with the (b) (4) and the originally named proposed MRTP. Therefore, the conclusions and associated assessments from the CCIS remain applicable.

Conclusion:

(b) (4)

[25] The mean composite score for Intention to Try among Adult Smokers is nearly identical for both the originally named proposed MRTP (mean score of 1.44; standard deviation (S.D.) = 0.90) and the (b) (4) (mean score of 1.43; S.D.= 0.90). Likewise, the mean composite score for Intention to Try among Non-Users is virtually the same for both the originally named proposed MRTP (mean score of 1.07; S.D.= 0.34) and the (b) (4) (mean score of 1.08; S.D.= 0.32). The mean composite score for Intention to Use among Adult Smokers is identical for both the originally named proposed MRTP and the (b) (4) with a mean score of 1.30 (S.D.= 0.75 and 0.72, respectively). Similarly, the mean composite score for Intention to Use among Non-Users is virtually the same for both the originally named proposed MRTP (mean score of 1.03; S.D.= 0.16) and the (b) (4) (mean score of 1.02; S.D.= 0.14). See *Appendix 1.2*.

[26] Exclusive is in relation to cigarette smoking; 84% of the MST User group reported no current cigarette smoking.

[27] For MST Users, the mean composite score for Intention to Try ranges from 3.30 (S.D.= 1.47) for the (b) (4) to 3.45 (S.D.= 1.59) for the originally named proposed MRTP. See *Appendix 1.2*. Although this difference is statistically significant at a level of $p<0.05$, the magnitude of the difference is small (0.15) and the scores fall within the same response category on the scale (absolute value of 3; "somewhat disagree" or "somewhat unlikely"). Also, the mean composite score for Intention to Use in MST Users ranges from 2.69 (S.D.= 1.40) for the (b) (4) to 2.89 (S.D.= 1.59) for the originally named proposed MRTP. See *Appendix 1.2*. Although this difference is statistically significant at a level of $p<0.05$, the magnitude of the difference is small (0.20) and the scores fall within the same response category on the scale (absolute value of 3; "somewhat disagree" or "somewhat unlikely").

(b) (4)

Question 2

Your MRTPA includes design parameter specifications but does not include data confirming that the target specifications are met. The target specifications serve to define the product, whereas test data demonstrate that the applicant can manufacture the product consistently. A product that is not consistently manufactured may have implications for the risk profile of the product. In order to confirm the target specifications are met, provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for all of the following smokeless tobacco design parameters for the proposed MRTP:

a. Leaf moisture (%) [(b) (4)]
b. Blend moisture (%) [(b) (4)]

Response

In response to this question, we provide:

- a summary of (see *Table 2.1*) and complete data set for leaf moisture (% oven volatiles (OV)) (b) (4) see *Appendix 2.1(and referenced appendices 2.7-2.9)*;
- a summary of (see *Table 2.2*) and complete data set for blend moisture (% OV) measured (b) (4), see *Appendix 2.1(and referenced appendices 2.7-2.9)*; and
- work instructions used for both leaf and blend moisture in effect at the time of testing (with reference to the corresponding ALCS standard test method(s) on which the work instruction is based), see *Appendices 2.2 - 2.6*. We previously identified the ALCS standard test methods in *MRTPA*, *Section 3.1, Table 3.1-24 and Table 3.1-25.*[28]

Response to a.

As set forth in our *MRTPA, Section 3.1.3.2.3*, re-drying during the leaf processing stage achieves a consistent % OV range prior to packing and aging. During re-drying, (b) (4) In *Table 2.1*, we provide a summary of leaf moisture (% OV) measured (b) (4) of the manufacturing process for the proposed MRTP. These data were collected in (b) (4) on hogsheads of tobacco used to manufacture the proposed MRTP in (b) (4) prior to submission of the MRTPA. The ranges for % OV provided in *Table 2.1* were previously provided in the MRTPA. See *MRTPA, Section 3.1.3.2.3.*

Table 2.1: Percent Oven Volatiles (% OV) Measured during (b) (4): Summary

Tobacco Type	Number of Production Days	n = hogsheads	Average (% OV)	Std. Dev.	Lower Limit	Target	Upper Limit
(b) (4)							

[28] We validated the ALCS standard test methods following our internal method validation guidelines. Our internal method validation guidelines are based upon ICH Harmonized Tripartite Guideline, "Validation of Analytical Procedures: Methodology Q2B", published in November 1996, and US FDA, Center for Drug Evaluation and Research, "Guidance for Industry – Analytical Procedures and Methods Validation, August 2000. The USSTC Quality Assurance (QA) Laboratories are not accredited to a national or international standard, the labs follow internal quality control procedures in accordance with the Altria Quality Requirements Manual (AQRM), see *MRTPA, Section 3.1.3.1*. Because the USSTC work instructions are based on the referenced ALCS standard test methods listed, with no deviations, these validations are applicable to the USSTC work instructions. See TPMF (b) (4), Amendment titled "(b) (4) (b) (4)," dated March 30, 2021, for the validation reports for (b) (4).

Response to b.

As set forth in our *MRTPA, Section 3.1.3.3.5*, (b) (4) . We measure % OV (as well as pH) at this stage (b) (4) In *Table 2.2*, we provide a summary of blend moisture measured (b) (4) of the manufacturing process for the proposed MRTP. We previously provided the target and range for % OV during this stage in the *MRTPA, Section 3.1.3.3.5, Table 3.1-12*.

Table 2.2: Percent Oven Volatiles (% OV) Measured (b) (4) : Summary

Lots[1]	Average (% OV)	Std. Dev.	Target and Range
(b) (4)			

[1] (b) (4)

Question 3

Your MRTPA provides some details on raw leaf processing steps, controls, and standard operating procedures (SOPs). However, you did not provide sufficient information on the leaf processing procedures specific to the proposed MRTP. This information is needed to fully characterize the proposed MRTP, including its harmful and potentially harmful constituent (HPHC) quantities and any variation in those quantities, in order to determine whether the product, as actually used, will significantly reduce the risk to individual tobacco users and benefit the health of the population as a whole. Provide all of the following:

a. Criteria for the grade, quality and moisture levels for the tobacco during the visual inspection in the receiving and staging process
b. Controls for rejecting tobacco during the visual inspections in the receiving and staging process. For example, (b) (4)
c. SOPs for testing crop protection agents (CPA), (b) (4)

Response

In response to this question, we provide the following:

Response to a.

In response to this question, we provide

- (b) (4) see *Appendix 3.1*,
- (b) (4) see *Appendix 3.2,* and
- (b) (4) see *Appendix 3.3* (redacted for irrelevant information).

which describe the steps for visually inspecting tobacco leaf (b) (4) during receiving and staging as described in *MRTPA, Section 3.1.3.2.1*.

Response to b.

In response to this question, we provide

- (b) (4) see *Appendix 3.4,* and
- (b) (4) see *Appendix 3.5*,

which describe the steps for performing an NPRM inspection, during receiving and staging as described in *MRTPA, Section 3.1.3.2.1*. (b) (4)

Response to c.

In response to this question, we provide:

- (b) (4) see *Appendix 3.6,* and
- (b) (4) see *Appendix 3.7,*

which describe the steps for collecting samples for analysis of crop protection agents (CPAs) (b) (4) as described in *MRTPA, Section 3.1.3.2.1*. (b) (4) See *MRTPA, Appendix 3.1-3 and Appendix 3.1-4*.

Samples that are collected per *Appendix 3.6 and Appendix 3.7* are shipped to a third-party ISO 17025 accredited laboratory, (b) (4) . located in (b) (4) , for

CPA analytical testing. (b) (4) utilizes their (b) (4) location (b) (4) s. The laboratories' test methods, which are all under scope of their ISO 17025 accreditations, are listed in *Table 3.1*. The certificates of accreditation for (b) (4) laboratories in (b) (4) and (b) (4) are provided in *Appendix 3.8 and Appendix 3.9*, respectively.

Table 3.1: List of (b) (4) Test Methods Used for the Analysis of Crop Protection Agents

CPA	SOP #	Title
(b) (4)		

Question 4

Your MRTPA provides multiple SOPs for determining percent oven volatiles (%OV) and pH in the original submission; however, it is unclear which SOPs for %OV and pH were used (b) (4) [redacted] Thus, specifying the SOPs used for %OV and pH is needed to determine whether appropriate methods were used to determine water content and pH of the finished tobacco product. Specify which %OV and pH protocols were used throughout the entire manufacturing process for the in-process tobacco product. This information is needed to fully characterize the proposed MRTP, including its HPHC quantities and any variation in those quantities, in order to determine whether the product, as actually used, will significantly reduce the risk to individual tobacco users and benefit the health of the population as a whole.

Response

We believe that the proposed MRTP is fully characterized in our MRTPA. Nevertheless, in response to this question, we provide:

- work instructions used to measure % OV and/or pH throughout the entire manufacturing process for the in-process tobacco product as described in *MRTPA, Section 3.1.3*. See *Table 4.1,* and
- the corresponding ALCS standard test method(s) for which the work instruction was based, with no deviations. See *Table 4.2*.

We previously identified the ALCS standard test methods in *MRTPA*, Section 3.1, *Table 3.1-21, Table 3.1-22, Table 3.1-24 and Table 3.1-25*.[29]

[29] We validated the ALCS standard test methods following our internal method validation guidelines. Our internal method validation guidelines are based upon ICH Harmonized Tripartite Guideline, "Validation of Analytical Procedures: Methodology Q2B", published in November 1996, and US FDA, Center for Drug Evaluation and Research, "Guidance for Industry – Analytical Procedures and Methods Validation, August 2000. The USSTC QA Laboratories are not accredited to a national or international standard, the labs follow internal quality control procedures in accordance with the Altria Quality Requirements Manual (AQRM), see *MRTPA, Section 3.1.3.1*. Because the USSTC work instructions in *Table 4.2* are based on the referenced ALCS standard test methods listed, with no deviations, these validations are applicable to the USSTC work instructions. See TPMF (b) (4), Amendment titled "(b) (4) d (b) (4)," dated March 30, 2021 for the validation reports for (b) (4) and see *Appendix 4.4* for the validation report for (b) (4)

Table 4.1: Processing Stages and Corresponding USSTC Work Instructions

Processing Stage	pH Work Instructions	% OV Work Instructions
(b) (4)		

Table 4.2: USSTC Work Instruction and Corresponding ALCS Standard Test Method

(b) (4)

Question 5

Your MRTPA provides general details on the manufacturing and processing of the finished product such as steps, controls, and SOPs. However, you did not provide sufficient information to demonstrate that the proposed MRTP is manufactured in a consistent manner. This information is needed to fully characterize the proposed MRTP, including its HPHC quantities and any variation in those quantities, in order to determine whether the product, as actually used, will significantly reduce the risk to individual tobacco users and benefit the health of the population as a whole. Provide all of the following:

a. A description of the storage facilities and conditions such as temperature and humidity for raw materials, ingredients, additives, and the finished products
b. Clarification on the specific facility location(s) where USSTC receives the tobacco from the growers and indicate if that location is different from the location that the leaves are packed and kept for storage and aging
c. Test method(s) and protocol(s) used to blend the tobacco leaf blend components for the (b) (4) during the manufacturing of the proposed MRTP
d. Step-by-step details of the recipe used for the (b) (4) and the test method and protocol used to calculate (b) (4)
e. Calculation used to determine the amount of (b) (4). You state this calculation relies on historical %OV, yet you did not provide this historical information. Provide historical %OV data
f. Facility Process Control Plan details for the leaf processing
g. Rejection and acceptance controls for the cutting process
h. (b) (4)
i. Calculations used to determine the ingredient quantities added during the (b) (4) process
j. Clarification on whether non-tobacco ingredients are tested when received to verify grade and purity of the ingredients
k. Certificates of Analysis (COAs) for all ingredients added to the tobacco
l. All procedures used to ensure that the raw materials, ingredients, and additives meet your specifications or requirements (e.g., procedures to verify the tobacco variety and nicotine content in the tobacco)
m. Protocols for the quality control and assurance programs that are used to ensure that the final finished product meets your specifications
n. Clarification on the manufacturing location where the finished tobacco product is packed
o. Methods for verifying the net contents of the finished product
p. Batch Acceptance requirements throughout the production process

Response

We state that we fully characterized the proposed MRTP in our MRTPA. Nevertheless, in response to this question, we provide the following information:

Response to a.

In response to this question, we provide a description of storage facilities and conditions: 1.) for tobacco and non-tobacco ingredients to be used in the proposed MRTP and 2.) for the proposed MRTP (i.e., finished product).

- Tobaccos used to manufacture the proposed MRTP are stored in warehouses. (b) (4)
- Non-tobacco ingredients are stored at manufacturing facilities (b) (4)
- The finished tobacco, (b) (4) See *MRTPA, Section 3.1.3.3.8*.
- Finally, when the proposed MRTP is manufactured it is (b) (4) See *MRTPA, Section 3.1.3.3.9*.

Response to b.

In response to this question, we provide a description of the locations where we receive tobacco for manufacturing the proposed MRTP.

- USSTC receives (b) (4)
- USSTC receives (b) (4)

Response to c.

In response to this question, we provide:

- (b) (4) see *Appendix 5.1*.
- (b) (4) see *Appendix 5.2*.

This work instruction sets forth the steps for preparing a leaf blend to meet the tobacco leaf blend recipe as described in *MRTPA, Section 3.1, Table 3.1-7 and Table 3.1-8*. (b) (4) in *MRTPA, Section 3.1, Table 3.1-6*.

Response to d.

In response to this question, we provide:

- (b) (4) see *Appendix 5.3*

This work instruction (b) (4)

Response to e.

In response to this question, (b) (4) See *MRTPA, Section 3.1, Table 3.1-4*.

Response to f.

In response to this question, we provide the following documents describing key process controls of acceptance requirements for the leaf processing stage as described in *MRTPA, Section 3.1.3.2*.

- (b) (4) [30] see *Appendix 5.4;*
- (b) (4) see *Response to Question 3, Appendix 3.1*;
- (b) (4) see *Response to Question 3, Appendix 3.4*;
- (b) (4) see *Response to Question 4*, *Appendix 4.1*; and

[30] (b) (4)

- (b) (4), see *Appendix 5.59* and (b) (4) see *Appendix 5.61.*

Response to g.

In response to this question, we provide:

- (b) (4) See *Appendix 5.5.*

(b) (4)

MRPTA, Section 3.1, Table 3.1-10.

Response to h.

In response to this question, (b) (4)

See *MRTPA, Section 3.1.*

Response to i.

In response to this question, (b) (4)

Table 5.1: (b) (4)

(b) (4)

[redacted]

[1] (b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

[redacted]

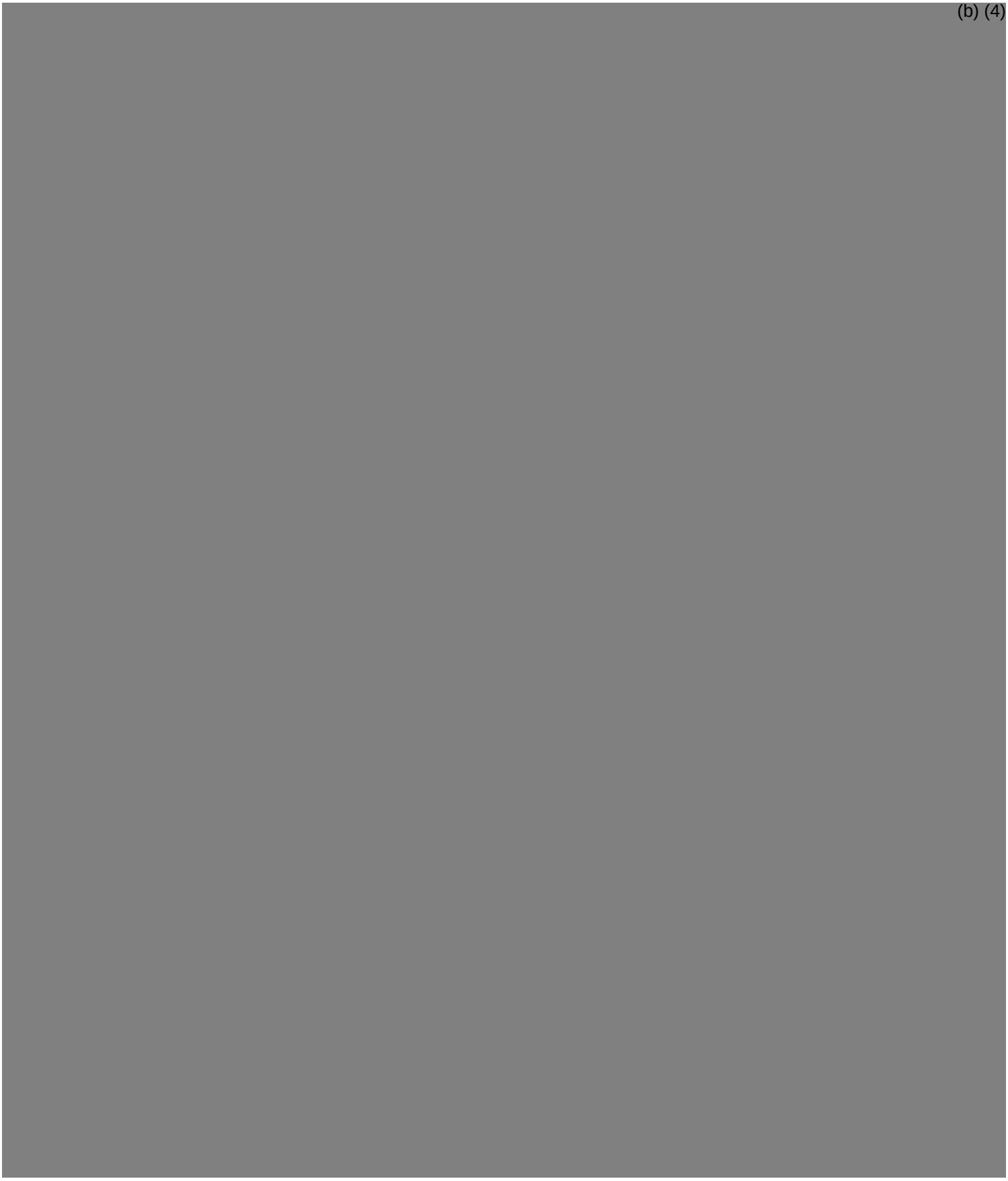
[redacted]

(b) (4)

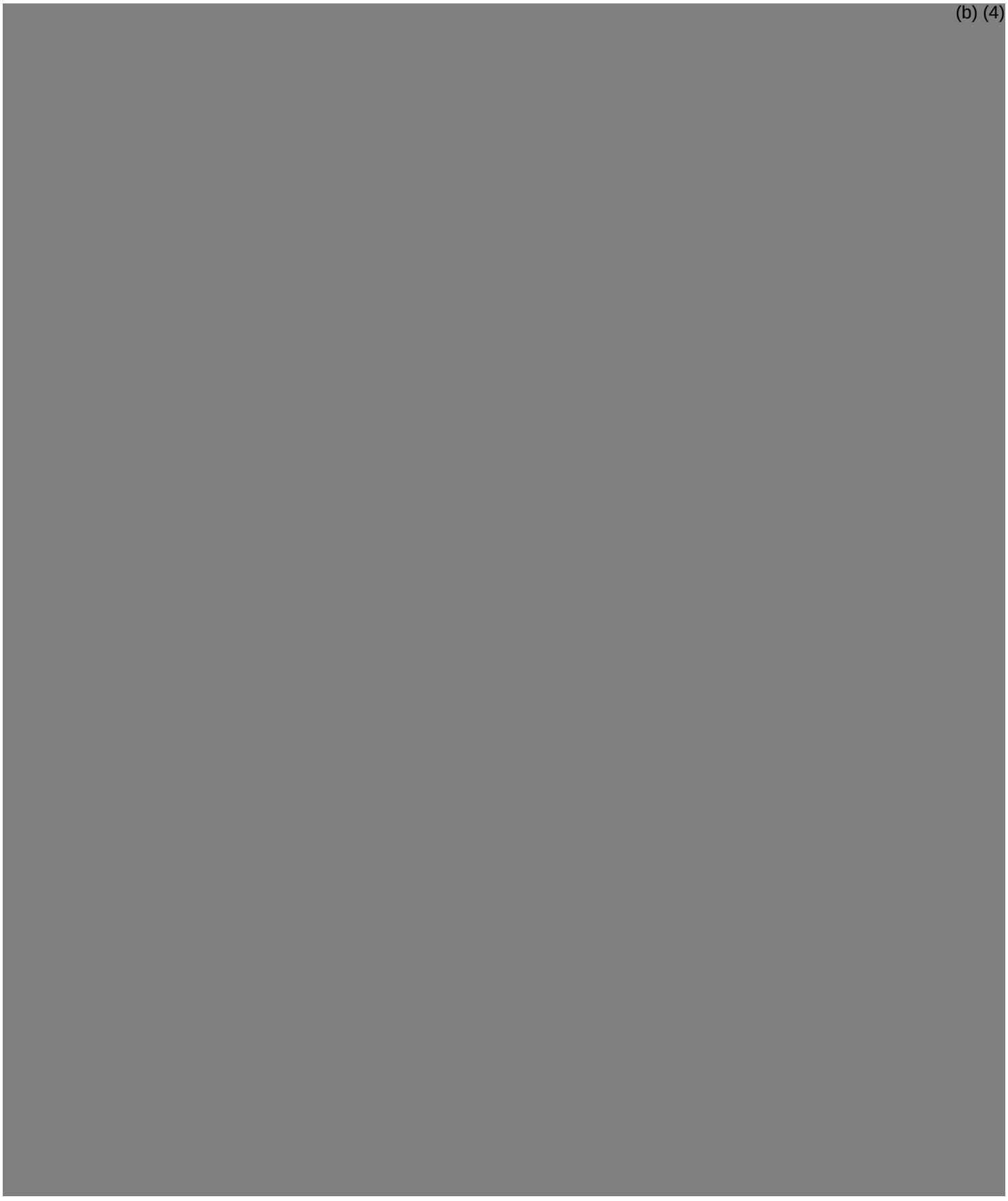
[redacted]

[31] (b) (4)

(b) (4)



(b) (4)



(b) (4)

Response to j.

In response to this question, (b) (4) (b) (4) (b) (4). We receive a Certificate of Analysis (COA) from the supplier (b) (4). See *Response to 5k* for COAs for non-tobacco ingredients and *Response to 5l* for procedures used to ensure that the non-tobacco ingredients meet specifications.

Response to k.

In response to this question, we provide COAs and an ingredient decoder for the non-tobacco ingredients listed in the *MRTPA, Section 3.1, Table 3.1-4*, see *Appendix 5.6 – Appendix 5.56*.

Response to l.

In response to this question, for non-tobacco ingredients, we provide:

- (b) (4) see *Appendix 5.57*. (b) (4)

In response to this question, for incoming tobacco, we provide:

- (b) (4) see *Response to Question 3a, Appendix 3.1*
- (b) (4) see *Response to Question 3a, Appendix 3.2.*

(b) (4)

Response to m.

In response to this question, we state that the *Response to p.* below provides the protocols for the quality controls and assurance programs used to ensure that the proposed MRTP meets the finished product design features described in *MRPTA, Section 3.1, Table 3.1-1.*

Response to n.

In response to this question, we state that the finished proposed MRTP will be packed at (b) (4)

Response to o.

In response to this question, we provide:

- (b) (4) see *Appendix 5.58.*

(b) (4)

Response to p.

In response to this question, we provide:

- (b) (4) see *Appendix 5.59*
- (b) (4), see *Appendix 5.60*
- (b) (4) see *Appendix 5.68*

These work instructions (b) (4)

The forms provided below are (b) (4)

(b) (4) set forth in the *MRTPA, Section 3.1, Figure 3.1-4*, we provide:

- (b) (4) see *Appendix 5.61*

(b) (4) as set forth in the *MRTPA, Section 3.1, Figure 3.1-5*, we provide

- (b) (4) see *Appendix 5.62*

(b) (4) as set forth in the *MRTPA, Section 3.1, Figure 3.1-5*, we provide:

- (b) (4) see *Appendix 5.63*
- (b) (4) see *Appendix 5.64*

(b) (4), as set forth in the *MRTPA, Section 3.1, Figure 3.1-5*, we provide:

- (b) (4) see *Appendix 5.65*
- (b) (4) see *Appendix 5.66*
- (b) (4) see *Appendix 5.69*
- (b) (4) see *Appendix 5.70*

Question 6

Your MRTPA lacks information about complex ingredients. For example, your MRTPA lacks the names, functions, quantities, and purity or grade of the ingredients in the following flavoring mixtures:

a. (b) (4)
b.
c.
d.
e.
f.
g.
h.
i.
j.
k.
l.
m.
n.
o.
p.
q.
r.
s.

Without knowing the identities and quantities of single ingredients comprising the complex ingredients, we cannot fully characterize the composition and evaluate the risks of your proposed MRTP. You need to distinguish between complex ingredients made to your specifications and those that are not made to your specifications. For all complex ingredients made to your specifications, provide complete information according to FDA's Guidance for Industry Listing of Ingredients in Tobacco Products. For complex ingredients that are not made to your specifications, you need to provide names, functions, quantities, and purity or grade of the ingredients. One approach to providing this information as part of your application would be to use Tobacco Product Master Files, which would allow your suppliers to submit confidential information directly to FDA in support of your application.

Response

In response to this question, we provide the identities and quantities of the subcomponents comprising the complex ingredients to be used in the proposed MRTP. In addition, we state that Artificial Pineapple Flavor is the only complex ingredient that is made to USSTC's specifications.

In *Table 6.1,* per FDA's Guidance for Listing Ingredients[32] we provide name, CAS #, function, grade and quantity for the subcomponents of (b) (4) (b) (4). This complex ingredient is supplied by (b) (4) The subcomponents making up this complex ingredient are indicated with a dash (-) before the name. (b) (4).

Table 6.1: (b) (4)

(b) (4)

A (b) (4)

For the other complex ingredients to be used in the proposed MRTP, (b) (4). In *Table 6.2*, we provide the name of the complex ingredient, a list of its subcomponents, the CAS # for each subcomponent, and the percentage of each subcomponent in the complex ingredient per the vendor's disclosure. The subcomponents making up the complex ingredients are indicated with a dash (-) before the name. All of the complex ingredients function as flavors and are food grade, except for (b) (4) which is a non-GRAS flavor.

[32] Guidance for Industry, Listing of Ingredients in Tobacco Products, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, November 2018, at 12.

Table 6.2: Composition of the Complex Ingredients (b) (4)

Complex Ingredient and its subcomponents	CAS Number	Percent of Complex Ingredient
(b) (4)		

Complex Ingredient and its subcomponents	CAS Number	Percent of Complex Ingredient
(b) (4)		

Complex Ingredient and its subcomponents	CAS Number	Percent of Complex Ingredient
(b) (4)		

N/A – Not Applicable
[A] (b) (4)
[B] Food grade flavor
[C] Non-GRAS flavor

Question 7

Your MRTPA provides summary data for acetaldehyde, arsenic, benzo[a]pyrene (B[a]P), cadmium, crotonaldehyde, formaldehyde, NNN, NNK, and nicotine measured in the proposed MRTP. You have submitted test protocols for HPHCs; however, you did not provide method validation summaries for each analytical method used for testing HPHCs. For example, precise, accurate, selective, and sensitive analytical methods for the quantitative evaluation of tobacco product constituents are critical for evaluation of your MRTP. Provide step-by-step testing protocol information including any deviation(s) from the test protocols, quantitative acceptance (pass/fail) criteria, complete data sets, and validation packets for all testing performed.

Response

In response to this question, we

- provide references to *MRTPA, Section 7.1 and Appendix 7.1-3 through Appendix 7.1-7* for step-by-step testing protocols, quantitative acceptance (pass/fail) criteria and complete data sets for each analytical SOP used for the measurements of acetaldehyde, arsenic, benzo[a]pyrene (B[a]P), cadmium, crotonaldehyde, formaldehyde, NNN, NNK, and nicotine.
- state that all testing was conducted without deviations from these testing protocols.
- refer to (b) (4) which includes all validation documents associated with each SOP referenced in *MRTPA, Section 7.1*. This TPMF also contains the SOP versions and certificates of accreditation to the ISO 17025:2005 standard as previously provided.

In the MRTPA submitted March 20, 2018, we provided step-by-step testing protocols and quantitative acceptance (pass/fail) criteria in *Appendix 7.1-3 through Appendix 7.1-7*. All testing was conducted without deviations from these testing protocols. In addition, we provided documentation (*Appendix 7.1-8 through Appendix 7.1-10)* that at the time of testing all methods included in this response were accredited to the ISO 17025:2005 standard by A2LA (Accreditation No. 0660.01). Complete data sets were provided in *Section 7.1, Table 7.1-16 through Table 7.1-25*. For all HPHC methods, the laboratory demonstrated performance through the use of quality control samples and participated in proficiency activities as part of the ISO 17025 accreditation process.

The validation documents for each SOP referenced in *MRTPA, Section 7.1*, can be found in (b) (4) SOP 095-5529, "Determination of Nicotine in Tobacco and Tobacco Products by GC Analysis," is based on the Centers for Disease Control (CDC) protocol for analysis of nicotine as published in the Federal Register and as such does not require validation for analysis of products within the scope of the method.[34]

In *Table 7.1* of this response, we provide details of the elapsed time between the date of manufacture and the date of HPHC testing for the five production lots of the candidate product associated with this MRTPA. By using the date of testing given in *Table 7.1*, the effective

[33] The validation reports associated with each analytical test method are cited in the method's reference section. To review the validation reports and other supporting documentation associated with a test method, we refer CTP to TPMF (b) (4) Amendment titled (b) (4) ," dated March 30, 2021. The validation reports are organized in the TPMF by the associated method number.

[34] *See* Department of Health and Human Services, Centers for Disease Control and Prevention, "Revised Protocol for Analysis of Nicotine, Total Moisture, and pH in Smokeless Tobacco Products", Federal Register, Vol. 74, No. 4, Wednesday, January 7, 2009, Notices, at 712 - 719.

version of each SOP,[35] the corresponding validation report,[36] and the applicable scope of ISO 17025 accreditation[37] may be referenced in TPMF (b) (4).

Table 7.1: Time Elapsed Between Date of Manufacture and Date of HPHC Testing for the Five Manufacturing Lots of the Proposed MRTP Associated with this MRTPA

Lot	Date of Manufacture	Date of Testing	Time Elapsed (Days)
(b) (4)			

(b) (4) conducted the testing for HPHCs. At the time of testing, the analytical test methods were accredited to the ISO 17025:2005 standard by A2LA (Accreditation No. (b) (4)) demonstrating the laboratory's technical competence and ability to produce precise and accurate test data.

In summary, we

- provided step-by-step testing protocols, quantitative acceptance (pass/fail) criteria and complete data sets for each analytical SOP used for the measurements of acetaldehyde, arsenic, benzo[a]pyrene (B[a]P), cadmium, crotonaldehyde, formaldehyde, NNN, NNK, and nicotine. See *MRTPA, Section 7.1 and Appendix 7.1.3 through Appendix 7.1.7;*
- did not deviate from testing protocols as written; and
- provided validation documents associated with each SOP referenced in *MRTPA, Section 7.1.* See (b) (4). This TPMF also contains the SOP versions and certificates of accreditation to the ISO 17025:2005 standard as previously provided.

[35] The analytical test methods are provided in Tobacco Product Master File (TPMF) (b) (4) Amendment titled "(b) (4)," dated March 29, 2021. Each test method in the TPMF is identified by its Method Number, version, and the effective date of the method. We refer CTP to the version of the method effective during the timeframe of testing.

[36] The validation reports associated with each analytical test method are cited in the method's reference section. To review the validation reports and other supporting documentation associated with a test method, we refer CTP to TPMF (b) (4) Amendment titled "(b) (4) (b) (4)," dated March 30, 2021. The validation reports are organized in the TPMF by the associated method number.

[37] To review accreditation documentation, we refer CTP to "Amendment to Tobacco Product Master File (b) (4) for Altria Client Services LLC – ALCS Analytical Science Laboratory's Certificates and Scope of Accreditation for ISO/IEC 17025," dated May 27, 2020. The certificates and scope of accreditation are organized in the TPMF by certificate date (i.e., issue date or revision date). We refer CTP to the certificate and scope of accreditation valid at the time of testing. All prior certificates are superseded by the subsequent certificate.

Question 8

Your MRTPA includes a comparison between the proposed MRTP and the marketplace of smokeless tobacco products, but this comparison raises concerns in that it compared archival data from a product that did not reflect the specific proposed MRTP under review to a range of moist snuff products from literature. Comparison of the proposed MRTP to the marketplace of tobacco products by FDA revealed that the proposed MRTP had elevations in HPHC quantities relative to other smokeless tobacco products. Specifically, there were increases in the following HPHCs:

- Moist Snuff
  - Arsenic (9%)
  - B[a]P (90%)
  - Cadmium (46%)
- Dry Snuff
  - Acetaldehyde (85%)
  - Arsenic (30%)
  - B[a]P (284%)
  - Cadmium (75%)
- Loose Leaf
  - Arsenic (122%)
  - B[a]P (3243%)
  - Cadmium (157%)
  - NNN (113%)
  - NNK (98%)
- Swedish Snus
  - Cadmium (165%)
  - NNN (427%)
  - NNK (349%)

Exposure to HPHCs present in smokeless tobacco is associated with a variety of toxicological hazards including both carcinogenic and non-carcinogenic endpoints. Provide scientific evidence and rationale about how exposure to these HPHCs may impact the population of tobacco users that may completely switch to or begin to dual use their current product(s) with the proposed MRTP.

Response

We provide the following scientific rationale and evidence in response to FDA's question regarding the impact of higher levels of certain HPHCs in the proposed MRTP relative to other smokeless tobacco (ST) products to adult tobacco users.

First, the proposed claim language is intended to draw the attention of adult smokers by emphasizing "IF YOU SMOKE, CONSIDER THIS." We believe, therefore, that adult cigarette smokers and dual users of cigarettes and ST products are most likely to switch to the proposed MRTP.

Second, the totality of scientific evidence should be considered when addressing this question, including overall HPHC profile, relevant comparator products, biomarkers of exposure (BOE), toxicological risk assessment and epidemiological evidence. Comparisons of HPHC levels must consider both increases and decreases. Moreover, HPHC comparisons should be based on the overall HPHC profile relative to moist smokeless tobacco (MST) products, the relevant comparator within ST products. Furthermore, biomarkers of exposure (BOEs) can provide a more accurate estimate of exposure to select HPHCs than the product chemistry analyses. A toxicological risk assessment will provide insights regarding the health risks. And, epidemiological studies provide health outcomes from long-term product use behavior under real-world conditions. Therefore, we assign greatest weight to the epidemiological studies in this hierarchy of evidence.

Finally, while there may be differences in the chemical measurements of HPHCs between ST products, compelling epidemiological evidence establishes that ST products sold in the U.S., including the proposed MRTP, have significantly lower lung cancer risk compared to cigarettes. See *MRTPA, Section 6.1.* Moreover, the proposed MRTP provides a choice to adult cigarette smokers and dual users for switching to noncombustible tobacco products, thereby allowing for a significant reduction in harm and the risk of tobacco-related disease to individual tobacco users.

In this response, we summarize how differences in select HPHCs between the proposed MRTP and other ST products will not result in meaningful differences in morbidity and mortality.

- While single point estimates of some HPHCs may be higher compared to other ST products, the overall HPHC profile of the proposed MRTP is within the range of MST products in the marketplace. MST products are the most appropriate comparator since they constitute the vast majority (74% - 80%)[38] of the ST products used in the U.S.
- Since HPHC levels of the proposed MRTP are within the range of MST products, completely switching to or dual use of the proposed MRTP with other MST products should not increase exposure to those HPHCs that can be characterized through biomarkers of exposure (BOEs).

[38] Our analysis of the ALCS Adult Tobacco Consumer Tracking (ATCT) data shows that the majority (about 80%) of ST users are MST users. This pattern is consistent from 2014-2020. Additionally, our analysis of PATH Wave 4 data indicates that among current ST product users, 74% reported using an MST brand as regular brand. Our analysis is based on the reported use of ST products (i.e., loose snus, moist snuff, dip, spit or chewing tobacco), by brand and sub-brand. See *Appendix 8.1.*

- The noncarcinogenic and carcinogenic toxicological risks based on a theoretical quantitative risk assessment (QRA) are not different for the proposed MRTP compared to MST products. Furthermore, the potential estimated exposure for some of the HPHCs, e.g., arsenic, cadmium and formaldehyde, in MST products including the proposed MRTP, is substantially lower than the toxicologically relevant thresholds set by authoritative bodies.
- Epidemiological evidence suggests no noteworthy increase in morbidity and mortality will occur if users of other ST products completely switch to or dual use the proposed MRTP. Moreover, our analyses of PATH[39] data demonstrates minimal likelihood of transitions from snus to ST products (including MST products) suggesting that other ST product users are not likely to completely switch to or dual use the proposed MRTP.

Importantly, as discussed extensively in our MRTPA, use of ST products available in the U.S. market presents substantially lower morbidity and mortality risks, particularly related to lung cancer, compared to cigarette smoking.[40] Since the proposed MRTP had a significant market share (approximately 40% of the ST category) during the time period of the epidemiological studies, these conclusions apply to the proposed MRTP. Therefore, cigarette smokers, the target audience for the proposed claim, who completely switch to the proposed MRTP will reduce their risk of lung cancer.

[39] We conducted analyses of PATH Wave 1 to Wave 4 longitudinal data based on adults continuing from Wave 1 to Wave 4. The analysis (see *Appendix 8.1*) focused on Wave 1 current users of snus or smokeless tobacco (ST) products (loose snus, moist snuff (i.e., MST), dip, spit or chewing tobacco) and assessed their ST product or snus use states at Wave 2 and Wave 4, respectively. Based on *Appendix 8.1*, we observe minimal likelihood of transitions between exclusive snus to exclusive ST product use as most of the transitions are not statistically reliable because the raw cell counts are less than 10.

[40] We note that following submission of the MRTPA, two recent publications report outcomes that are worth noting for this application. Inoue-Choi et al. (2019) reported that current ST use was associated with a higher risk of mortality from heart disease and smoking-related cancer relative to nontobacco users. The sample size for some of the smoking-related cancers among ST users were fewer than five individuals and the values were not reported for confidentiality. Importantly, the all-cause mortality and lung cancer mortality risks among ST users were lower than cigarette smokers. The authors report that overall mortality risk was lower among ST users (HR=1.36, 95% CI =1.17 to 1.59) relative to current cigarette smokers (HR =2.23, 95% CI =2.13 to 2.33). Additionally, the lung cancer mortality risk (HR=2.68, 95% CI= 0.95 to 7.51) was not statistically significantly different compared to nontobacco users and was substantially lower compared to cigarette smokers (HR=15.49, 95% CI=12.64 to 18.99). Therefore, these results provide additional evidence in support of the proposed modified risk claim. Additionally, Xu et al. (2021) report that upon continued lifetime use, male current exclusive cigarette smokers, aged 25 to 29 years would lose 8.1 quality adjusted life years – QALYs (SE= 0.09), and male current exclusive ST users aged 25 to 34 would lose 4.1 QALYs (SE = 0.22), compared to never users of tobacco. While the estimated QALY for ST users was high it was about half of that calculated for smokers. Some of the limitations noted by the authors include recall bias regarding tobacco product use and health-related quality of life measurements. Both publications corroborate our conclusions in the application that ST use, while not risk-free, is substantially less hazardous than cigarette smoking.

I. The overall HPHC profile of the proposed MRTP is within the range of MST products, the most prevalent ST products sold in the U.S.

While FDA did not provide an explanation for the derivation of the percentage increases in selected HPHCs in its Question 8, based on information provided by FDA,[41] it appears that the calculations are based on comparison of HPHC levels for the proposed MRTP compared to single point (average) values for entire category of ST products (i.e., moist snuff, dry snuff, loose leaf, Swedish snus). See *Table 8-1*. Such an approach has limitations.

Table 8.1: FDA's Comparison of HPHCs in ST Products by Category

Constituent[1]	Unit	Copenhagen® Snuff Fine Cut Mean Quantity (5 lots combined)	Moist Snuff Mean Quantity	% Difference	Dry Snuff Mean Quantity	% Difference	Loose Leaf Mean Quantity	% Difference	Swedish Snus Mean Quantity	% Difference
Acetaldehyde	µg/g	6.3	35.7	↓82	3.4	↑85	N/A	N/A	21.6	↓71
Arsenic[2]	ng/g	233	214	↑9	179	↑30	105	↑122	N/A	N/A
Benzo[a]pyrene	ng/g	117	61.6	↑90	30.5	↑284	3.5	↑3243	N/A	N/A
Cadmium[2]	ng/g	1537	1052	↑46	879	↑75	599	↑157	579	↑165
Crotonaldehyde	µg/g	N/A	2.98	N/A	13.33	N/A	N/A	N/A	N/A	N/A
Formaldehyde[2]	µg/g	1.58	8.43	↓81	3.18	↓50	N/A	N/A	15.7	↓90
NNN	ng/g	3825	4058	↓6	5535	↓31	1798	↑113	726	↑427
NNK	ng/g	1034	1394	↓26	2522	↓59	523	↑98	230	↑349
Total Nicotine	mg/g	12.5	12	↑4	15.8	↓21	6.2	↑102	8.71	↑44
Free Nicotine	mg/g	3.92	4.2	↓7	0.7	↑460	0.04	↑9700	5.65	↓31

Source: FDA's Information Briefing Document February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, page 9, Table 2.

[1]Data in table are reported on a "dry weight basis" (DWB) except for total and free nicotine, which are reported "as is" (wet weight basis). Carbonyl data for moist snuff and dry snuff are from Stepanov et al.(2008); TNSAs, metals, and nicotine data for moist snuff, dry snuff, and loose leaf are from Borgerding et al.(2012); Swedish snus levels are reported as an average of data from Swedish Match 2014 MRTP applications.

[2] The values provided indicate that potential exposure to this HPHC is less than the EPA IRIS non-cancer RfD (arsenic: 0.0003 mg/kg/day; cadmium: 0.0005 mg/kg/day; formaldehyde: 0.2 mg/kg/day).

First, FDA did not consider the prevalence of use or the market share of the comparator ST products. For example, according to Adult Tobacco Consumer Tracking (ATCT), more than 80% of past-30-day ST product users are MST users with 70% using MST exclusively (i.e., not using snus or chewing tobacco).[42] Additionally, PATH Wave 4 data demonstrates that 74% of ST product users reported using MST regularly.[43] In addition, market data from 2011 – 2019 indicate that MST products represent at least 90% of the overall ST market share in the U.S. (Delnevo, Hrywna, Miller Lo, & Wackowski, 2020). And, Tomar reports that "[m]oist snuff, an orally used product, is by far the leading ST category in the United States . . .." (Tomar, 2019). Therefore, MST is the relevant comparator within the ST product category.

[41] FDA's information Briefing Document February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, page 9, Table 2.
[42] See *Appendix 8.1*.
[43] See *Appendix 8.1*.

Second, instead of a single point comparison, the relevant comparison is the range of HPHCs across the MST subcategory of ST products because the range is a better representation of ST products actually used in the U.S. marketplace. FDA's single point mean approach is limited because it uses published values for different products obtained at different time points, measured in different laboratories where the analytical methods may also be different. As demonstrated in *Table 8-2*, the HPHC levels measured in the proposed MRTP are within the range of those HPHCs for MST reported by Stepanov et al. and Borgerding et al. (on which FDA relied for their HPHC comparisons).

Third, FDA's question only considered HPHCs that were higher and does not take into consideration HPHCs that are lower as set forth in *Table 8-1*. According to *Table 8-1*, four of seven HPHCs are lower for the proposed MRTP compared to the mean for the MST product category. The proposed MRTP has lower levels of acetaldehyde (82%), formaldehyde (81%), NNK (26%) and NNN (6%) compared to MST products. See *Table 8-1*.

Table 8-2 demonstrates that the HPHCs for the proposed MRTP are within the range of MST products. Therefore, while single point estimates of some HPHCs may be higher, or lower, compared to other ST products, the overall HPHC profile of the proposed MRTP is within the range of MST products, which constitute the majority of the ST products used in the U.S.

Table 8.2: HPHC Data for the Proposed MRTP Compared to the Range for MST Products in the U.S. (2006-2007)

Constituent[1]	Unit	Copenhagen® Snuff Fine Cut Mean[44] Quantity (5 lots combined) DWB[2]	MST Range from FDA's cited references[3]
Acetaldehyde	µg/g	6.3	17.1-72.3
Arsenic	ng/g	233	108-312
Benzo[a]pyrene	ng/g	117	0.6-193.0
Cadmium	ng/g	1537	355-1871
Crotonaldehyde	µg/g	BLOQ	0.984-6.35
Formaldehyde	µg/g	1.58	6.58-10.6
NNN	ng/g	3825	659-12770
NNK	ng/g	1034	250-6761

[1]Data are reported on a "dry weight basis" - DWB. BLOQ = below level of quantitation. The LOQ for crotonaldehyde was 0.05 µg/g (on an as-is sample basis). Using the average OV from the proposed MRTP (54.4%), the resulting dry-basis LOQ value for crotonaldehyde would be <0.092 µg/g.

[2]Source: See *MRTPA, Section 7.1, Table 7.1-15*.

[3]Sources: Carbonyl data from Stepanov et al.(2008); TSNAs, metals and B[a]P from Borgerding et al.(2012).

[44] Using a mean value for the proposed MRTP is appropriate here because the limitations noted above do not apply. We used five lots of the same product, measured under identical controlled analytical conditions.

Finally, in its question, FDA indicates that "this comparison raises concerns in that it compared archival data from a product that did not reflect the specific proposed MRTP." We clarify that we did not use archival data. The HPHC data provided in the MRTPA, and in this response, are for the specific proposed MRTP (i.e., GF1200194), see *MRTPA, Section 7.1*. We manufactured the proposed MRTP for purposes of evaluating HPHCs for the application. Specifically, production lots 01000 and 01001 were manufactured on March 8, 2017, and production lots 01004, 01005 and 01006 were manufactured on June 2, 2017.

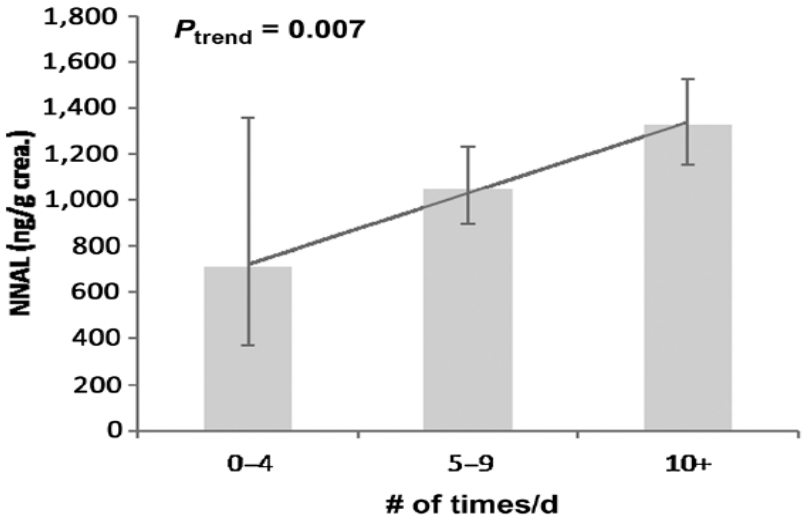
II. Completely switching to or dual use of the proposed MRTP should not increase exposure to HPHCs compared to the range of other MST products sold in the U.S.

We expect that completely switching to or dual use of the proposed MRTP with other MST products will not increase exposure to those HPHCs that can be characterized through BOEs because the HPHC levels are within range of MST products.

We note that biomarkers are not available to determine exposure for some HPHCs, e.g., acetaldehyde and formaldehyde. Moreover, it is not feasible to determine the changes in biomarker levels due to the excessively long half-life for some HPHCs, e.g., approximately 14 years for cadmium (Suwazono et al., 2009). And, exposure to other HPHCs is confounded by sources other than tobacco products, e.g., environmental exposure to B[a]P (IARC, 2012). Despite these limitations, because HPHC levels are within the range, we expect exposure to be within the range of other MST products as well.

Additionally, product use behavior plays a greater role in determining BOE levels than potential differences in chemical measurements of HPHCs. Substantial variability in BOE levels has been reported in human biomarker studies (Cheng et al., 2020). For example, urinary NNAL levels (a biomarker for NNK exposure) ranged from 600 ng/g cr to 1200 ng/g cr. The authors attribute one of the reasons for this variability to differences in use behavior (0-4 times per day versus more than 10 times per day). See *Figure 8.1*.

Figure 8.1: Dose Response Relationship Between Biomarker Levels and Use Behavior



Source: Cheng et al., (2020), Figure 2.

Similar variability has also been reported by others for total NNAL as well as other BOEs. For example, based on the mean and standard deviation values reported by Prasad et al. (2016), the percent coefficient of variation among MST consumers for total NNAL was ~96% and ~132% for 1-hydroxypyrene (biomarker for exposure to polycyclic aromatic hydrocarbons). Rostron et al. (2015) reported wide confidence intervals (CI) for NNAL (583.0 pg/mg creatinine, 95% CI, 445.2–763.5) and high variability for other BOEs.

This variability in BOEs may be explained by the significant variability in MST product use behavior. For example, Hatsukami et al. (1999) observed that MST product users (seeking treatment for tobacco cessation) report using an average of 3.7 cans per week (SD = 2.5, range 1-22 cans per week). The wide range reported by the authors indicates that while on average adult MST consumers use about a half can per day, there is significant variability in use behavior. Given that the proposed MRTP is an MST product, the frequency and quantity of use should not be vastly different compared to other MST products as determined from historical marketplace data based on actual use behavior. As set forth in *MRTPA, Section 3.2, Table 3.2.-5*, adult MST consumers generally used about half a can of MST on days used. Based on our ATCT data, adult Copenhagen® Snuff consumers reported using an average of 0.56 cans/day (ranging from <1/4 to >1.5 cans/day). While there are subtle differences in use behavior, these differences are within the variability observed in *MRTPA, Section 3.2* and as reported by Hatsukami et al. (1999). Therefore, since the use behavior of the proposed MRTP is within the range of that reported for MST products, and the HPHC levels are within the range as well, we can reasonably expect that the exposure to HPHCs will also be within the range of exposure reported for MST products.

Overall, completely switching to or dual use of the proposed MRTP with other MST products (the predominant category of ST products sold in the U.S.), will not increase exposure to the those HPHCs that can be characterized through BOEs.

III. The toxicological risk profile of the proposed MRTP is not higher compared to other MST products sold in the U.S.

The proposed MRTP does not exhibit a higher toxicological risk profile, as estimated by the Hazard Index (HI) and Excess Lifetime Cancer Risk (ELCR), compared to MST products. Furthermore, exposure to overall HPHCs in the proposed MRTP over a lifetime of typical use is below established non-cancer toxicological thresholds (HI < 1) which is similar to the MST category. The potential estimated exposure for some of the HPHCs, e.g., arsenic, cadmium and formaldehyde, is substantially lower than the toxicologically relevant thresholds set by authoritative bodies (U.S. EPA, 1989a, 1990, 1991a).

We conducted a theoretical Quantitative Risk Assessment (QRA) of the proposed MRTP compared to MST products[45] sold in the U.S. to establish the toxicological risk profile of the tobacco products based on HPHC levels. The QRA is derived from the approach published by Marano et al. (2018) and applies U.S. EPA risk assessment guidance (U.S. EPA, 1989b, 2002, 2009a, 2014) to the abbreviated HPHC list provided by FDA for ST products (CTP, 2012). In order to address FDA's question, for this QRA, we used the mean values reported by FDA[46] for MST.

For toxicological risk profile comparison, we utilize HPHC levels in the proposed MRTP (5-lots combined) and MST products (*Table 8.3*). While we believe ranges are a better representation of ST products actually used in the U.S. marketplace, nevertheless, to answer FDA's question regarding impact to tobacco users based on single point estimates of HPHCs, we conducted this toxicological assessment using those single point estimates.

[45] As set forth above in Section I., MST is the relevant comparator within the ST product category. According to ATCT, more than 80% of past-30-day ST product users are MST users with 70% using MST exclusively (i.e., not using snus or chewing tobacco). Additionally, PATH Wave 4 data also shows among ST product users, 74% reported using MST regularly. In addition, market data from 2011 – 2019 indicate that MST products represent at least 90% of the overall ST market share in the U.S. (Delnevo et al., 2020). And, Tomar reports that "[m]oist snuff, an orally used product, is by far the leading ST category in the United States . . .." (Tomar, 2019).

[46] See FDA's Information Briefing Document February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, page 9, Table 2. (*Table 8.1*).

Table 8.3: Measured HPHC Levels in the Proposed MRTP Compared to Mean HPHC Levels in MST Products Reported by FDA

HPHC[1]	Dry Weight Basis (Mean Value)		% Difference[3]
	Copenhagen Snuff Fine Cut (5-lots combined)	MST[2]	
Acetaldehyde (µg/g)	6.3	35.7	-82
As (ng/g)	233	214	9
B[a]P (ng/g)	117	61.6	90
Cd (ng/g)	1537	1052	46
Crotonaldehyde (µg/g)	BLOQ	2.98	N/A
Formaldehyde (µg/g)	1.58	8.43	-81
NNN (ng/g)	3825	4058	-6
NNK (ng/g)	1034	1394	-26

BLOQ: Below Limit of Quantitation

[1] Source: FDA Draft Guidance 2012: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act; 77 Fed. Reg. 20034 (April 3, 2012). HPHC = Harmful and Potentially Harmful Constituent; B[a]P = Benzo[a]pyrene; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = N-nitrosonornicotine.

[2] Source: *Table 8.1*, FDA's Information Briefing Document February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, page 9, Table 2.

[3] $((\text{Mean}_{\text{Copenhagen Snuff Fine Cut}} - \text{Mean}_{\text{MST}}) / \text{Mean}_{\text{MST}}) * 100$; rounded to the nearest whole number

As recognized in CTP's draft guidance document (2012), the evaluated HPHCs (*Table 8.3*) represent several different chemical classes and constitute a representative sample of HPHCs in ST products; therefore, the constituents considered in the composite QRA are representative of potential differences in the trends of cumulative hazard and risk between the proposed MRTP and MST. Qualitative or semi-quantitative differences (see *Table 8.3*) in HPHC levels cannot be used to determine differences in toxicological risk between the proposed MRTP and MST products. Therefore, we use a theoretical QRA to compare HPHC levels for MST products, as reported by FDA, to the measured yield of HPHCs in the proposed MRTP. This approach is consistent with CTP's position on HPHC comparisons (CTP, 2019).[47]

Calculation of Chronic Daily Intakes (CDIs) for Cancer and Non-Cancer Risk Assessment

We calculated CDIs for the proposed MRTP and MST using the values in *Table 8.3*. Averaging Time (AT) varies based on the type of effect assessed, cancer or non-cancer, which results in distinct CDIs for cancer or non-cancer calculations (Marano et al., 2018). The CDI for cancer risk assessment is averaged over total intake per lifetime (70 years) multiplied by a body weight. The CDI for non-cancer risk assessment is averaged over intake per exposure duration (51 years) multiplied by body weight. CDI is represented by the following equation:

[47] Although CTP's memo states that the approach is currently limited to SE pathway comparisons, CTP noted that it would continue to evaluate applicability in the PMTA and MRTP context.

$$CDI_{c,nc} = \frac{C \times TC \times ABS \times EF \times ED}{BW \times AT_{c,nc}}$$

where:

CDI_c – chronic daily intake, for cancer risk assessment (mg/kg/day)
CDI_{nc} – chronic daily intake, for noncancer risk assessment (mg/kg/day)
C – measured HPHC yield or HPHC values from literature (mean, mg/g tobacco)
TC – tobacco consumption (g/day)
ABS – HPHC absorption rate (unitless)
EF – exposure frequency (days/year)
ED – exposure duration (years)
BW – body weight (kg)
AT_c – averaging time, for cancer risk assessment (days)
AT_{nc} – averaging time, for noncancer risk assessment (days)

The values for each parameter in the CDI equation above are provided in *Table 8.4* and calculated CDI values for the proposed MRTP and MST are provided in *Table 8.5*.

Table 8.4: Exposure Parameters and Assumptions

Parameter	Symbol	Value	Unit	Source
Tobacco Consumption	TC	12	g/day	(U.S. EPA, 2017b)
Absorption	ABS	100	Percent	Maximum Value
Exposure Frequency	EF	365	Days/Year	Maximum Value[1]
Exposure Duration	ED	51	Years	(U.S. EPA, 1989a, 2014, 2017a)[1]
Body Weight	BW	70	kg	(U.S. EPA, 1997a)
Averaging Time, Non-cancer	AT_c	18,615	Days	(U.S. EPA, 1989b, 2009b, 2014)[a]
Averaging Time, Cancer	AT_{nc}	25,550	Days	(U.S. EPA, 1989b, 2009b, 2014)[a]

[1] EF, ED, AT values used in the risk assessment are adapted from Marano et al. (2018).

Table 8.5: Cancer and Non-Cancer Chronic Daily Intakes (CDIs) for the Proposed MRTP and MST

HPHC[1]	CDI (mg/kg/day)			
	Copenhagen® Snuff Fine Cut		MST	
	Cancer	Non-cancer	Cancer	Non-cancer
Acetaldehyde (µg/g)	7.87E-04	1.08E-03	4.46E-03	6.12E-03
Arsenic (ng/g)	2.91E-05	3.99E-05	2.67E-05	3.67E-05
B[a]P (ng/g)	1.46E-05	2.01E-05	7.69E-06	1.06E-05
Cadmium (ng/g)	1.92E-04	2.63E-04	1.31E-04	1.80E-04
Crotonaldehyde (µg/g)	N/A[2]	N/A	3.72E-04	5.11E-04
Formaldehyde (µg/g)	1.97E-04	2.71E-04	1.05E-03	1.45E-03
NNN (ng/g)	1.29E-04	1.77E-04	1.74E-04	2.39E-04
NNK (ng/g)	4.78E-04	6.56E-04	5.07E-04	6.96E-04

[1]Source: FDA Draft Guidance 2012: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act; 77 Fed. Reg. 20034 (April 3, 2012). HPHC = Harmful and Potentially Harmful Constituent; B[a]P = Benzo[a]pyrene; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = N-nitrosonornicotine.

[2]N/A: not available because crotonaldehyde in the proposed MRTP is BLOQ.

Calculation of Excess Lifetime Cancer Risk (ELCR) and Hazard Quotient (HQ) Values

CDI values were used to calculate ELCR and HQ for each HPHC using the following equations:

$$ELCR = CDI_{cancer} \times CSF$$

and,

$$HQ = \frac{CDI_{non-cancer}}{RfD}$$

Where:

CDI – chronic daily intake (mg/kg/day)
CSF – cancer slope factor for oral route of exposure $(mg/kg/day)^{-1}$
RfD – reference dose for oral route of exposure (mg/kg/day)
ELCR – estimated lifetime cancer risk (unitless)
HQ – hazard quotient (unitless)

The RfDs and CSFs used in the ELCR and HQ calculations are provided in *Table 8.6*. We sourced reference values from the U.S. Environmental Protection Agency Integrated Risk Information System (IRIS). Where reference values were not reported in IRIS, we used California Environmental Protection Agency (CalEPA) and Texas Commission on Environmental Quality (TCEQ). We provide calculated individual ELCR and HQ values for the proposed MRTP and MST products in *Table 8.7*.

Table 8.6: Toxicological Reference Values Used to Estimate Hazard Quotient (HQ) and Excess Lifetime Cancer Risk (ELCR)

HPHC[1]	CASRN	Oral CSFs (mg/kg/day)$^{-1}$ for ELCR calculations	Oral Non-cancer RfDs (mg/kg/day) for HQ calculations
Acetaldehyde	75-07-0	No value available	1.00E-01 (TCEQ, 2009)
Arsenic	7440-38-2	1.50E+00 (U.S. EPA, 1995)	3.00E-04 (U.S. EPA, 1991a)
B[a]P	50-32-8	1.00E+00 (U.S. EPA, 2017a)	3.00E-04 (U.S. EPA, 2017a)
Cadmium	7440-43-9	No value available	1.00E-03 (U.S. EPA, 1989a)
Crotonaldehyde	123-73-9	1.90E+00 (U.S. EPA, 1997b)	1.00E-03 (U.S. EPA, 1991b)
Formaldehyde	50-00-0	2.10E-02 (OEHHA, 2009)	2.00E-01 (U.S. EPA, 1990)
NNK	64091-91-4	4.90E+01 (OEHHA, 2001)	No value available
NNN	16543-55-8	1.40E+00 (OEHHA, 1992)	No value available

[1] Source: FDA Draft Guidance 2012: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act; 77 Fed. Reg. 20034 (April 3, 2012). HPHC = Harmful and Potentially Harmful Constituent; B[a]P = Benzo[a]pyrene; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = N-nitrosonornicotine.

Table 8.7: Individual Hazard Quotient (HQ) and Excess Lifetime Cancer Risk (ELCR)Values for the Proposed MRTP and MST

HPHC[1]	Copenhagen® Snuff Fine Cut		MST	
	HQ[2]	ELCR[3]	HQ[2]	ELCR[3]
Acetaldehyde	1.08E-02	N/A	6.12E-02	N/A
Arsenic	1.33E-01	4.37E-05	1.22E-01	4.01E-05
B[a]P	6.69E-02	1.46E-05	3.52E-02	7.69E-06
Cadmium	2.63E-01	N/A	1.80E-01	N/A
Crotonaldehyde	N/A	N/A	5.11E-01	7.07E-04
Formaldehyde	1.35E-03	4.14E-06	7.23E-03	2.21E-05
NNK	N/A	6.33E-03	N/A	8.53E-03
NNN	N/A	6.69E-04	N/A	7.10E-04

[1]Source: FDA Draft Guidance 2012: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act; 77 Fed. Reg. 20034 (April 3, 2012). HPHC = Harmful and Potentially Harmful Constituent; B[a]P = Benzo[a]pyrene; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = N-nitrosonornicotine.

[2] HQ is a unitless probability of non-cancer risk or ratio of exposure to oral Reference Doses (RfDs) shown in *Table 8.6*.

[3] ELCR is a unitless probability (e.g., 1 in 10,000 chance) of cancer risk calculated from oral Cancer Slope Factors (CSFs) shown in *Table 8.6*.

N/A: not applicable because either the HPHC levels were BLOQ (i.e., crotonaldehyde in the proposed MRTP) or an RfD was not available (NNN and NNK) or a CSF was not available (cadmium and acetaldehyde).

Results and Discussion of the Toxicological QRA

Overall, the results of the QRA support that the noncarcinogenic and carcinogenic toxicological risks are not different for the proposed MRTP compared to MST products.

While Total ELCR (sum of individual ELCRs) and HI (sum of individual HQs) cannot be used to assess absolute risk,[48] these values provide useful metrics for comparing the relative toxicological risk of the proposed MRTP to MST products based on overall HPHC profile.[49] For the proposed MRTP, HI is ~ 48% lower and Total ELCR is ~29% lower compared to MST products. See *Figure 8.2*. While the proposed MRTP has higher levels of arsenic (9%) and B[a]P (90%) compared to other MST products, it also has lower levels of crotonaldehyde (BLOQ) and NNK (26%), as indicated in *Table 8.1*. Furthermore, based on EPA and OEHHA CSF values (see *Table 8.6*), crotonaldehyde is roughly 2 times more potent as a carcinogen than B[a]P, while NNK is nearly 30 times more potent as a carcinogen than arsenic and 49 times more potent as a carcinogen than B[a]P (OEHHA, 2001; U.S. EPA, 1995, 1997b, 2017a). As a result, the estimated total ELCR in the proposed MRTP is lower compared to MST products. In addition, as noted by FDA[50] (see *Table 8.1* above) the potential exposure to arsenic, cadmium and formaldehyde is lower than the toxicologically relevant thresholds for non-cancer effects set by authoritative bodies, i.e., EPA IRIS non-cancer reference dose (U.S. EPA, 1989a, 1990, 1991a). Additionally, HI for the proposed MRTP and MST products is less than one, indicating that additive exposure to HPHCs in these products over a lifetime of typical use is below established non-cancer toxicological thresholds.

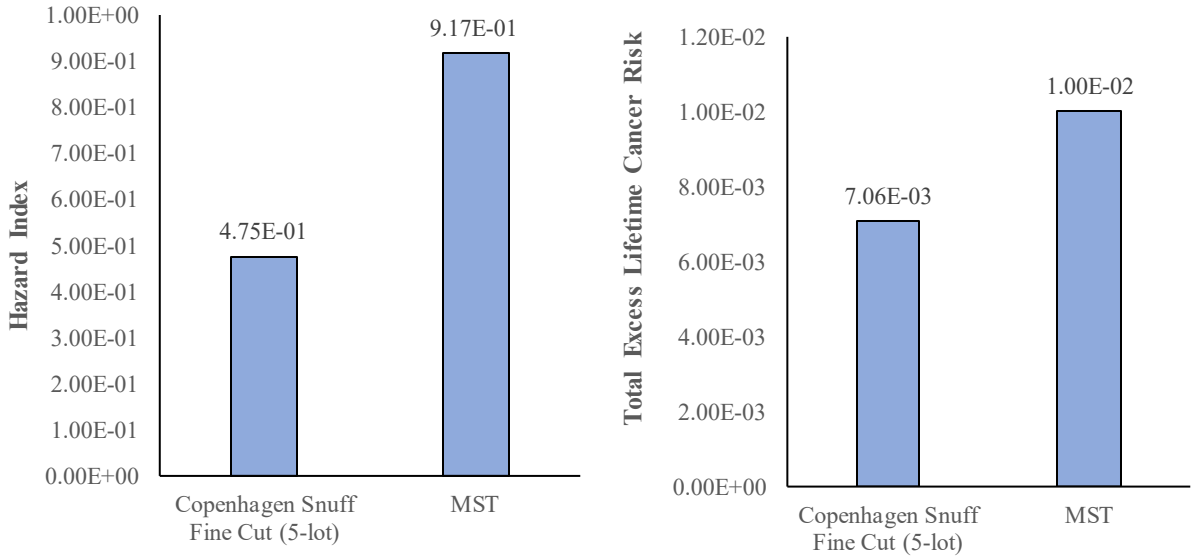
Overall, the proposed MRTP does not exhibit a higher toxicological risk profile, as estimated by the Hazard Index (HI) and Excess Lifetime Cancer Risk (ELCR), compared to MST products. Comparison of the overall HPHC profiles indicates that the toxicological risk profile of the proposed MRTP is not higher compared to other MST products sold in U.S.

[48] Due to limitations in data underlying the CSF values, the total ELCR cannot be used to assess absolute cancer risks. Also, ELCR and HI do not correspond to absolute risk because they consider only one tobacco consumption rate (e.g., 12 g/day) and exposure scenario (e.g., over a lifetime).

[49] We did not quantify the statistical differences between MST and the proposed MRTP because of the potential confounding effects from inter-laboratory variation and because HPHC values for MST were collected from multiple different sources.

[50] FDA's information Briefing Document February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, page 9, Table 2.

Figure 8.2: Hazard Index (HI) and Excess Lifetime Cancer Risk (ELCR) in the Proposed MRTP Compared to MST



IV. Epidemiological evidence suggests no noteworthy increase in morbidity and mortality and there is low likelihood of completely switching from or dual using the proposed MRTP with other ST products.

Although we rely on multiple lines of evidence to address FDA's question, we assign significant weight to the epidemiological studies described here, as they provide the health outcome from long-term product use behavior under real-world conditions. We focus on the epidemiological evidence for adult ST product users to address this question.

We recognize that epidemiological studies rarely identify specific products used by the cohorts studied, limiting the ability to draw inferences directly related to specific products. Furthermore, ST users often misclassify ST product use and case-control studies are subject to recall bias. Nonetheless, as indicated in our MRTPA (See *MRTPA, Executive Summary, Section 2.3.3.2*), MST products were the predominant form of ST[51] products used and the proposed MRTP accounted for a sizeable market share (~40%) during the time period of the major U.S. epidemiological studies.

[51] As illustrated in *MRTPA, Section 2.3, Figure 2.3-6,* MST products already accounted for nearly half of the ST category in 1972. Since then, the market share of MST products had steadily grown, accounting for half the category by the early 1980s, and 75% by the late 1980s. MST's rise to dominate the ST category coincides with the timing of major epidemiology studies of ST products conducted in the U.S. Collectively, these epidemiology studies span 1972 to 2011. Over the time period studied, therefore, the health effects of using smokeless tobacco products, as reported by U.S. epidemiological data, were increasingly associated with the use of MST.

Completely switching from other ST products to the proposed MRTP will not substantially increase morbidity and mortality.

We would expect that, for those ST users who switch to the proposed MRTP, there would be no substantial change in health risk. Rather, the major change in health risk related to ST use remains with adult smokers who stop smoking and completely switch to the proposed MRTP. Exclusive use of ST products available in the U.S., results in far lower serious consequences to health than smoking conventional cigarettes, primarily driven by the meaningful differences in lung cancer risk (Fisher, Tan-Torres, Gaworski, Black, & Sarkar, 2019; Inoue-Choi et al., 2019).

Few studies in the published literature address the changes in health risk related to switching among ST products. Henley at al. (2005) report mortality risks among chewing tobacco users that were former snuff[52] users, likely indicating impact of switching from chewing tobacco to snuff. None of the causes of death reported in the analysis were statistically significant in this group except for lung cancer. While the point estimate for the hazard ratio for lung cancer was high (HR=9.78) (See *MRTPA, Section 6.1, Table 6.1-23),* the wide confidence intervals (95 percent CI: 3.58-26.7) and small sample size (n=4) limit the reliability of the point estimate. Furthermore, other researchers (Foulds & Ramstrom, 2006) questioned the bioplausibility of this observation. The rationale is likely because there is no direct pulmonary exposure. Furthermore, the compelling evidence presented in our application (see *Section 6.1*), indicates that ST users have substantially lower lung cancer hazard ratios than cigarette smokers. Foulds et al. (2006) also suggested that the mortality risk estimates could be confounded by misclassification and inaccurate characterization of prior smoking history. Due to the considerable statistical uncertainty, definitive conclusions cannot be drawn from Henley et al. (2005) study reporting switching data for ST products.

While many publications do not characterize specific ST products used, some publications (Henley et al., 2005; Rodu & Cole, 2002; Timberlake, Nikitin, Johnson, & Altekruse, 2017) indeed report health risks or mortality risks from exclusive snuff users and exclusive chewing tobacco users. We gain further insights regarding impact of switching from other ST products to the proposed MRTP product by assessing this evidence.

As demonstrated in *Section 6.1, Tables 6.1-12 through 6.12-14*, the currently available scientific information does not indicate major biologically relevant differences in the health risks between exclusive use of snuff and chewing tobacco. Our Linked Mortality Analysis (See *MRTPA, Appendix 7.4.1-1*) demonstrates that the mortality risks for all-cause, malignant neoplasms and diseases of the heart are comparable between exclusive chewing tobacco users and snuff users.

We recognize that "Swedish snus type products" are currently in the U.S. market; however, epidemiological evidence in the U.S. population with these Swedish snus type products is insufficient. Nevertheless, it is worth noting that in Sweden, male lung cancer death rates have continued to decline (Rodu & Cole, 2009), which may relate to the decline in cigarette consumption and switching to snus among Swedish males.

[52] Snuff is generally synonymous with MST. However, snuff could also include dry snuff, which differs from MST. However, prevalence of dry snuff use has generally been low and is now almost non-existent. Therefore, we consider data related to snuff use to be relevant to MST unless information is available to indicate otherwise.

Some investigators have suggested that different chemical composition among MST products could lead to differences in health risk (Borgida et al., 2015; Cheng et al., 2020). However, as noted by FDA in its briefing document[53] for the February 2019 Tobacco Products Scientific Advisory Committee (TPSAC) meeting "[b]ased on nonclinical data alone, it is difficult to determine how varying levels of HPHCs between [the proposed MRTP] and other tobacco products impact risk of disease in humans." Given the results of the Henley et al. study (2005) where switching between two different ST products such as chewing tobacco and snuff failed to demonstrate a substantial impact on health risk, we conclude that the chemical composition differences between ST products, although measurable, would be largely inconsequential to major health risk outcomes measured by current epidemiology methods. Switching from other ST products to the proposed MRTP will not result in discernable differences in the health outcomes.

Starting dual use of the proposed MRTP with other ST products will not substantially increase morbidity and mortality.

While the best option for any adult tobacco consumer is to completely quit using all tobacco products, some users of other ST products may transition to the proposed MRTP and dual use the two ST products.

There are limited studies that report impact of dual use of MST products and other ST products. Henley et al. (2005) analyzed the American Cancer Society's CPS-II data to compare mortality risks for exclusive snuff users and exclusive chewing tobacco users as well as dual users of snuff and chewing tobacco relative to never tobacco users. The adjusted mortality risks were reported for only a few outcomes *(*see *Table 8.8)* and were modestly higher among dual users for all-causes, cerebrovascular diseases and other causes categories, and modestly lower for all cancers, cardiovascular and coronary heart diseases relative to exclusive snuff users. No consistent trend was observed in the morality risks and, due to the small sample size and relatively small magnitude of differences, definitive conclusions cannot be made regarding potential health impact of dual use of snuff and chewing tobacco relative to exclusive use of snuff or chewing tobacco.

[53] FDA's information Briefing Document February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, page 9, Table 2.

Table 8.8: Mortality Hazard Ratios (HR) and 95% CIs Associated with the Use of ST Products Among Men Who Never Used Any Other Tobacco Product, CPS-II, 1982–2000

Cause of death	ST product use	Number of deaths	Multivariate-adjusted HR (95% CI)[1]
All causes[2]	Exclusive Chew	366	1.16 (1.05 – 1.29)
	Exclusive Snuff	70	1.25 (0.98 – 1.59)
	Chew and Snuff	82	1.36 (1.09-1.69)
All cancers[3]	Exclusive Chew	113	1.23 (1.02 – 1.49)
	Exclusive Snuff	14	0.93 (0.55 – 1.57)
	Chew and Snuff	18	1.02 (0.64 – 1.63)
Cardiovascular Disease[4]	Exclusive Chew	186	1.26 (1.09 – 1.46)
	Exclusive Snuff	36	1.39 (0.99 – 1.92)
	Chew and Snuff	37	1.26 (0.91 – 1.75)
Coronary Heart Disease[5]	Exclusive Chew	111	1.25 (1.03 – 1.51)
	Exclusive Snuff	24	1.59 (1.06 – 2.39)
	Chew and Snuff	23	1.31 (0.87 – 1.98)
Cerebrovascular Disease[6]	Exclusive Chew	45	1.38 (1.02 – 1.86)
	Exclusive Snuff	4	0.62 (0.23 – 1.67)
	Chew and Snuff	17	2.57 (1.59 – 4.17)
Other Causes	Exclusive Chew	166	1.07 (0.92 – 1.25)
	Exclusive Snuff	29	1.07 (0.74 – 1.54)
	Chew and Snuff	41	1.29 (0.95 – 1.76)

[1]Cox models adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake, and aspirin use.
[2]Analysis for all causes excludes men who reported prevalent cancer, heart disease, diabetes, or stroke in 1982 (due to disease exclusions the number of all cause deaths differs from the summed total of specific causes of death).
[3]Analyses for cancers exclude men who reported prevalent cancer in 1982.
[4]Analysis for cardiovascular disease excludes men who reported prevalent heart disease, diabetes, or stroke in 1982.
[5]Analysis for coronary heart disease excludes men who reported prevalent heart disease or diabetes in 1982.
[6]Analysis for stroke excludes men who reported prevalent stroke in 1982.

Timberlake et al. (2017) report (see *Table 6.1-12)* that use of both snuff and chewing tobacco resulted in a small, but statistically significant, excess risk for mortality from all causes and coronary heart disease (CHD). Additionally, current users who used snuff alone had an excess mortality risk from CHD. While the point estimates were higher among dual users, the impact of these differences compared to exclusive snuff or chewing tobacco users is unclear. The authors noted that the absence of known, potentially confounding CHD risk factors in the data was a study limitation that raises the possibility of a non-causal association. Additionally, according to the authors, discrepancy between the higher prevalence of ever using chewing tobacco relative to the low market share suggests potential misclassification of self-reported ST types, which could confound inferences regarding impact of dual use of snuff and chewing tobacco.

Finally, our own analysis of the Linked Mortality dataset confirmed no substantial risk difference between the two product types suggesting that dual use of the proposed MRTP with other ST products may not impact mortality risks.

Overall, due to the limited and inconsistent evidence, the impact of dual use of the proposed MRTP and other ST products is unlikely to result in significant adverse health outcomes.

Minimal likelihood exists that users of other ST products will completely switch to or dual use the proposed MRTP.

Secondary analyses of data from national surveys[54] demonstrate that prevalence of different subcategories of ST products are relatively stable over time. The prevalence of dry snuff use has generally been low, is now almost non-existent in the U.S., and cannot be assessed in national surveys. See *Appendix 8.1*. A longitudinal analysis of PATH data also indicates relatively low likelihood of transitions between ST product categories. For example, only 1 out of 60 exclusive snus users (not using loose snus, moist snuff, dip, spit or chewing tobacco (ST use)) in PATH Wave 1 completely switched to exclusive ST use in Wave 2. And, 6 out of 60 transition to dual use (snus and ST). In Wave 4, 7 out of 60 exclusive snus users from Wave 1 completely switched to exclusive ST use and 6 out of 60 transition to dual use. We only reported raw cell counts as most of the transitions are not statistically reliable. These data suggest that exclusive dry snuff, loose leaf and snus users, which comprise a relatively small percentage of ST product users in the U.S., are minimally likely to switch to or dual use MST products. Therefore, there is minimal likelihood of transitions from other ST products to the proposed MRTP.

Additionally, we note that snus use is a very different behavior compared to MST use. Snus is a spitless product, in a pouch format, placed under the upper lip. The proposed MRTP is a finely cut loose leaf, non-pouched product that is consumed as a "pinch of tobacco" placed under the lower lip. Use of the proposed MRTP requires spitting. Therefore, it is unlikely that snus users will adopt such a different use behavior and switch to or begin dual use of the proposed MRTP.

[54] We conducted cross-sectional analyses using PATH data from Waves 1 to Wave 4 (2013-2018) to evaluate the proportions of adult snus and ST product users (i.e., loose snus, moist snuff, dip, spit or chewing tobacco) (See *Appendix 8.1*). We assessed transitions within ST product use by evaluating those respondents who were snus or ST product users in Wave 1 and their subsequent use behavior states in Waves 2 and 4 (see *Appendix 8.1*). . Our analysis of the ALCS ATCT data between the time period 2014-2020 indicates that the majority (about 80%) of ST product users are MST users and prevalence of different subcategories (MST, Chewing tobacco and snus) remains relatively stable during this time period.

Importantly, ST products sold in the U.S. including the proposed MRTP, have significantly lower lung cancer risk compared to cigarettes. And, the proposed MRTP provides a choice to adult cigarette smokers and dual users when switching to noncombustible tobacco products.

V. Conclusions

We present compelling scientific rationale and evidence that differences in HPHC levels in the proposed MRTP, relative to other ST products, will not impact the population of tobacco users that may completely switch to or begin to dual use their current product(s) with the proposed MRTP. As noted by FDA in its briefing document[55] "[b]ased on nonclinical data alone, it is difficult to determine how varying levels of HPHCs between [the proposed MRTP] and other tobacco products impact risk of disease in humans." We assess the population impact based on epidemiological studies to which we assign the greatest weight in the hierarchy of evidence. We conclude that the chemical composition differences between ST products, although measurable, would be largely inconsequential to major health risk outcomes.

The totality of evidence is summarized below:

- While single point estimates of some HPHCs may be higher compared to other ST products, the overall HPHC profile of the proposed MRTP is within the range of MST products, the most appropriate comparator. See **Section I**.
- Completely switching to or dual use of the proposed MRTP from other MST products sold in the U.S. should not increase exposure to HPHCs. See **Section II**.
- Our theoretical quantitative risk assessment (QRA) demonstrates that the noncarcinogenic and carcinogenic toxicological risks are not different for the proposed MRTP compared to MST products. See **Section III**.
- Epidemiological evidence suggests no noteworthy increase in morbidity and mortality will occur if users of other ST products completely switch to or dual use the proposed MRTP. And, there is low likelihood of these transitions. See **Section IV**.

Importantly, as discussed extensively in our MRTPA, use of ST products available in the U.S. market presents substantially lower morbidity and mortality risks compared to cigarette smoking, particularly related to lung cancer, the focus of the modified risk claim. Since the proposed MRTP had a significant market share (approximately 40% of the ST category) during the time period of the epidemiological studies, these conclusions apply to the proposed MRTP. Adult smokers and dual users should have choices in ST products. And, the proposed MRTP, for which we provided compelling evidence in the application, provides a choice. Moreover, the impact of complete switching from or dual use of the proposed MRTP with other tobacco products can be best assessed in post-market surveillance, under real-world use behavior, after authorization of the proposed modified risk claim.

[55] FDA's information Briefing Document February 6-7, 2019 Meeting of TPSAC on MRTPA MR0000108 from U.S. Smokeless Tobacco Company, page 9, Table 2.

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