FDA U.S. FOOD & DRUG ADMINISTRATION

Scientific Review of a Modified Risk Tobacco Product Application (MRTPA): Technical Project Lead (TPL) Review

SUBMISSION INFORMATION			
Applicant	U.S. Smokeless Tobacco Company LLC		
Product Manufacturer	U.S. Smokeless Tobacco Company LLC		
Submission Date	March 19, 2018	**FDA Receipt Date**	March 20, 2018
Purpose	☒ Risk Modification (911(g)(1) order) ☐ Exposure Modification (911(g)(2) order)		
Claims	USSTC is seeking a risk modification order under Section 911 (g)(I) of the FD&C Act for the pre-existing product Copenhagen Snuff Fine Cut (GF1200194), which the applicant has proposed to rename Copenhagen® Classic Snuff. USSTC requests that FDA designate the candidate product as a modified risk tobacco product and permit marketing of the candidate product with the following proposed modified risk claim, as provided in the proposed advertising and labeling: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer."		
Amendments			
MR0000113, MR0000120, MR0000121, MR0000125, MR0000126, MR0000149, MR0000193, MR0000199 and MR0000202			
Cross-Referenced Submissions			
(b) (4) and GF1200194			

Attributes[1,2,3]	**Tobacco Product**
STN	**MR0000108**
Product Name	Copenhagen Classic Snuff
Product Category	Smokeless Tobacco
Product Sub-Category	Loose Moist Snuff
Package Type	Fiberboard Can/Metal Lid
Package Quantity	34.02 grams
Characterizing Flavor	Tobacco
Nicotine Source	Tobacco
Additional Properties	Tobacco cut size: (b) (4) Cuts Per Inch (CPI)

Discipline	**Cycle 1**		**Cycle 2**	
	Reviewer(s)	**Review Date**	**Reviewer(s)**	**Review Date**
Engineering	Rashele Moore	3/22/2021	Cao Chung	2/23/2023

[1] Effective April 14, 2022, FDA's authority to regulate tobacco products was extended to include tobacco products containing nicotine from any source. https://www.congress.gov/bill/117th-congress/house-bill/2471

[2] The characterizing flavor previously identified as "None" has been updated in FDA records to "Tobacco" to accurately reflect that the product provides a tobacco characterizing flavor from the filler. As such, this product does not have any change in characterizing flavor.

[3] Finalized scientific reviews may not reflect the referenced product characterizing flavor and nicotine source.

Chemistry	Stephanie Daniels	3/22/2021	Selena Russell	2/17/2023
Microbiology	Prashanthi Mulinti	3/24/2021	Not applicable (N/A)	N/A
Toxicology	Mary Irwin	3/22/2021	Rebecca Danam	2/16/2023
Social Science	Aura Lee Morse	3/23/2021	Aura Lee Morse	2/16/2023
Behavioral Clinical Pharmacology	Steven Meredith	3/22/2021	Not applicable (N/A)	N/A
Medical	Theresa Watkins-Bryant	3/24/2021	Not applicable (N/A)	N/A
Epidemiology	Hannah Day	3/25/2021	Terrence Lee	2/16/2023
Statistics	Juan C. Vivar	3/22/2021	Not applicable (N/A)	N/A
Environmental Science	William E.Brenner	3/25/2021	William E. Brenner	10/21/2022
OCE – DPAL	Melissa R. View	3/22/2021	Adeola Obajemu	2/22/2023
OCE – DEM/BIMO	Arnon M. Dayak	3/22/2021	Abraham Agyapong	3/28/2022

Consultations	**Cycle 1**		**Cycle 2**	
(Discipline/ Office)	**Reviewer(s)**	**Review Date**	**Reviewer(s)**	**Review Date**
TPST	Not applicable (N/A)	N/A	Kimberly R. Lindsey	3/14/2022
OHCE	Not applicable (N/A)	N/A	Emily Talbert	2/21/2023

Recommended Action(s)
Issue a modified risk granted order for the product subject of this review.

Technical Project Lead (TPL):

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CAPT Robin Toblin, Ph.D., M.P.H.
Director
Division of Research and Knowledge Integration

Signatory Decision: Concur with TPL recommendation and basis of recommendation

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Todd Cecil, Ph.D.
Acting Director
Office of Science

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1. Executive Summary

On March 20, 2018, the Food and Drug Administration (FDA) received a Modified Risk Tobacco Product Application (MRTPA) from Altria Client Services LLC (ALCS), submitted on behalf of U.S. Smokeless Tobacco Company LLC (USSTC) for its pre-existing Copenhagen Snuff Fine Cut loose moist snuff smokeless tobacco product (GF1200194). The application requested authorization under Section 911(g)(1) to market the product with the following risk modification claim: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer."

(b) (4) . The MRTPA did not include this information. The missing information was addressed in a deficiency along with seven other deficiencies sent on March 26, 2021. In response (MR0000199), the applicant presented a plan (b) (4) .

In examining the product characterization of the proposed MRTP, we found that the stability data did not raise microbial product stability concerns. However, I needed additional information to determine whether the product could be manufactured in a consistent way and 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, would significantly reduce the risk to individual tobacco users and benefit the health of the population as a whole. This missing information was addressed in a deficiency. The applicant's responses addressed the deficiencies in an acceptable manner to the disciplines who put forth the deficiencies (Engineering, Chemistry, and Toxicology). As TPL, I concur and find that the product can be manufactured consistently and can now be fully characterized. Therefore, the HPHC data initially submitted by the company is valid and can be analyzed as was submitted, and a definitive assessment of risk of the proposed MRTP relative to other ST products could be undertaken.

[4] (b) (4) .

In examining claim substantiation and the risks to individual health of the proposed MRTP, the applicant used data from the smokeless tobacco (ST) product category and bridged to the proposed MRTP, which is an acceptable approach. Compared to cigarette smoking, ST use poses lower risks of certain health outcomes. Specifically, those who completely switched from cigarettes to ST had generally lower risks for lung cancer, heart disease, oral cancer, and stroke (Henley et al. 2007).

Overall, consistent with the Tobacco Products Scientific Advisory Committee (TPSAC), I found that the claim was substantiated: switching completely to the proposed MRTP from cigarettes will confer a lower risk of lung cancer. The evidence also suggests switching completely to the proposed MRTP would lower HPHC exposure relative to smoking as well as reduce risk of morbidity and mortality for several other diseases relative to smoking.

However, because the proposed MRTP is a harmful product, my final assessment of the individual health risks of the product, including risks relative to other ST products, was subject to the product chemistry. Well-characterized product chemistry is required to draw firm conclusions on individual health risk, especially compared to users of other ST products. Ultimately, the assessment of individual health is required to determine the impact of authorization to the population. A deficiency was sent requesting that the applicant provide scientific evidence and rationale about how exposure to HPHCs in the proposed MRTP may impact the population of tobacco users that may completely switch to the proposed MRTP or begin to dual use their current product(s) with the proposed MRTP, particularly in comparison to other ST products. In response, the applicant indicated that the appropriate comparison for HPHCs for the proposed MRTP was other moist smokeless tobacco (MST, also referred to as moist snuff) products based on its share of the ST marketplace. As TPL, I agree with this approach. Through an offsetting analysis, Toxicology determined that the higher levels of some HPHCs in the proposed MRTP relative to the MST category were offset by the lower levels of other HPHCs. Specifically, lower levels of NNK and free nicotine offset the higher levels of benzo[a]pyrene (BaP), and cadmium from a carcinogenic perspective.

Next, I examined population-level effects of the proposed MRTP, including consumer understanding (e.g., whether the labeling and advertising would enable consumers to understand the modified risk information) and use behavior (e.g., the likelihood that current smokers would completely switch from cigarettes to the proposed MRTP). In examining consumer understanding, the Claim Comprehension and Intentions (CCI) study provided sufficient evidence to meet the basic statutory requirements that support appropriate consumer understanding of the proposed modified risk claim and its significance in the context of total health. After seeing the advertisement with the modified risk claim, participants understood that the absolute risk of developing lung cancer is lower for a person who exclusively uses the proposed MRTP daily than for a person who smokes cigarettes daily. Participants also understood that using the proposed MRTP still poses health risks, and that someone who only uses the proposed MRTP daily would likely experience a negative impact to their health. Finally, participants understood that using the proposed MRTP is not less risky than using other MST products, and that the risk of using the proposed MRTP is greater than that of using nicotine replacement therapy (NRT), quitting all tobacco, and never using tobacco products. I also examined if the applicant assessed a consumer's understanding that a user must completely switch to the product (from cigarettes) in order to reap the benefit. The applicant did not do that. I believe that this limitation is mitigated by the fact that the claim itself directs potential users that they can reduce their risk by "switching completely." Still, the extent to which consumers understand that the proposed MRTP must be used exclusively and that dual users must switch completely should be monitored in postmarket surveillance as has been the case in previous MRTP authorizations.

Although the CCI study suggested the modified risk claim did not significantly affect risk perceptions, it is understandable that participants' beliefs did not change especially with a one-time exposure. It is difficult to change people's beliefs and persistent misperceptions about the relative risks of ST compared to cigarettes, including the misperception that particular products are as harmful as cigarettes. This is seen in the literature and was supported by submitted data; on average, participants in the CCI study rated the overall health risk of using the proposed MRTP similarly to how they rated that of smoking cigarettes. Authorization would serve to increase the information's credibility and believability to the public and help combat the persistent misperception. Because the statutory requirements were met and the repeated exposure in the real world to the claim following authorization would likely increase its effects on consumer perceptions and intentions (Hornik, 2002), the applicant demonstrated that the proposed MRTP enables the public to understand the modified risk information specific to the proposed MRTP and its relative significance in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products.

While the basic requirements related to consumer understanding were met, the CCI study had limitations in its design and findings. I believe the applicant could have provided more compelling evidence through a number of changes. As noted above, one change would have been to assess consumer understanding of the need to switch completely; however, as explained above, that limitation is mitigated by the fact that the claim itself directs potential users that they can reduce their risk by "switching completely." Another design limitation was that the applicant only required participants to examine the proposed labeling one time and did not assess if the participants opted to look at the exposure additional times to determine a dose-response relationship; requiring multiple exposures would have been optimal as would have determining the number and length of times that participants optionally examined the proposed labeling. It is likely that the findings do not reflect the full real-world impact of the claim, which is likely to happen over a period of time as the idea gains more credibility and general awareness among the public. Thus, the findings likely underestimate the potential impact of the claim on consumers' perceptions. The applicant also assessed participants before and after exposure on a host of perception and intention items leaving participants subject to testing effects; testing only after exposure would have allowed a more definitive assessment of the impact of the claim and LLA itself. Section 3.3 and the Social Science review describe these methodological concerns in more detail. However, it is difficult to know to what extent this particular study design element affected results. Additionally, because this methodology has been used in similar studies and is a common study design, we believe the findings are informative; if anything, the applicant may have found fewer null effects had they used a post-test only design. Despite these limitations, I believe the applicant has met the statutory requirements for basic understanding of modified risk: participants understand that the proposed MRTP causes harm and that it is more harmful than quitting or NRT and the label directs users that they must switch completely to derive the benefits of the claim (in this case, a reduced risk of lung cancer relative to cigarettes).

Epidemiology examined current use behavior, patterns of use, intentions to use, and modeling. It is worth noting that the model used inputs from the CCI study, including its aforementioned limitations, limiting its utility in weighing the evidence. Currently, ST use in the United States is low, but dual use with cigarettes is substantial. Patterns of switching indicate that the likelihood of completely switching from either exclusive cigarette or dual use to exclusive ST use remains quite low (Jackson, Ren et al. 2021). Though the applicant's CCI study corroborated the current patterns by demonstrating low to moderate levels of interest in using the proposed MRTP among those who stand to benefit (i.e., smokers, dual users), this must be examined in the context of misperceptions about the relative harms of ST relative to cigarettes also shown in the CCI study as noted above. The repeated exposure to the

modified risk claim that would occur if the proposed MRTP were to be authorized would provide tobacco users with basic, substantiated information relevant to their health, opening the possibility of moving users of combustible products to a product with modified risk.

Based on the broader literature and limited data from the CCI study and consistent with TPSAC's concerns, I expect that the level of interest in using the proposed MRTP among those who stand to benefit most—current smokers—will be relatively low, and that exposure to the modified risk claim will have a limited effect on this. While ideally, the applicant could have demonstrated that some cigarette smokers were interested in switching, the literature finds a small group of smokers that do switch to ST. With the Copenhagen brand representing the largest market share among ST products, the MRTP may appeal to a large number of ST users though still a minority of smokers — those who are open to the category of ST. In examining whether the proposed MRTP provides a strong enough subjective effect and sensory experience to encourage complete switching, BCP found that the abuse liability for the proposed MRTP is greater than use of FDA-approved cessation aids, but less than that associated with cigarette smoking. This suggests that for those tobacco users who wish to reduce their tobacco-related risks, but do not wish or are not able to quit altogether, the proposed MRTP is a viable alternative. With targeted marketing toward cigarette smokers of brands of the applicant's parent company, there is a large segment of current smokers who may receive direct marketing materials regarding the proposed MRTP, which may present them with new information about the relative lung cancer risk. Appealing to that group of smokers and persuading them to completely switch to a less harmful alternative presents an opportunity to benefit population health.

The group that the proposed MRTP may be most likely to impact is current dual users who could reduce their individual risk by switching completely. Perhaps unsurprisingly, current dual users of smokeless products reported the highest mean levels of intentions to use the product. I expect that the MRTP will influence some proportion of these users to stop smoking and use the product exclusively, which would significantly reduce their individual risk and help benefit population health. Given the brand's market share and the over (b) (4) dual users of Copenhagen in the U.S., this is a particularly ripe population who would benefit from the proposed MRTP. In addition, it is notable that dual use Copenhagen users consume more of their Copenhagen product daily and smoke fewer cigarettes daily than do dual users of other ST products; this suggests that dual users of the applicant's products may have an easier time switching to exclusive use of the proposed MRTP, since the balance of the use of the two products may be weighted more toward Copenhagen use compared to that of dual users of other ST products. Overall, by enabling people who smoke to switch completely, the proposed MRTP would benefit population health. Taken together the evidence provides support that the proposed MRTP would increase exclusive use of Copenhagen Classic Snuff among adult tobacco consumers who would benefit from complete switching, including both smokers and dual users of cigarette and ST products.

While the applicant's population model also supports this conclusion and indicates that the proposed MRTP would yield modest health benefits for the population, I assigned less weight to this evidence due to its limitations. Although I agree with the conclusion that the population modeling tools and approach were appropriate, a significant limitation is that many behavioral inputs into the model were derived from non-statistically significant findings in the CCI study, which led to considerable uncertainty regarding the model's findings. While the applicant's population health model indicates that the proposed MRTP would yield modest health benefits for the population, the results of the population model are dependent on the behavioral inputs and would therefore differ (and could even show a net negative impact) if the behavioral inputs were different. Because of this, I assigned minimal weight to the population model, and instead relied on other findings such as consumer understanding of the claim

in the CCI study and the broader literature on tobacco use behavior to reach conclusions about the population health impact.

Regarding the impact to non-users, specifically to youth, national estimates suggest that use of ST among youth is low (2.3%) and is declining over time and that the likelihood of youth initiating on an ST product is low. However, this varies by rurality with rural youth use of ST at roughly twice the rate of urban youth (Buettner-Schmidt et al., 2019), a concern substantial enough that the FDA's Real Cost Campaign has a series of ads targeted at rural youth use of ST with the tag line "smokeless doesn't mean harmless." While Copenhagen appears to be perhaps the most popular brand among youth who use ST, the applicant's CCI study, though it did not include youth, showed that non-users (including young adults) had virtually no intentions to try or use the proposed MRTP. However, given the association between risk perceptions and initiation, there is a potential risk of any MRTP to youth. Accordingly, if authorized, MRTP marketing should be targeted to maximize exposure to intended users and prevent exposure among youth, especially given the popularity of the applicant's brand among youth ST users.

In conclusion, I conducted a thorough scientific review of the information contained in the MRTPA, and considered the recommendations from TPSAC, comments, data, and information submitted to FDA by interested persons, and other scientific information identified by the agency from other sources. After examining the totality of evidence across scientific reviews, I found that the proposed modified risk claim is scientifically accurate: smokers who switch completely to the proposed MRTP will have a lower risk of lung cancer than if they continued to smoke. Furthermore, the data support a benefit to population health through reductions in overall morbidity and mortality associated with the use of the proposed MRTP, relative to cigarette smoking, that would not be offset by nonusers initiating with the product nor users of other ST products switching to the proposed MRTP. In addition, despite the limitations in the CCI study, the applicant demonstrated that consumers were able to sufficiently comprehend the information concerning modified risk and understand the relative significance of such information in the context of total health. Therefore, I recommend issuing a Modified Risk Granted Order (MRGO) to USSTC for Copenhagen Classic Snuff, MR0000108.

2. Regulatory Information

2.1 Regulatory History

On March 20, 2018, the Food and Drug Administration (FDA) received a Modified Risk Tobacco Product Application (MRTPA) from Altria Client Services LLC (ALCS), submitted on behalf of U.S. Smokeless Tobacco Company LLC (USSTC) for its Copenhagen Snuff Fine Cut tobacco product (GF1200194). The application requested authorization under Section 911(g)(1) to market the product with the following risk modification claim: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." (b) (4)

(b) (4)

(b) (4)

- March 20, 2018: FDA received an MRTPA (MR0000108) from the applicant for its pre-existing Copenhagen Snuff Fine Cut loose moist snuff smokeless tobacco product (GF1200194).
- April 10, 2018: FDA received an unsolicited amendment (MR0000113) containing updates to Appendix 7.3.2-15 CCI Study SSAP Syntax Code in MR0000108.

(b) (4)

- July 10, 2018: FDA issued an A/I Request letter for MR0000108.
- July 11, 2018: FDA received an unsolicited amendment (MR0000120) containing a tabulated master bibliography index to the original application for MR0000108.
- July 18, 2018: FDA received an unsolicited amendment (MR0000121) containing an updated version of Table 7.1-17 included in Section 7.1 of the original application for MR0000108.

- August 8, 2018: FDA received the applicant's response (MR0000125) to the July 10, 2018, FDA A/I Request letter for MR0000108.
- August 23, 2018: FDA held a teleconference with the applicant to request the applicant check the formatting and resend the specific files and folders as some of the files and folders in amendment MR0000125 were unable to be located or opened for MR0000108.
- August 27, 2018: FDA received a solicited amendment (MR0000126) containing responses to the information requested on August 23, 2018, for MR0000108.
- September 14, 2018: FDA issued a Filing letter for MR0000108.
- September 21, 2018: FDA opened a docket for public comment on MR0000108.
- January 24, 2019: FDA held a teleconference with the applicant to request clarifications on minor modifications and HPHC data for MR0000108.
- February 1, 2019: FDA received a solicited amendment (MR0000149) containing responses to the clarification questions requested on January 24, 2019, for MR0000108.
- February 6-7, 2019: FDA held a TPSAC meeting at FDA White Oak Conference Center for MR0000108.
- (b) (4)
- January 21, 2020: FDA closed the application docket for public comment for MR0000108.
- March 26, 2021: FDA issued a Deficiency Letter for MR0000108
- April 8, 2021: USSTC responded that it would provide a response to the Deficiency Letter by September 30, 2021 (MR0000193) for MR0000108.
- September 29, 2021: USSTC submitted a solicited amendment in response to the Deficiency Letter (MR0000199) for MR0000108.
- On March 7, 2022, FDA sent an email to the applicant requesting they provide information regarding (b) (4) by submitting a general correspondence letter to the FDA Document Control Center. The RHPM documented this in a telecon for MR0000108.
- March 9, 2022: FDA received a solicited amendment (MR0000202) containing information requested on March 7, 2022, for MR0000108.
- March 14, 2022: FDA re-opened the docket for public comment for the last three amendments received for MR0000108.
- May 13, 2022: FDA re-closed the docket for public comment for MR0000108.

(b) (4)

(b) (4)

In response to Deficiency #1 of the Deficiency letter issued on March 26, 2021, for MR0000108, the applicant (b) (4)

discussion of that review is in section 3.3.2.

(b) (4)

As TPL, I find that Deficiency #1 was adequately addressed (b) (4)

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2.2 Public Availability

Pursuant to Section 911(e) of the Food, Drug, and Cosmetic (FD&C) Act, FDA made the applicant's MRTPA available to the public. Matters in the application that are trade secrets or otherwise confidential, commercial information were redacted in a manner consistent with other applications. The docket for public comment on this MRTPA was open from September 21, 2018, to January 21, 2020. During this period, FDA received a total of 58 (30 unique) submissions from individuals, academia, and other organizations. In addition to legal and advocacy issues, the comments included independent

consumer perception information, critiques of the applicant's studies and interpretation of findings, and concerns about potential appeal to youth. The docket was reopened on March 14, 2022, to May 13, 2022, to receive comments about the amendments and all available application materials. FDA received a total of one finalized submission and one draft submission from non-profit organizations during this period. The comments largely focused on concerns about whether the applicant's response addressed the deficiencies identified by FDA. The issues and concerns raised in both rounds of public comments were also identified during FDA's scientific review of the applications. FDA considered all significant comments when making the final determination. Specific comments were addressed in the discipline reviews.

2.3 TPSAC Meeting

Pursuant to Section 911(f) of the FD&C Act, FDA referred the MRTPA to TPSAC, and TPSAC reported its recommendations on the application during an open public committee meeting held on February 6-7, 2019. TPSAC discussed FDA's preliminary assessment of the MRTPA. FDA posed three specific questions to TPSAC for discussion; committee members were asked to vote on one of them. A brief summary, based on FDA's meeting Summary Minutes, is provided below. Meeting materials, including complete meeting transcripts, are available on FDA's website.[6]

To start, FDA asked TPSAC to discuss the available scientific evidence and vote on the extent to which the proposed modified risk claim is scientifically substantiated by that evidence (voting options were yes, no, or abstain). Overall, TPSAC agreed that the proposed claim was accurate based on the strength of the scientific evidence: eight of the nine voting members voted "yes". The ninth member abstained, noting concerns about potential confounding factors (e.g., length of smoking history, genetic risk) that may impact the veracity of the statement on an individual basis, while also appreciating the simplicity and specificity of the statement.

Next, TPSAC turned to the topic of consumer understanding and perception of the modified risk information in the proposed advertising. FDA asked TPSAC to discuss the potential implications of the proposed modified risk information on consumer understanding and perceptions. Overall, TPSAC expressed the opinion that this was a clear and focused statement that could inform consumers' understanding of the relative risk of tobacco products. There was some concern about whether consumers understood the need for complete switching because it was not directly assessed in the applicant's CCI study. TPSAC noted that the study failed to demonstrate that the claim affected perceptions. However, they also noted the context of pre-existing beliefs about the harms of ST use and the limited impact of a brief, single-sitting exposure as compared to a full marketing campaign. Overall, TPSAC found no evidence that the proposed claim would increase population harm or that people interpreted it as meaning the product was risk-free.

Finally, TPSAC discussed potential users of the proposed MRTP. Specifically, FDA asked: "What is the likelihood that cigarette smokers will switch completely to Copenhagen Snuff Fine Cut?" and "Considering the health risks from the use of Copenhagen Snuff Fine Cut and those who may be likely to use the product, what are the groups of potential concern (e.g., users of smokeless tobacco products with lower HPHC quantities, youth)?" In response to these questions, the committee expressed concern that, given how difficult it is to quit smoking completely, and the product's past lack of popularity relative to cigarettes, it seems unlikely that the proposed MRTP would lead to substantial change in smokers' behavior. There was some speculation about whether smokers would see a tradeoff in

[6] https://www.fda.gov/advisory-committees/tobacco-products-scientific-advisory-committee/2019-tpsac-meeting-materials-and-information

complete switching to the proposed MRTP between lower risk of lung cancer and a (perceived) increased risk of oral cancer. The committee also discussed concerns about the likelihood of dual use. TPSAC also discussed the challenges of predicting behavior and the importance of postmarket surveillance, especially for youth, former smokers, users of ST products with fewer HPHCs, and pregnant persons. These concerns are addressed in Section 3.

3. Scientific Review

Ten Office of Science (OS) scientific disciplines reviewed the applicant's MRTPA -- Engineering, Chemistry, Microbiology, Toxicology, Medical, Behavioral and Clinical Pharmacology (BCP), Epidemiology, Social Science, Statistics, and Environmental Science -- and two Office of Compliance and Enforcement (OCE) divisions (Division of Product Compliance [DPC] and Division of Promotion, Advertising, and Labeling [DPAL]) to determine whether the MRTPA met the 911(g)(1) marketing authorization criteria.

This assessment integrates the lines of evidence from the discipline reviews regarding the proposed MRTP and its potential effects on individual health and tobacco use behavior, including tobacco use initiation, to determine whether the applicant has demonstrated that marketing of the proposed MRTP, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

3.1 Potential Impact of Proposed MRTP to Individual Users - Product Characterization

This section describes the product design and composition and examines whether the application sufficiently describes the product itself, how it is made, and the consistency of the manufacturing of the product. This information is necessary to fully understand the product science, which, in turn, influences the potential health risks of the product. The section will summarize the findings of the Engineering, Chemistry, and Microbiology reviews. The OCE DEM review identified no significant compliance issues or process deficiencies during the manufacturing inspection conducted in 2016 and upon receipt of this MRTPA in 2018, concurred with the Office of Science's (OS) recommendation that additional inspections were not necessary, and thus, were not performed. Upon receipt of the amendment (MR0000199), FDA learned of an additional manufacturing site. Based on its similarity and the use of the same processes and procedures, OCE DEM determined that an inspection was not necessary and was, therefore, not performed on this site.

The applicant describes Copenhagen Classic Snuff as a loose, non-portioned, fine cut moist smokeless tobacco (MST) product. The applicant has been manufacturing variants of the proposed MRTP since 1822, with the earliest documented manufacturing process dating back to 1905. The applicant states that a pinch of the product is intended to be placed into the mouth between the cheek or lip and gum. The user typically holds the product in the mouth, expectorates the "juice" produced during use, and removes the product from the mouth after use. Some users swallow the "juice" produced during use instead of spitting.

MR0000108	
Product Name	Copenhagen Classic Snuff
Product Form	Non-Portioned Loose

Package Size	34.02 g per can
Product ID/Universal Product Code (UPC)	0-731071-91
Product Category	Smokeless Tobacco Product
Product Sub-Category	Moist Snuff

3.1.1 Engineering

The Engineering review describes and examines the engineering design and principles of operation of the proposed MRTP as well as the manufacturing process and performance tolerances for the product.

Product Design: All total moisture test data the applicant initially provided fell within the range limits. Based on the test data, range limits, and method (CDC Method 095-3371), the applicant had demonstrated that the proposed MRTP's total moisture, (b) (4) (b) (4), can be produced in a controlled process.

The applicant provided the target specification for tobacco cut size and provided sufficient information on the cutting process to ensure that the fine cut snuff can be manufactured consistently. However, the applicant had not submitted the complete test data needed to fully characterize the product. Though the target specification and range limits were provided for the blend moisture and leaf moisture, the applicant did not provide the test data to confirm that the specifications are met. The assessment of these design parameters is necessary to understand the comprehensive design of the proposed MRTP as each parameter contributes to the overall constituent yields. Tobacco moisture may affect microbial growth in the product, extraction efficiency, and total exposure to nicotine, NNN, and NNK (US FDA, 2013; Gale et al., 2013). Accordingly, the Engineering review concluded that the product had not been fully characterized because the application lacked test data for leaf moisture and blend moisture, which are obtained during the production process. This missing information was addressed in a deficiency.

Principles of Operation, Manufacturing Process, and Quality Control: The applicant had provided an adequate description of the principles of operation of the product from an Engineering perspective. Engineering reviewed the information provided describing the manufacturing process: from receiving and staging of the tobacco received from growers to the steps of producing the product (i.e., (b) (4) (b) (4)). Engineering also reviewed the manufacturing controls in place, which include (b) (4) (b) (4). Based on this review, Engineering determined the application was missing information regarding manufacturing process and controls including the test method and protocols used at the (b) (4) stages. These methods allow FDA to assess the quality control measures the applicant undertakes to ensure consistent manufacturing. Such information is necessary to confidently characterize the relative health risks of the product by ensuring that the levels of HPHCs reported through product testing reflect what an individual would be exposed to through regular use of the product. This missing information was addressed, along with related manufacturing information identified in the Chemistry review (discussed below), in deficiencies.

In summary, the Engineering review concluded that the MRTPA did not contain adequate information with respect to the following:

- Information to ensure that the product meets manufacturing specifications and that the product is manufactured in a consistent manner that minimizes the variability in product quality

- Manufacturing information such as quality control measures and performance testing to verify the product design including the leaf moisture and blend moisture parameters

Engineering noted two deficiencies, one of which was combined with a Chemistry review deficiency.

As TPL, I agreed with the Engineering conclusion that this MRTPA provided insufficient information for the FDA to fully understand what the product is, how it is made, and whether it is a product that can be manufactured in a consistent manner. I needed this information to fully evaluate the risk profile of the product. Because inconsistent manufacturing could potentially lead to varying quantities of HPHCs being delivered to an individual user, I needed this information to be able to make a complete assessment of individual health risks. FDA would be unable to fully evaluate the public health impact of the proposed MRTP related to tobacco-related diseases or abuse liability if a critical component such as HPHCs – as represented in the applications – is subject to change in unknown ways because of the applicant's lack of raw tobacco and manufacturing controls. Thus, I recommended conveying the deficiencies to the applicant.

Subsequently, in MR0000199, the applicant addressed all items in the deficiencies associated with Engineering (#2 and #5).

Deficiency #2 requested test data for leaf moisture and blend moisture to confirm target specifications were met to demonstrate that the applicant can manufacture the product consistently. The applicant provided %OV test data collected from 2012 to 2015 for leaf moisture during the (b) (4) (b) (4) stage and for blend moisture collected during the (b) (4) stage of the manufacturing process. Test data for leaf and blend moisture were consistent and fell within the specified range limits. In addition, the applicant provided work instructions and test protocols, including the current version of (b) (4) . The work instructions, test protocols, and test data demonstrate that the product can be manufactured consistently and are sufficient from an Engineering perspective.

Deficiency #5 (joint with Chemistry) requested 16 components of manufacturing and processing of the finished product such as steps, controls, and standard operating procedures (SOPs). This information was 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. Engineering found that the applicant provided information that is sufficient to demonstrate that product manufacturing is well-controlled. The calculation, clarification, descriptions, and documents provided by the applicant to address the 16-part deficiency are summarized below. Further evaluation of Deficiency #5 can be found in the Chemistry review.

- Descriptions of their storage facilities stating that tobaccos used to manufacture the proposed MRTP are stored in warehouses (b) (4) . Temperature and humidity controls affect product stability, however in their first cycle review, Microbiology concluded that stability data for the proposed MRTP are sufficient from a microbial product perspective.
- Clarification that the (b) (4) .
- Test methods and protocols for the (b) (4) process, including (b) (4) and an (b) (4) .

- Work instructions (b) (4) that include step-by-step details (b) (4) (b) (4) .
- (b) (4) In addition, the applicant refers to Table 3.1-9 in Section 3.1 of the original submission (MR0000108) for clarification and calculations used to determine the amount of (b) (4) .
- (b) (4)
- Work instruction (b) (4) to address (b) (4) process.
- Clarification (b) (4)
- (b) (4)
- (b) (4) . The applicant receives Certificates of Analysis (COAs) from their suppliers and verifies with product specifications.
- All COAs for all non-tobacco ingredients listed in Table 3.1-4 in section 3.1 of their original submission (MR0000108). The applicant states that the supplier makes (b) (4) flavor to meet the applicant's specification using the (b) (4)
- Work instructions with procedures used to ensure that the raw materials, ingredients, additives, and incoming tobacco meet the applicant's specifications include (b) (4) , (b) (4) . The applicant states (b) (4) (b) (4) .
- Documents showing protocols for quality control and assurance programs ensuring the finished product meets the applicant's specification. See the last bullet for details.
- Clarification that (b) (4) , (b) (4) .
- Work instructions (b) (4) (b) (4)
- Work instructions and documents with protocols for the quality control and assurance programs used to ensure that the finished product meets the applicant's specification and batch acceptance requirements throughout the production process, including (b) (4) 24, (b) (4) .

In summary, the Engineering review concluded that the information provided by the applicant in response to Engineering's deficiencies is adequate to fully characterize the proposed MRTP and demonstrate that the proposed MRTP is manufactured in a consistent manner from an Engineering perspective.

As TPL, I agree with the Engineering conclusion. I find that the applicant now has provided sufficient information to fully characterize and evaluate the proposed MRTP from an Engineering perspective, has provided details on how it is manufactured, and demonstrated that it can be manufactured in a consistent manner. Now that I have this information, I am able to characterize the product and understand its potential risks relative to other ST products, in particular, to determine whether the product, as actually used, would significantly reduce the risk to individual tobacco users and benefit the health of the population as a whole.

3.1.2 Chemistry

The Chemistry review assessed the product's ingredients, manufacturing processes, and controls that can affect the product composition, chemical stability, and HPHC analysis for the proposed MRTP.

Product Formulation: The product design features relevant to chemistry are specifications and upper and lower limits for the final pH, the final percentage of oven volatiles (%OV), and container closure system (i.e., composition of the can and lid). While the applicant provided ingredient quantities and functions for the fiberboard can and metal lid materials used for the container closure system, the MRTPA lacked information such as inks, and grade of the container closure system ingredients and seal. This prevented Chemistry from fully evaluating the ingredients in the container closure system or evaluating the ability of the manufacturer to produce the product consistently. Without this information, FDA could not make a full assessment of individual health risks due to the potential variability in the product. This missing information was addressed in a deficiency.

Copenhagen Classic Snuff is a loose moist snuff that consists of 34.02 grams of loose tobacco packaged in a fiberboard can with a metal lid. Based on the original MRTPA (MR0000108) and amendment (MR0000121), the candidate product tobacco blend comprises (b) (4) tobacco types: (b) (4) mg/g (b) (4) (b) (4) mg/g (b) (4) mg/g (b) (4) y and (b) (4) mg/g (b) (4) tobacco, along with other ingredients such as salts, flavorings, humectants, and buffering agents. The applicant indicates that the product is designed to contain between (b) (4) % %OV as moisture content and have a pH value between (b) (4).

Other than tobacco, the basic formulation for the proposed MRTP consists of flavorings, processing aids, various salts, and humectants. Of these, the two most abundant ingredients (b) (4) mg/g), reported as a (b) (4); and the complex flavor (b) (4) /g). Many of the ingredients other than tobacco are listed as flavors, which are mostly present at very low concentrations (parts per million or parts per billion levels). Many of the flavors are complex ingredients. However, the applicant did not provide a list of the individual ingredients and quantities for the complex ingredients regarding which ingredients are made to the applicant's specifications and which are not, nor the necessary accompanying information from those distinctions as relates to health hazards (i.e., lung cancer). The absence of information on individual ingredients, grade, and quantities limited FDA's ability to characterize the product and evaluate the potential impact of the complex flavors. This missing information was addressed in a deficiency.

Finally, although many of the flavoring ingredients such as (b) (4) (b) (4) oil, and (b) (4) account for only (b) (4) % of the finished product by weight, these ingredients are potential permeation enhancers. Small amounts of permeation enhancers in an ST product may increase relative exposures and absorption of HPHCs relative to other ST products that do not contain these ingredients (Vaddi et al., 2002; Boukhatem et al., 2013). However, at this time, there is no conclusive evidence about any negative effects of these particular potential permeation

enhancers; therefore, inclusion of these ingredients did not rise to the level of a deficiency. See Section 3.2.1 for further discussion of this topic.

Manufacturing Steps and Controls: The applicant has submitted some detailed information on the manufacturing practices and process for this product. However, like Engineering, Chemistry identified missing information regarding manufacturing steps and quality control measures specific to the proposed MRTP. The absence of this information prevented Chemistry from verifying that the leaf processing procedure for the proposed MRTP is consistent and the proposed MRTP can be manufactured on a consistent basis from lot to lot. This information is necessary to fully evaluate individual health risks. This missing information was addressed in a deficiency.

Performance Criteria: The applicant describes the manufacturing performance criteria for the products. Performance criteria are parameters that reflect expected outcomes based on design specifications or other inputs and describe the functional performance criteria expected for a material, component, or product. The MRTPA has provided the design specifications for the finished product, which include target values and lower and upper limits for pH and moisture. The applicant has provided testing data as performance criteria on five different lots in section 7.1 of the MRTPA, demonstrating that the proposed MRTP meets the (b) (4) , %OV, and pH specifications. However, the applicant did not provide information regarding the procedures undertaken when finished product batches exceed %OV and pH upper tolerance levels, which rendered Chemistry unable to determine the full variability of the product. The applicant also did not mention whether the final %OV and final pH were tested before or after packaging. This helps determine the duration of time prior to the product being placed on the shelf with the idea that after packaging may be better since there is less time between the last test and when a consumer purchases the product. Testing before packaging would also be acceptable if the applicant can demonstrate that the product is stable. For these reasons, specifications for final product moisture, pH, and (b) (4) were insufficient to assure that product variability does not affect levels of exposure and risk to users. This missing information was addressed in a deficiency.

Stability: The applicant submitted stability data for the shelf-life of the proposed MRTP. The purpose of the chemical stability testing is to ensure HPHC quantities are not changing over time (i.e., during storage and use). The analytical and microbial stability testing was conducted over the shelf-life of the proposed MRTP (b) (4) after manufacture).

Evaluation of the potential impact of stability of the proposed MRTP for pH, %OV, nitrates, nitrites, NNN, NNK, and water activity (a_w) demonstrated the expected microbiological stability of the candidate tobacco product through its shelf-life. There were decreases in pH, NNN, %OV, and a_w and increases in NNK, nitrate, and nitrite over the (b) (4) testing period. Though there was a 29% increase in nitrite over the (b) (4) period and nitrite concentration in ST can influence tobacco-specific nitrosamine (TSNA) production, Chemistry deferred to Microbiology on this assessment; Microbiology concluded this increase in nitrite of Copenhagen Classic Snuff is not of concern based on the decrease (1%) in NNN and a minor increase (3%) in NNK over the shelf life of the product.

Product Analyses: The applicant reported quantities of nine HPHCs--acetaldehyde, arsenic, BaP, cadmium, crotonaldehyde, formaldehyde, NNN, NNK, and nicotine (total and free) -- in addition to moisture and pH for the proposed MRTP on a wet (“as is”) and dry weight basis.

The initial Chemistry review evaluated the HPHCs of the candidate product relative to cigarette smoke and other ST products. Given the limited applicability of the former (e.g., differences in routes of administration affect exposure), the discussion below focuses on the comparison to other ST products.

Chemistry compared the HPHC quantities reported by the applicant for the proposed MRTP in Section 7.1 to published literature for different ST types (i.e., moist snuff, dry snuff, loose leaf, snus) (see Table 1). Preliminary evaluation of one set of samples shows that quantities for some HPHCs in the proposed MRTP are similar to or lower than those of other currently marketed ST products, and some are higher (Table 1). This evaluation was contingent upon the findings of missing information regarding the analytical test methods used to generate the HPHC data information requested in the deficiencies.

In particular, the proposed MRTP has lower quantities of the following HPHCs compared to other ST products:

- Acetaldehyde (71% − 82%) compared to moist snuff and Swedish snus
- Formaldehyde (50% − 90%) compared to moist snuff, dry snuff, and Swedish snus
- NNN (6% − 31%) compared to other moist snuff and dry snuff
- NNK (26% − 59%) compared to other moist snuff and dry snuff
- Total nicotine (21%) compared to dry snuff
- Free nicotine (7% − 31%) compared to moist snuff and Swedish snus

The proposed MRTP has higher quantities of the following HPHCs compared to other ST products:

- Acetaldehyde (85%) compared to dry snuff
- Arsenic (9% − 122%) compared to moist snuff, dry snuff, and loose leaf
- BaP (90% − 3,243%) compared to moist snuff, dry snuff, and loose leaf
- Cadmium (46% − 165%) compared to moist snuff, dry snuff, loose leaf, and Swedish snus
- Total nicotine (4% − 102%) compared to moist snuff, loose leaf, and Swedish snus
- NNN (113% − 427%) compared to loose leaf and Swedish snus
- NNK (98% − 349%) compared to loose leaf and Swedish snus
- Free nicotine (460% − 9,700%) compared to dry snuff and loose leaf

Table 1. FDA Comparison of HPHCs in Copenhagen Classic Snuff Compared to Other ST Categories

Constituent (Unit)	Copenhagen Classic Snuff, 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/P	N/A	21.6	↓71
Arsenic (ng/g)	233	214	↑ 9	179	↑ 30	105	↑ 122	N/P	N/A
Benzo[a]pyrene (ng/g)	117	61.6	↑ 90	30.5	↑ 284	3.5	↑ 3,243	N/P	N/A
Cadmium (ng/g)	1537	1052	↑ 46	879	↑ 75	599	↑ 157	579	↑ 165

Crotonaldehyde (µg/g)	BLOQ	2.98	N/A	13.33	N/A	N/P	N/A	N/P	N/A
Formaldehyde (µg/g)	1.58	8.43	↓ 81	3.18	↓ 50	N/P	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	↑ 9,700	5.65	↓31

*Data in Table 1: 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, MF et al., 2012; Swedish snus levels are reported as an average of data from Swedish Match 2014 MRTP application. Data reported on a dry weight basis (DWB) except for free nicotine, pH, and moisture which are reported "as is" (wet weight basis); N/P= Not Provided; N/A = Not Applicable; BLOQ= Below Limit of Quantitation

FDA Product Analyses for HPHC Verification: To verify chemical and physical data submitted by the applicant, FDA requested that FDA's Southeast Tobacco Laboratory (STL) independently perform testing on NNN and NNK on September 21, 2018. Chemical testing was conducted on fresh cans of the proposed MRTP and analysis of the samples were taken "as-is". Analysis of NNN and NNK was performed using a STL in-house SOP (TSNA Analysis in Tobacco by UPLC/MS/MS). As seen in Table 2, mean quantities for NNN and NNK reported by STL are similar to data for NNN and NNK submitted by USSTC in the original MRTPA. There were minor differences in the methods between the two laboratories used to test NNN and NNK. However, a two one-sided test calculation determined the values reported from STL and USSTC for NNN and NNK to be analytically equivalent.

Table 2. Verification of TSNAs in Copenhagen Classic Snuff (as is)

Constituents	Unit	STL			USSTC		
		Mean	Std. Dev	N	Mean	Std. Dev	N
NNN	ng/g	1689	103	21	1746	63	35
NNK	ng/g	452	79	21	472	65	35

N= Number of Replicates

Finally, the Chemistry review identified missing information related to the product analyses. In particular, the information provided by the applicant regarding SOPs used to determine the levels of the HPHCs in the proposed MRTP appeared to be adequate. However, the applicant did not provide validation reports (e.g., accuracy, precision, selectivity, linearity and range, limit of detection, limit of quantification) to demonstrate the validity of the methods for any of the SOPs. Clarification was also needed on the SOPs used to determine pH and %OV. Because the applicant did not include complete information on the analytical test methods used to generate the HPHC data for the proposed MRTP, Chemistry was not able to determine an accurate assessment of the differences in the HPHC quantities

between the proposed MRTP and other ST products, which impacted the ability to fully weigh the impact on individual health risk. This missing information was addressed in a deficiency.

Based on preliminary evaluation, Chemistry concluded that the increased quantities of the HPHCs in the proposed MRTP compared to other ST products raise potential concerns regarding the relative risks of the tobacco product.

In summary, Chemistry concluded that the applicant did not provide sufficient information (e.g., composition, product design, manufacturing processes) to fully characterize the proposed MRTP and to ensure that the proposed MRTP will be manufactured in a consistent manner. This information is necessary to accurately determine the HPHC quantities in the product and any variation in those quantities. Without this information, I could not determine whether the product, as actually used, would significantly reduce the risk to individual tobacco users and benefit the health of the population as a whole. Accordingly, Chemistry noted five deficiencies, which are listed in Section 6. Two of these deficiencies were jointly submitted with other disciplines (Engineering and Toxicology, respectively).

As TPL, I agreed with the Chemistry conclusion that the application provided insufficient information to fully characterize and evaluate the proposed MRTP, how it is manufactured, and whether it can be manufactured in a consistent manner. I needed this information to characterize the product and understand its potential risks relative to other ST products, in particular. I recommended conveying these deficiencies to USSTC.

The applicant provided a response to these five deficiencies in MR0000199. Chemistry provided a second review specific to this response.

Deficiency #3 requested three specific criteria, controls, and SOPs as relates to leaf processing procedures. This information was 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. The applicant provided work instructions, definitions, and acceptance criteria used (b) (4) . The information provided on (b) (4) (b) (4) steps, controls, and SOPs does not raise concerns from Chemistry's perspective. As TPL, I find that this deficiency was adequately addressed.

Deficiency #4 requested specification %OV and pH protocols used throughout the entire manufacturing process in order 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. The applicant provided information on the %OV and pH protocols used in tobacco processing and manufacturing stages and corresponding work instructions. (b) (4) The applicant adequately specified which %OV and pH protocols were used throughout the entire manufacturing

process for the in-process tobacco product. The information provided does not raise concerns from Chemistry's perspective. As TPL, I find that this deficiency was adequately addressed.

Deficiency #5 was joint with Engineering and requested 16 components of manufacturing and processing of the finished product such as steps, controls, and SOPs in order 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. The applicant provided clarifications, work instructions, and batch report forms addressing each part of this deficiency. The work instructions provide (b) (4) This information with the (b) (4) and requirements, provided in the original application, gives a more complete picture of (b) (4) (b) (4) , which do not raise concerns from this discipline's perspective. The information provided demonstrates that the product is manufactured in a consistent manner that minimizes the variability in product quality and does not raise concerns from Chemistry's perspective. As TPL, I find that this deficiency was adequately addressed.

Deficiency #6 was joint with Toxicology and requested clarification of complex ingredients made to the applicant's specifications and those not, and for those made to the applicant's specifications, to provide complete information. For those not made to the applicant's specifications, specific information was requested. This information was requested in order to fully characterize the composition and evaluate the risks of the proposed MRTP. The applicant provided single chemical ingredients for all the complex flavors listed in the deficiency, including target values and ranges (in units of mg/g of product). The information provided on complex flavor does not raise concerns from Chemistry's perspective. The toxicological impacts of the ingredients are deferred to Toxicology. As TPL, I find that this deficiency was adequately addressed from the Chemistry perspective.

Deficiency #7 requested method validation summaries for each analytical method used for testing HPHCs in order to properly evaluate the proposed MRTP. The applicant provided (b) (4) (b) (4) This information does not raise concerns from Chemistry's perspective. As TPL, I find that this deficiency was adequately addressed.

The information provided by these deficiencies was necessary for Chemistry to be able to accurately determine the HPHC quantities in the product and any variation in those quantities. Because Chemistry found the applicant's response to the deficiencies to be sufficient, Chemistry is now able to fully characterize the proposed MRTP, including its HPHC quantities and any variation in those quantities.

To that end, upon request from Toxicology, Chemistry assessed the response to Deficiency #8 (originally put forth by Toxicology), which examined the individual health risks of the proposed MRTP relative to other ST products, including its HPHC quantities and any variation in those quantities. Based on the applicants' assertion, which FDA accepted, regarding MST being the appropriate category, analyses during this second round of review used the MST sub-category as the comparator. Chemistry consulted Statistics who determined that the applicant's comparisons of mean quantities to mean quantity ranges were not statistically appropriate because a range may indicate much more variability in the data than the true variability. Moreover, the applicant did not provide measures of range variability. Chemistry and Statistics instead provided appropriate nonparametric methods to analyze the data to ensure appropriate comparisons between HPHC yields from the proposed MRTP and published MST data. That

analysis is contained in Table 3 below. That comparison shows that the proposed MRTP yielded higher BaP, higher cadmium, lower NNK, and lower free nicotine quantities than published MST data. Additionally, the proposed MRTP yielded equivalent (i.e., not statistically significantly different) quantities of arsenic, NNN, and total nicotine. This finding is consistent with the HPHCs discussed in Deficiency #8 for MST comparisons. Toxicology (see Section 3.2.1) evaluated whether the applicant provided 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.

Table 3. HPHC quantity comparisons in the proposed MRTP and published moist snuff data[24,25,[1]]

Constituent	Unit	Proposed MRTP			Moist Snuff			p- value (Wilcoxon rank-sum test)
		N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)	
Acetaldehyde	µg/g	35	6.3 (2.5)	4.67 (4.35-9.27)	4 [a]	36.7 (25.70)	28.70 (17.95- 55.45)	NA
Arsenic	ng/g	35	232.7 (23.6)	225.00 (218.00-245.00)	27	211.9 (70.1)	226.00 (151.00-261.00)	0.3560
Benzo[a]pyrene	ng/g	35	117.1 (19.9)	130.00 (94.90-134.00)	32	57.7 (51.5)	58.80 (1.85- 75.60)	**<.0001***
Cadmium	ng/g	35	1536.9 (243.3)	1660.00 (1256.00-1741.00)	28	1014.4 (401.8)	1075.00 (603.50-1307.50)	**<.0001***
Crotonaldehyde	µg/g	2 [b]	0.11 (0.01)	0.11 (0.11-0.12)	4 [a]	3.5 (2.2)	3.26 (2.11- 4.82)	N/A
Formaldehyde	µg/g	35	1.6 (0.2)	1.58 (1.46-1.70)	4[a]	8.4 (2.0)	8.24 (6.76-10.07)	N/A
NNK	ng/g	35	1033.7 (139.2)	944.00 (919.00-1181.00)	26	1461.2 (1307.2)	1260.00 (887.00-1476.00)	**0.0338***
NNN	ng/g	35	3824.6 (152.6)	3847.00 (3656.00-3944.00)	32	3924.9 (2595.8)	4291.00 (1102.50-4772.00)	0.3123
Total Nicotine	mg/g	35	12.5 (0.2)	12.50 (12.30-12.60)	28	12.1 (2.0)	12.90 (11.07-13.37)	0.0732
Free Nicotine	mg/g	35	3.9 (0.2)	3.84 (3.80-3.95)	28	4.5 (1.8)	4.74 (3.16-5.79)	**0.0373***

[1] [a] Data are only from Stepanova et al. (2008). [b] Low replicate number because many replicate measurements were BLOQ = below limit of quantitation. * Statistically significant. N/A = Not applicable because sample size is small. IQR = Interquartile range (25th percentile – 75th percentile). Nicotine and moisture quantities are in wet weight ("as-is") and all other constituents dry weight basis (DWB).

In summary, following the applicant's response to the deficiencies laid out by Chemistry, the applicant adequately addressed the Chemistry aspects of Deficiencies 3-8 in their amendment. From a Chemistry perspective, the applicant provided manufacturing and testing information to fully characterize the proposed MRTP, including demonstrating consistent manufacturing by providing %OV and pH of the finished product and throughout manufacturing steps, HPHC quantities in the finished product, finished product stability data, and demonstrated the reliability of the testing methods and results. This allows FDA to understand the product's risk relative to cigarettes and other MST products. Manufacturing information was also evaluated by Engineering. Ingredients and HPHC differences between the proposed MRTP and other products were further evaluated by Toxicology (see Section 3.1.2).

As TPL, I agree with the Chemistry conclusions. I find that the applicant now has provided sufficient information to fully characterize and evaluate the proposed MRTP, has provided adequate details on how it is manufactured, and demonstrated that it can be manufactured in a consistent manner. Now that I have this information, I can characterize the product and understand its potential risks relative to cigarettes and other ST products, in particular, to determine whether the product, as actually used, would significantly reduce the risk to individual tobacco users and benefit the health of the population as a whole

3.1.3 Microbiology

The Microbiology review focused on characterizing the product stability of the MRTP (as it relates to microbiology), factors that can potentially affect the microbial stability of the product (e.g., manufacturing processes, ingredients, additives), and ensuring well-controlled manufacturing of the product.

Product Description and Formulation: From a Microbiology perspective, the tobacco product ingredients of most concern are those that could affect microbial growth, such as humectants and preservatives. Based on the product stability data in the application, the additions of a humectant (b) (4) and preservative (b) (4) to the proposed MRTP do not raise concerns from a microbial product stability perspective.

Manufacturing Steps and Controls: The key manufacturing step of the proposed MRTP, as related to microbiology, is the (b) (4) process (i.e., (b) (4)). The applicant provided detailed information on the f (b) (4) process including (b) (4) . In addition, the applicant also provided adequate information on the storage conditions and container closure system of the proposed MRTP but did not indicate whether a formal method exists (b) (4) (b) (4) . However, product stability information submitted by the applicant, as described below, adequately addressed this concern.

Product Stability: Microbiology also evaluated the stability testing evaluated by Chemistry to ensure that the product is microbiologically stable during the expected storage period and does not result in an increased risk to public health as the product sits in storage. The review concluded that the stability data do not raise microbial product stability concerns.

Product Analyses: To further assess the product stability data submitted by the applicant, microbiological (total aerobic microbial count (TAMC) and total yeast and mold count (TYMC)) and physical (a_w) testing of the proposed MRTP was performed by FDA's A2LA-certified Southeast Food and Feed Laboratory (SFFL) and compared to the applicant's stability testing data. The a_w, TAMC, and TYMC data submitted by the applicant were verified by testing performed by FDA SFFL. a_w and TYMC data provided by SFFL is comparable to data provided by the applicant. The TAMC measured by SFFL is lower when compared to that of the applicant, but that difference is acceptable from a Microbiology perspective and does not raise concerns from a microbial product stability perspective.

Additionally, the physical, chemical, and microbiological stability attributes of the proposed MRTP were compared to other comparator (ST) products. After analyzing the physical, chemical, and microbiological stability data of the proposed MRTP submitted by the applicant and comparing it with the data from published journals on several moist snuff products, FDA concluded that the pH and OV% of the proposed MRTP are similar to other moist snuff products on the U.S. market. However, the nitrate level of the proposed MRTP is higher than the average level observed in other moist snuff products, and the

levels of nitrite, NNN and NNK are lower than that of other moist snuff products. The high TAMC count of 10^6 is not unexpected because it is a (b) (4) tobacco product. Moreover, the TAMC levels are comparable to other moist snuff products on the U.S. market. The undetectable TYMC in the proposed MRTP (as measured by SFFL) further confirmed the applicant's claim that USSTC's MST products are inherently non-supportive to the proliferation of yeasts and molds.

In summary, the Microbiology review concluded that the applicant provided adequate microbiology-related information to demonstrate full product characterization and stability over product shelf life and to address factors that can potentially affect the microbial stability of the product. Microbiology also concluded that the application had adequate quality control information.

As TPL, I agree with the Microbiology conclusion.

3.1.4 Conclusions: Product Characterization

The applicant describes Copenhagen Classic Snuff as a loose, non-portioned, fine cut moist snuff ST product. The product is made with a tobacco blend comprising (b) (4) , along with ingredients such as salts, flavorings, humectants, and buffering agents. The applicant reported quantities of nine HPHCs in one set of samples --acetaldehyde, arsenic, BaP, cadmium, crotonaldehyde, formaldehyde, NNN, NNK, and nicotine (total and free).

Microbiology concluded that the stability data did not raise microbial product stability concerns. Engineering and Chemistry found missing information related to manufacturing and controls across numerous constructs, which prevented FDA from determining if the product could be manufactured consistently as well as from fully characterizing the product. These analyses, in turn, would allow Toxicology to examine toxicities associated with HPHCs, which would impact individual health risk, and ultimately population health benefit. The missing information was conveyed through six deficiencies (one of which was joint with Toxicology). Accordingly, in MR0000199, the applicant responded to the conveyed deficiencies. As described above, the applicant's responses addressed the deficiencies in an acceptable manner to both Engineering and Chemistry allowing full product characterization and ensuring consistent manufacturing. To support Toxicology's analyses, Chemistry also examined HPHC levels and quantities relative to other MST products. This test found the BaP and cadmium quantities in the proposed MRTP to be significantly higher than those in MST, whereas NNK and free nicotine quantities are significantly higher in MST than in the proposed MRTP.

In summary, as TPL, I agree with the conclusions of Engineering, Chemistry, and Microbiology and find that the product can be manufactured consistently and can now be fully characterized. Therefore, the HPHC data initially submitted by the company is valid and can be analyzed as was submitted. I also concur with the joint decision of Epidemiology, Statistics, Chemistry, and Toxicology that, as requested and stated by the applicant, it is appropriate to compare HPHCs in the proposed MRTP to only other MST products as opposed to the whole class of ST products given that MST comprises the vast majority of the ST marketplace. Analyses conducted following the applicant's response to the deficiency letter were done using the MST sub-category as the comparator for HPHCs. With these data, we now have complete product analysis information to fully characterize the proposed MRTP, including its HPHC quantities and any variation in those quantities, which allows FDA to understand the product's risk relative to other ST products, which have implications for an individual user's health risk.

3.2 Relative Health Risks to Individuals & Claim Substantiation

This section examines the evidence provided by the applicant in order to evaluate the statutory requirements for an MRTPA to demonstrate that the proposed MRTP—as actually used by consumers—will significantly reduce the harm and risk of tobacco-related disease to individual tobacco users. This section includes an assessment of the health risks relative to non-use and use of other tobacco products. It will also examine whether the proposed modified risk information is scientifically accurate in order to substantiate the claim. The section will review evidence provided by Toxicology, BCP, Medical, and Epidemiology reviewers. OCE's review did not reveal any data integrity or human subject protection concerns. OCE concurred with OS's recommendation that a BIMO inspection for the protocol and associated sites is not needed at this time and this conclusion remained unchanged after an additional site was identified in MR0000199. No additional inspections were conducted.

3.2.1 Toxicology

This subsection describes the Toxicology review of the scientific information contained in the MRTPA, including review of HPHC information, published nonclinical toxicology studies submitted, and published literature regarding the marketplace of cigarettes and ST products.

Comparison to cigarettes: The applicant provided HPHC data for one set of samples for the proposed MRTP. To compare this preliminary information to the marketplace of cigarettes, contingent upon the findings of missing information regarding the analytical test methods requested in the deficiencies, potential daily intake levels were calculated using the 90th percentile use information provided by the applicant in section 3.2 of the application and published literature. Compared to cigarettes, the potential daily intakes of acetaldehyde and formaldehyde with the use of the proposed MRTP were lower, but were higher (~325-5700-fold) for arsenic, B[a]P, cadmium, NNN, and NNK. Differences in route of exposure between cigarettes (i.e., inhalation of combustible product) and the proposed MRTP (i.e., oral absorption and a lack of direct pulmonary exposure) would affect the overall toxicity of the HPHCs present in the proposed MRTP relative to cigarettes. In nonclinical animal models, oral exposure to arsenic, BaP, NNN, and NNK was associated with lung cancer. However, the applicant did not provide any information that would allow calculation of user exposure and did not discuss the concerns raised by the nonclinical evidence showing that HPHCs associated with the proposed MRTP cause lung cancer.

In addition to these HPHCs, the applicant provided information regarding the ingredients used in the proposed MRTP. Many of these ingredients were complex ingredients that were mixtures that went undefined by the applicant, limiting the ability to interpret the toxicity of such complex ingredients as described in the Chemistry review. This missing information was addressed in a deficiency.

The applicant also submitted information regarding potential permeation enhancers, which are non-tobacco ingredients not found in cigarette smoke. Though permeation enhancers may increase the absorption of HPHCs, and therefore, alter the potential toxicity of this product, the applicant did not provide information on such interactions, as noted by Chemistry. Furthermore, the inclusion of such chemicals may confound the calculation of user exposure, and ultimately, comparative disease risk. However, at this time, there is no conclusive evidence about any negative effects of these particular potential permeation enhancers (i.e., (b) (4)) via the buccal route. Therefore, while these potential permeation enhancers are present and may influence the overall exposure to HPHCs, no deficiency was conveyed at this time.

In assessing the provided literature, the discipline noted 59 non-clinical studies related to the claim of decreased risk of lung cancer relative to cigarettes. There were five studies that included the Copenhagen brand. While these articles did show dysplasia of the oral mucosa and promotion of viral-

mediated carcinogenesis, they did not contain a comparison of ST products to cigarettes, limiting their utility. Furthermore, because other studies submitted to examine the effects of ST use on oral carcinogenesis did not examine the lungs of the animals, the reviewers determined the studies were irrelevant to the proposed modified risk claim. Thus, Toxicology did not have enough information to substantiate the claim based on the evidence they reviewed alone and recommended that this missing information be addressed in a deficiency.

Comparison to other ST Products: Toxicology referenced Chemistry's preliminary review of the HPHC information provided by the applicant, contingent upon the findings of missing information regarding the analytical test methods requested in the deficiencies and compared it to the mean values available in published literature for other ST products in the marketplace, including moist snuff, dry snuff, loose leaf, and Swedish snus products. Comparing quantities of measured HPHCs from the proposed MRTP to the mean values in published literature for other ST products showed relatively similar quantities for some HPHCs and lower quantities for some others; however, there were notably higher quantities of acetaldehyde (85% compared to dry snuff), arsenic (9-122% compared to dry snuff, moist snuff, and loose leaf), BaP (90-3243% compared to moist snuff, dry snuff, and loose leaf), cadmium (46-165% compared to moist snuff, dry snuff, loose leaf, and Swedish snus); NNN (113-427% compared to loose leaf and Swedish snus), and NNK (98-349% compared to loose leaf and Swedish snus). These higher quantities could potentially increase health risks (e.g., variety of cancers, cardiotoxicity, reproductive/developmental toxicities) associated with exposure to these HPHCs if users of some other ST products dual used or switched to the proposed MRTP. The implications of these findings were not discussed. This missing information was addressed in a deficiency.

Comparison to Never Use: In addition, the proposed MRTP was compared to never use. ST, in general, is carcinogenic through a mutagenic mode of action, capable of modulating carcinogenicity, and associated with cardiovascular endpoints (e.g., vasodilation, increased heart rate), periodontal disease, and reproductive/developmental toxicities. Numerous studies have shown that ST use can cause addiction, precancerous oral lesions, oral cancer, esophageal cancer, pancreatic cancer, and reproductive and developmental toxicities. In terms of involuntary exposure, Toxicology notes that because the proposed MRTP is not combusted, it is unlikely that adult non-users would be involuntarily exposed. However, nicotine poisoning is a possibility in children who are inadvertently exposed to the proposed MRTP.

In summary, the initial Toxicology review concluded the following:

- The toxicology information reviewed was not sufficient to substantiate the claim on its own; the review noted higher quantities of certain carcinogenic HPHCs relative to cigarette smoke, but also acknowledged that differences in routes of exposure would be expected to affect the overall toxicity of the HPHCs present in the proposed MRTP. Toxicology concluded that without additional information to quantify the differences in routes of exposure, the HPHC data may have limited utility for assessing potential differences in specific health effects when comparing the proposed MRTP to cigarettes.
- In a preliminary assessment, the proposed MRTP has lower quantities of some HPHCs, and higher quantities of others compared to other ST products, which could potentially increase health risk relative to other ST products.[7]

[7] These data are preliminary because they are contingent upon the findings of missing information regarding the analytical test methods as requested in a deficiency.

- The proposed MRTP also contains potential permeation enhancers, which could increase health risk. At this time, the literature is inconclusive regarding any negative effects of these specific potential permeation enhancers.
- The published literature the applicant provided was limited in its utility because it only included five studies that potentially used the candidate product.
- The scientific literature has established that ST use causes health risks: precancerous oral lesions, oral cancer, esophageal cancer, pancreatic cancer, and cardiovascular, reproductive, and developmental toxicities.

Toxicology listed three deficiencies, which are listed in Section 6. This included one deficiency jointly submitted with Chemistry.

As TPL, I largely concurred with these preliminary substantive conclusions. As noted in Section 3.1.4, I recommended conveying the joint deficiency with Chemistry. Toxicology also noted a deficiency in the data provided regarding the implications of HPHC quantities in the product, especially where these quantities appear higher than other marketed ST products. As this information is related to our overall understanding of the relative risks of the product, I agreed with the request for the applicant to discuss the implications of these data for potential MRTP users and recommended conveying this deficiency to the applicant.

With respect to claim substantiation, the toxicologic evidence is informative but not determinative to make this finding. In determining claim substantiation and individual health risks relative to cigarettes, there is a large body of longitudinal epidemiologic studies submitted by the applicant and in the extant literature that can be relied on to determine long-term health effects including the risk for lung cancer. Because of this, I did not recommend conveying a Toxicology deficiency that requests additional information related to claim substantiation.

In response to the deficiency letter, the applicant provided responses to each of the deficiencies.

As described in section 3.1.2, Deficiency #6 was joint with Chemistry and requested clarification of complex ingredients made to the applicant's specifications and those not, and for those made to the applicant's specifications, to provide complete information. For those not made to the applicant's specifications, specific information was requested. This information was requested in order to fully characterize the composition and evaluate the risks of the proposed MRTP. The applicant provided single chemical ingredients for all the complex flavors listed in the deficiency, including target values and ranges (in units of mg/g of product). The information provided on complex flavor did not raise concerns from Chemistry's perspective. Likewise, evaluation of the information provided by the applicant regarding these ingredients did not identify any concerns from a Toxicological perspective. As the TPL, I agree that this deficiency was adequately addressed.

Deficiency #8 requested that the applicant provide scientific evidence and rationale about how exposure to HPHCs in ST 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, particularly in comparison to other ST products. As described in Section 3.1.2., the applicant stated that because the vast majority of the marketplace was MST, the appropriate comparison for HPHCs was other MST products. Epidemiology confirmed this assertion and therefore, Chemistry and Toxicology determined this comparison was a reasonable approach, and therefore, compared HPHCs to levels in other MST products. Therefore, the portion of the deficiency related to dry snuff, loose leaf, and Swedish snus is resolved.

As analyzed by the applicant, comparison to the means of the MST product category indicated that arsenic, BaP, and cadmium were higher in the proposed MRTP. However, as described in 3.1.2, Statistics did not find the methods used by the applicant to be statistically appropriate because a range may indicate much more variability in the data than the true variability. Instead, Statistics recommended non-parametric tests and the use of medians. When Chemistry conducted those analyses, only BaP and Cadmium were higher while NNK and free nicotine were lower. Because the analyses in the first Chemistry and Toxicology reviews utilized means and not medians and because they both initially listed arsenic as higher, to be thorough, Toxicology examined both means and medians. Thus, though Chemistry did not find that arsenic was higher for the proposed MRTP compared to the MST subcategory, Toxicology analyzed arsenic using the means methodology to ensure the original deficiency was fully addressed. However, in terms of analyses that weighed into my decision making, arsenic was not considered because there were no differences once the more statistically appropriate analyses were conducted.

To look at the totality of exposures from HPHCs, Toxicology used FDA/CTP's scientific approach to evaluation of HPHC comparisons between tobacco products, which has evolved as documented in the memorandum *"Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in application review", signed February 25, 2022*. Briefly, this approach focuses on HPHC increases and decreases that are analytically non-equivalent between two tobacco products. The toxicity endpoints of the analytically non-equivalent HPHCs are central to the toxicological comparison between two tobacco products. An HPHC decrease that has a toxicity endpoint different from that of an HPHC that is increased cannot offset the HPHC increase. At this time, carcinogenic endpoints are considered equivalent. For example, an HPHC increase that evidence indicates increases liver cancer risk can be offset by a decrease in an HPHC that evidence indicates increases lung cancer risk. The analysis of non-cancer endpoints is more complicated than that of cancer endpoints. For example, the respiratory irritation of formaldehyde cannot be offset by a decrease in an HPHC that is not a respiratory toxicant (e.g., benzene might offset formaldehyde in terms of carcinogenicity, but cannot offset the respiratory effects of formaldehyde, because it is not a respiratory toxicant). HPHC measurements that are analytically equivalent are considered unchanged between the two compared products. The equivalence testing is determined by Chemistry using the "two one-sided t-test" procedure or TOST (Memo: *Equivalence Testing for SE Evaluations, signed February 24, 2017*).

Through this offsetting analysis and using the more statistically appropriate medians that Chemistry did, Toxicology determined by, that the higher levels of some HPHCs relative to the MST category were offset by the lower levels of other HPHCs. Specifically, utilizing medians, lower levels of NNK and free nicotine offset the higher levels of BaP and cadmium from a carcinogenic perspective. Further, Toxicology determined that non-cancer toxicities resulting from potential exposure to higher levels of BaP and cadmium as compared to other MST products were not a concern due to values remaining below the reference doses established by the Environmental Protection Agency (EPA).

In summary, from a Toxicological perspective, the carcinogenic and non-carcinogenic concerns associated with higher mean levels of HPHCs (i.e., arsenic, BaP, cadmium) are offset by reductions in other HPHCs in Copenhagen Classic Snuff compared to other MST products in the marketplace. When comparing the median levels of the HPHCs as recommended by Statistics and utilized in the Chemistry review, the higher levels of BaP and cadmium were then offset by lower levels of NNK and free nicotine.

Therefore, at this time, Toxicology reports that both deficiencies have been addressed and there are no further toxicological concerns.

As TPL, I concur with Toxicology's assessment to utilize the MST sub-category as the comparison for this analysis. While Toxicology opted to assess both the means and median comparisons, per Statistics and Chemistry, the more appropriate comparison is through the medians. Because NNK and free nicotine were lower than the median levels of MST products, this offset the higher levels of BaP and cadmium. In totality, the higher levels of BaP and cadmium are not of concern with respect to both the carcinogenic and non-carcinogenic endpoints.

3.2.2 Clinical

3.2.2.1 Medical

To assess the clinical aspects of the individual health effects, the Medical review examined adverse events (AEs) and biomarkers of potential harm (BOPH).

The application referenced cross-sectional studies in the literature that examine BOPH in ST users compared to cigarette smokers and non-tobacco users. Compared to cigarette smokers, ST users showed significantly lower levels of markers associated with inflammation (i.e., IL-12(p70), sICAM-1, IL-8) (Nordskog et al., 2015). BOPH are associated with lipid metabolism pathways (Prasad et al., 2016). In addition, measurement of other BOPH yielded significantly lower levels of lipid metabolism pathways, high-sensitivity-C reactive protein (CRP), and blood constituents (i.e., white blood cells, monocytes, lymphocytes, fibrinogen and hemoglobin, hematocrit) in ST users compared to cigarette smokers (Marano et al., 2015; Prasad et al., 2016). Across BOPH, the levels of markers were comparable between ST users and non-tobacco users (Nordskog et al., 2015; Prasad et al., 2016). No studies were discussed comparing BOPH between users of different ST products underscoring the need for the information requested in the deficiencies put forth by other disciplines.

The Medical review also examined AEs reported in the application. The applicant provided a summary of AEs from the clinical study; however, these AE data are limited because this was a small, short-term pharmacokinetic study. The applicant notes there were 22 AEs that were primarily mild in severity and either unlikely or not related to the test product. No deaths, Serious Adverse Events (SAEs) or discontinuation of subjects secondary to AEs were reported. The applicant also submitted AE information from the ALCS Consumer Call Center on USSTC's MST products sold in the marketplace including Copenhagen Classic Snuff. Thus, the utility of this information is limited given that the applicant did not disaggregate the AEs specific to Copenhagen Classic Snuff. The applicant did note that USSTC sold over 4.4 billion cans of MST products and received 1,353 calls from consumers with 2,546 associated AEs during January 2012-June 2017. The majority (84.3%) of these cases were coded as mild in severity and the system organ class with the highest incidence of AEs was the gastrointestinal system. There were 203 moderate cases, seven severe cases, and three SAEs.

In summary, the Medical review concluded that the scope of its review was constrained in that, aside from the one clinical (pharmacokinetics) study, the application did not include clinical evidence specific to the proposed MRTP to inform an assessment of individual health risk. Although the applicant cited several cross-sectional studies examining BOPH between ST and cigarette users, the applicant relies most heavily on the epidemiologic evidence to support its application. Finally, Medical concluded the AE data compiled from both the clinical study and the ALCS Consumer Call Center do not provide information sufficient to assess claim substantiation.

As TPL, I agree that the scope of the Medical review did not include sufficient evidence to inform conclusions about individual health risk or claim substantiation, and that this information was instead within the scope of the Epidemiology review. The epidemiological evidence and how it informs conclusions about individual health risk and claim substantiation are discussed below in Section 3.2.3. Based on the availability of this evidence and other data, I concurred with Medical's recommendation to not convey a deficiency.

3.2.2.2 Behavioral and Clinical Pharmacology (BCP)

The BCP review utilized the peer-reviewed scientific literature to examine biomarkers of tobacco exposure. BCP's review of the applicant's clinical (pharmacokinetics) study is discussed below in Section 3.4.1.

In comparing ST HPHC exposure with cigarette HPHC exposure, evidence suggests that exclusive use of ST leads to greater exposure to nicotine and NNK than cigarettes. In particular, studies that examined the longer-term effects of tobacco use and exposure have shown that exclusive ST users (includes users of "chewing tobacco and snuff") have higher levels of serum cotinine (a metabolite of nicotine) and NNAL (a metabolite of NNK) than exclusive smokers (e.g., Campbell, Brown, Jones, Marano, & Borgerding, 2015; Rostron, Chang, van Bemmel, Xia, & Blount, 2015). On the other hand, exposure to some other tobacco-related HPHCs and their biomarkers (e.g., S-PMA, 3-HPMA) tends to be lower in ST users than cigarette smokers and similar in ST users and non-tobacco users (e.g., Campbell et al., 2015); however, concentrations of plasma lead may be higher in ST users than non-tobacco users (e.g., Rostron et al., 2015).

Within the ST category, there is also evidence of variability in HPHC exposure between product types, as one might expect based on differences in HPHC quantities as described in preliminary results by Chemistry, pending data requested in the deficiencies. Evidence suggests that exposure to NNK may also be greater from the proposed MRTP and other MST products relative to snus. In particular, Hatsukami and colleagues (2004) showed that NNAL levels decreased in participants of a clinical study who switched from brands of ST marketed in the U.S. to Swedish snus.

In addition, biomarker studies discussed above (i.e., Campbell et al., 2015) showed no evidence of substantially reduced exposure to nicotine or other HPHCs in dual users compared to exclusive users of ST or cigarettes. Thus, the available evidence discussed here suggests any reductions in exposure to HPHCs the proposed MRTP could confer would come only with completely switching from combustible tobacco products to the proposed MRTP.

Finally, no studies compared the risks of HPHC exposure associated with complete switching to the proposed MRTP with the risks associated with continued smoking, quitting altogether, or using an FDA-approved cessation aid. However, the evidence reviewed above suggests that the risks associated with complete switching to the proposed MRTP are likely greater than those associated with complete switching to an FDA-approved cessation aid and quitting altogether and likely less than those associated with continued smoking. Finally, the evidence suggests that many biomarkers of exposure are similar in ST users and non-tobacco users.

In summary, the BCP review concluded that the MRTPA had adequate information to conclude the following:

- ST use, in general, is associated with higher levels of exposure to some HPHCs and lower levels of others compared to cigarette smokers.
- ST use, in general, exposes users to greater HPHCs than cessation aids and no tobacco use

- There is some variation in exposure to HPHCs within the ST category – preliminary data suggest Copenhagen has higher HPHCs than some other ST products (i.e., snus); however, product characterization issues must be resolved to be confident in these findings, as laid out in the deficiencies.

As TPL, I concur with BCP's findings, but as noted in the Toxicology section, it is challenging to directly compare HPHC exposure between ST and cigarettes due to their different routes of exposure (i.e., buccal vs. inhalation). Because there is an abundance of literature on long-term epidemiologic health outcomes, I am relying on the Epidemiology review to compare ST use to cigarette smoking.

3.2.3 Epidemiology

The Epidemiology review is based on the applicant's analysis of national survey data, including its linked mortality analyses and published long-term observational epidemiological evidence of mortality risks according to tobacco use status.

ST products, including those referred to as chew, snuff, dip and spit, have been used in the U.S. for over a century. Thus, epidemiological evidence is available through peer-reviewed, published, cohort, case-control, and cross-sectional studies of the health risks of ST. No long-term epidemiological data are available pertaining specifically to the use of Copenhagen Snuff Fine Cut. Instead, the applicant summarized evidence from the published literature and conducted analyses of federal datasets of the health risks associated with ST use to draw inferences regarding the risk for tobacco-related diseases related to the proposed MRTP. The applicant states this published data is relevant because: (1) MST was the primary form of ST used in the U.S. at the time of these studies; (2) USSTC products generally, and specifically Copenhagen Snuff Fine Cut, held large market shares at the time of the studies; and (3) (according to the applicant) the product has not changed substantially since the time of the studies, with the exception of a decrease in TSNAs. Indeed, market data indicate that Copenhagen Snuff Fine Cut accounted for nearly 19-44% of the MST market in the time periods studied (1985-2005). Furthermore, the applicant provided literature demonstrating the decrease in TSNA over time and states that by the late 1990s, USSTC had reduced TSNA levels in its products by almost 90% (compared to the 1970s), and there is some evidence to suggest that harmful TSNA levels may have been higher in the time period of the published studies than in the proposed MRTP (Fischer et al., 2012).

Substantiation of the Claim:

ST is not combusted, and it is not inhaled; thus, it does not trigger the physiological processes that lead to lung cancer among cigarette smokers (International Agency for Research on Cancer 2007b). However, ST products contain NNK, a potent carcinogen that targets the lung (Yuan et al., 2012).

Using never users as a common referent, the applicant's National Longitudinal Mortality Study (NLMS) linked mortality analysis found similar point estimates for lung cancer mortality in complete switchers (i.e., those who switched from cigarettes to exclusive ST use: hazard ratio [HR]=5.34, 95% confidence interval [CI] 2.04-14.02) and cigarette quitters (HR=5.65, 95% CI=4.33-7.38), which was lower than the HR for continued smokers compared to never users (HR=11.52, 95% CI=8.74-15.19).

Compared to never use, cigarette smoking poses substantial risks of lung cancer (US DHHS, 2014), whereas meta-analyses found that U.S. ST products have not been consistently associated with increased lung cancer risk (Boffetta et al., 2008; Lee & Hamling, 2009; Henley et al., 2005). Furthermore, in individual studies that have found associations between ST use and lung cancer mortality, risk is substantially lower than what is seen in cigarette smokers compared to never users.

To FDA's knowledge, Henley et al. (2007) is the only published study that examined disease risk associated with sequential product use. In addition to users and quitters, they examined switchers, or those who exclusively smoked cigarettes and then switched to exclusive use of ST at the time of or after quitting smoking. In this U.S. study, "… relative risks for lung cancer were elevated in switchers vs. never tobacco users (HR=5.61)". After twenty years of follow-up, switchers still had higher rates of lung cancer mortality than quitters (HR=1.46, 95% CI=1.24-1.73) (Henley et al., 2007).

To examine that finding in the context of risk of complete switching relative to continued smoking, FDA conducted analyses of the findings from Thun et al. (2013) using former cigarette smokers (i.e., quitters) rather than never tobacco users as the common referent. FDA then examined the rate of death from lung cancer comparing continued smokers to quitters and found that the HR was 5.0. This is much higher than the HR from the Henley analyses comparing the rates of death from lung cancer between switchers and quitters (HR=1.46). In total, the epidemiological evidence assessed suggests that the relative risks for lung cancer are lower for switchers than for continued smokers.

Based on the lack of combustion and magnitude of the reductions in relative risks between continuing smokers and switchers, as well as on mechanistic evidence, Epidemiology determined that the proposed modified risk statement "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer" is scientifically accurate.

Relative Health Risks to Individuals:

To examine whether the proposed MRTP would significantly reduce the harm and risk of tobacco-related disease to individual tobacco users, the Epidemiology review examined the health risks of diseases other than lung cancer, and how these risks compared to smoking, other ST product use, complete switching (i.e., from cigarettes to exclusive ST use), or quitting cigarettes, and to never use. The 2012 IARC monograph "Personal Habits and Indoor Combustions" concluded that there was sufficient evidence to indicate the carcinogenicity of ST in humans and further stated that ST causes oral cancer, esophageal cancer, and pancreatic cancer (International Agency for Research on Cancer, 2012). One U.S. meta-analysis also reported an association between ST and fatal myocardial infarction and stroke (Boffetta & Straif, 2009). Data on all-cause mortality from individual studies are mixed (Henley et al., 2005; Accortt et al., 2002; Timberlake et al., 2017). Lastly, while there is relatively little information on ST use among U.S. women, several studies from Sweden have found an association between ST use and adverse pregnancy outcomes (Wikstrom et al., 2010; Baba et al., 2012; England et al., 2003).

The applicant's linked mortality analysis showed no significant differences in HRs between current exclusive ST users and non-users for lung cancer, all-cause mortality, all-cancer mortality, or mortality from diseases of the heart. In general, the HRs were lower for ST users than cigarette smokers. The point estimates for switchers and quitters generally fell between the point estimates for ST users who never used cigarettes and cigarette users. It should be noted that the number of deaths among ST users in the sample is small. For all cause-mortality, there were fewer than 50 deaths among current ST users who never smoked, so the sample may be underpowered to detect a difference.

In the literature, Henley et al. (2007) reported similar findings for the risks for heart disease, oral cancer, stroke, and all causes as they did for lung cancer, where switchers had higher rates of death compared to quitters, but generally lower mortality rates than those of current smokers.

Compared to other ST products, two studies that examined specific types of ST found no evidence of differences in disease risk in snuff users compared to chew users (Henley et al., 2005, Timberlake et al., 2017). Epidemiological studies have observed differences in risks associated with U.S. ST product use compared with Swedish snus product use (Lee & Hamling, 2009; Boffetta &Straif, 2009; Rostron et al.,

2018). This difference may be due to generally lower levels of HPHCs, such as TSNAs, found in Swedish snus products. These data allow us to specifically conclude that exposure to Copenhagen Classic Snuff is riskier than exposure to Swedish snus.

In summary, the Epidemiology review found that the MRTPA provided sufficient evidence to conclude the following:

- The epidemiological literature regarding health risks associated with ST is relevant to the MRTPA given the market share of the proposed MRTP during the time period covered by these studies.
- The claim was found to be scientifically accurate – complete switching from cigarettes to ST products, including the proposed MRTP, reduces the risks of lung cancer compared to continued smoking when both are compared to never users.
- ST, including the proposed MRTP, causes oral cancer, esophageal cancer, pancreatic cancer, fatal myocardial infarction, stroke, and possibly mortality from any illness or injury; individual health risks for exclusive ST use are higher than for never users, but lower than those of cigarette users.
- Individual health risks are higher for people who completely switch from cigarettes to ST than those who quit tobacco, but lower than continued smoking for lung cancer, heart disease, oral cancer, and stroke.

As TPL, I agree with Epidemiology's findings that the claim is supported by the available long-term epidemiological evidence. In addition, the data support the conclusion that relative to cigarette smoking, the proposed MRTP is associated with reductions in overall morbidity and mortality.

3.2.4 Conclusions: Claim Substantiation and Individual Health Risks

To evaluate individual health risks of the product, Toxicology, Medical, BCP, and Epidemiology reviewed evidence about HPHCs, biomarkers of exposure and potential harm, and health outcomes, respectively. Because of the substantial market share of Copenhagen Snuff Fine Cut, Epidemiology concluded it was appropriate to draw inferences about the health risks of the proposed MRTP, Copenhagen Classic Snuff, based on the available evidence. Given the availability of long-term epidemiological data providing direct evidence on health outcomes associated with ST use, biomarker evidence is of relatively less value to assess claim substantiation and individual health risks. Accordingly, long-term epidemiological evidence is the focus of the conclusions that followed.

In comparison to never use of tobacco, use of ST exposes users to HPHCs and poses health risks. In comparison to cigarette smoking, ST use poses lower risks of certain health outcomes, including lung cancer. Indeed, TPSAC voted 8 to 0 (with one abstention) that the claim was supported by the scientific evidence, and particularly the epidemiologic evidence. In addition to a lower risk of lung cancer, the literature and the applicant's own analysis suggest lower HPHC exposure as well as reduced risk of morbidity and mortality for other diseases relative to smoking, supporting the conclusion that this product would significantly reduce the risk and harm of disease among those who completely switched to it from cigarette smoking.

There is relatively limited information that can be used to evaluate the health risks of the proposed MRTP compared to other ST products. Although the proposed MRTP poses lower risk relative to cigarettes, it is nevertheless a harmful tobacco product, posing greater health risks relative to no tobacco use, NRT, and Swedish snus. Due to the aforementioned incomplete manufacturing and product

characterization, initial Toxicological assessments of the proposed MRTP relative to ST were preliminary. The comparisons did find that the proposed MRTP had higher levels of some HPHCs relative to other ST so a deficiency requested that the applicant provide scientific evidence and rationale about how exposure to HPHCs in other ST products may impact the population of tobacco users that may completely switch to or begin to dual use their current ST product(s) with the proposed MRTP. The applicant responded that due to MST comprising most of the ST market, MST was the appropriate comparator rather than the universe of ST products. Toxicology concurred as do I as TPL. Therefore, the portion of the deficiency related to dry snuff, loose leaf, and Swedish snus was resolved. Toxicology analyzed the proposed MRTP's HPHC data compared to MST using a methodology that examines the risks of HPHCs collectively for a product. They determined that the lower levels of NNK and free nicotine in the proposed MRTP offset the higher levels of BaP and Cadmium from a carcinogenic perspective, rectifying concerns in the preliminary analysis.

Overall, therefore, I maintain that the evidence supports claim substantiation: switching completely to the proposed MRTP from cigarettes will confer a lower risk of lung cancer. In addition, because other ST users could switch to the MRTP, it was critical to determine the relative risks of this product to other ST products. Knowing that the vast majority of ST users are MST users and that the higher level of some HPHCs in the proposed MRTP are offset by lower levels as compared to other MST products, I find that even if some ST users were to switch brands, the proposed MRTP, as actually used by consumers, will significantly reduce the risk to individual tobacco users and benefit population health.

3.3 Consumer Understanding and Perceptions

This section of the review discusses information related to consumer understanding and perceptions of the MRTP. Consumer understanding and perceptions are psychological constructs considered precursors to intentions to use the product. Understanding—or comprehension of the claim content—is relevant to the potential population health impact of the marketing of the proposed MRTP to the extent that it affects who uses the product and how they use it. Relatedly, Section 911(h)(1) of the FD&C Act requires that advertising and labeling concerning the proposed MRTP enable the public to understand the modified risk information and the relative significance of such information in the context of total health and in relation to all diseases and health-related conditions associated with the use of tobacco products.

3.3.1 Social Science

Labels, Labeling, and Advertising (LLA) with Proposed Modified Risk Information

The applicant proposes a single modified risk claim: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." The applicant provided the following sample label, labeling, and advertising (LLA) materials that contain this modified risk claim: print advertisement, direct mail advertisement, email advertisement, website pop-up screen, promotional card, bottom can label, and point of sale materials. USSTC stated that its marketing and advertising plans have features that will reduce the risk of youth uptake, including advertising in periodicals with predominantly adult readership, maintaining age-restricted brand websites, and using an age-verified consumer database for marketing communications, among other strategies. The Social Science review observes that the applicant's planned advertising and promotions include non-targeted marketing techniques, such as a display in the parking lot or on the outside door of a retail outlet, that may expose youth to advertisements containing modified risk information.

The applicant conducted one quantitative study, the Claim Comprehension and Intentions (CCI) study, to examine the effects of the modified risk claim on perceptions and behavioral intentions. The study used

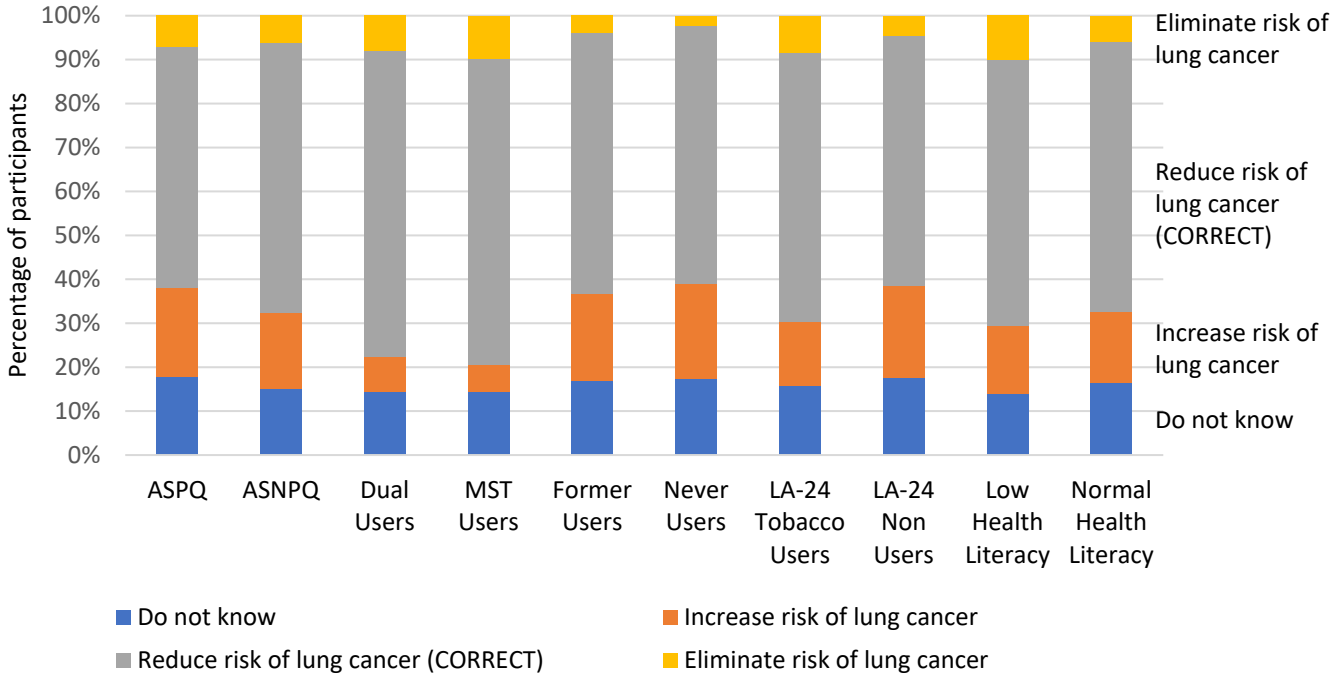
a quasi-experimental, pre-test-post-test, mixed design. Participants were assigned to one of two study conditions: viewing an advertisement either with the modified risk claim (test condition) or without the claim (control condition). Outcomes included behavioral intentions (discussed below in Section 3.4), claim recognition, and risk perceptions. The study examined a number of different risk perceptions, as discussed in the Social Science review. Here, I focus on those most relevant to determining whether the claim enables consumers to understand the risks of the product in the context of total health: perceptions of lung cancer risk, overall perceptions of health risks, and perceptions of health risks compared with smoking cessation and NRT use. Other relevant risk perceptions and how they affect the overall consumer understanding assessment, including perceptions of overall health risk relative to cigarettes and risk perceptions relative to other smokeless tobacco products, are discussed in the Social Science review. Note that risk perception measures assessed absolute risk perceptions; the applicant compared absolute risk perceptions in order to indirectly measure relative risk perceptions.

The study employed a non-probability sample of 5,871 adult participants: a main study sample of 4,927 adult participants and a separate oversample of 944 young adult participants. Participants in the main sample were categorized as one of the following tobacco user subgroups: adult smokers planning to quit (ASPQ), adult smokers not planning to quit (ASNPQ), dual users, (i.e., people that concurrently use MST and cigarettes), MST users, former users (i.e., former users of any tobacco product who are currently not using any tobacco product), and never users (i.e., never users of any tobacco product). The sample of young adults were participants of the minimum legal age to purchase tobacco (at the time of the study) up to age 24 (LA-24) and were categorized as either tobacco users or tobacco nonusers. The applicant did not provide findings for the overall sample, but rather only by subgroup.

Claim Recognition: At the end of the survey, a claim recognition item prompted participants in the test condition to look at the ad again and then identify the correct claim text from a list of answer options. The question read: “Please look at this ad again. Regardless of what you believe to be true, please answer the question based on the information shown in this ad. Based only on the information shown in this ad, smokers who switch completely from cigarettes to Copenhagen Snuff: Increase the risk of lung cancer, Reduce the risk of lung cancer [correct answer], Eliminate the risk of lung cancer, or Do not know.”

Results show that, across all subgroups, a majority of participants (55-70%) correctly identified the claim text (Figure 1). These findings suggest that just over half of participants noticed and processed the claim text sufficiently to recognize and select it from the list of response options. For the remaining participants, it is unclear whether they noticed the claim but did not read it, they read the claim but did not understand or believe it, did not notice the claim, or something else. Accordingly, when interpreting study findings, bear in mind that they include responses from all participants—a sizeable proportion of whom may not have noticed or may not have read the claim. See also the Limitations section below regarding the lack of a manipulation check.

Figure 1. *Distribution of responses to the claim comprehension measure, test condition only.*



Perceptions of Lung Cancer Risk:

First, in assessing whether consumers will understand the modified risk information in the context of total health, it is important that consumers understand the nature of the risk reduction purported by the proposed MRTP. As lung cancer is the subject of the modified risk claim, perceptions of lung cancer risk are informative to assessing the extent to which participants understand the risk of lung cancer from the proposed MRTP relative to cigarette smoking. Participants' ratings of the absolute likelihood that a person who uses only Copenhagen Snuff daily would develop lung cancer were consistently lower than their ratings of the absolute likelihood that a person who only smokes cigarettes daily would develop lung cancer. This was true across all tobacco user groups. Among participants who viewed the modified risk advertisement, post-test ratings of the risk of lung cancer for someone using Copenhagen Snuff ranged from 39-70% (across user groups) and from 67%-86% (across user groups) for a person who smokes cigarettes daily. Note, the applicant did not conduct testing to establish whether these differences were statistically significant. Mean risk perception scores at post-test are shown below in Figure 2. I would have liked to have seen these findings aggregated across groups, which would have given the data more power and a more precise estimate as these ranges are large. While the aggregation would be helpful, the pattern of effects is similar across user groups, suggesting that were the data to be aggregated, the overall finding would likely remain the same (i.e., participants rated the absolute likelihood of developing lung cancer to be higher with cigarettes than the absolute likelihood of developing lung cancer from Copenhagen snuff). Taken together, these findings suggest that participants correctly understand that cigarettes are more likely to cause lung cancer than Copenhagen Snuff.

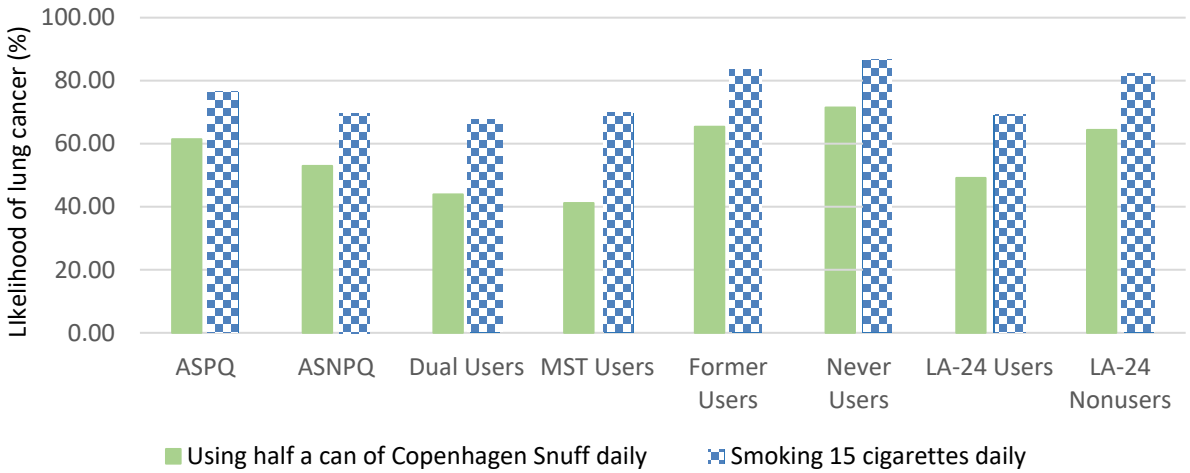
Post-test ratings did not appear to differ from pre-test ratings, suggesting that the claim did not impact participants' understanding of the relative risk of lung cancer. While ideally, I would have liked the experiment to have shown that participants' beliefs around the claims are influenced by the claim, this is

not a requisite for demonstrating an appropriate understanding of the proposed MRTP in three areas: 1) relative harm compared to NRT or quitting completely, 2) that the proposed MRTP is not harmless, and 3) that consumers understand they need to switch completely to the proposed MRTP. As discussed elsewhere, given the ingrained misperceptions around relative harms of different tobacco products and the role of nicotine, it is understandable that participants' beliefs were not changed by a brief one-time exposure. Because the proposed MRTP is a smokeless product, a subset of consumers likely already perceived the product to be lower than cigarettes in terms of lung cancer risk, potentially making it more challenging to detect an effect of the claim about lung cancer, as compared to claims about other health effects. For example, a latent profile analysis of smokers' perceptions of snus, another product type in the ST category, found that a little over half perceived snus as posing lower risks for lung cancer compared to cigarettes, with smaller subsets perceiving snus to pose lower risks than cigarettes for heart disease or oral cancer (Wackowski, Ray & Stapleton, 2019).

Finally, the absolute levels of perceived risk suggest that consumers perhaps overestimated the absolute lung cancer risk in a person who uses only Copenhagen Snuff, perceiving the risk to be only modestly lower than in a person who only smokes cigarettes. As lung cancer risk perceptions were essentially unchanged from pre-test and did not statistically differ between the test and control conditions, this suggests that any overestimation of lung cancer risk was not a result of consumers' misunderstanding the modified risk claim, but instead reflects what consumers already believed. This is consistent with the literature, which indicates that some U.S. consumers believe that ST use causes lung cancer, even though lung cancer has not been conclusively linked to exclusive ST use (Adkison, Bansal-Travers, Smith, O'Connor, & Hyland, 2014).

As noted by TPSAC and consistent with the literature (Hornik, 2002), the success of a message relies on having adequate exposure. Because participants were only required to view the label once, it is not surprising that participants' beliefs were not changed. Often an audience needs not only multiple exposures to a message, but multiple methods of exposure to effectively process message content. Even a well-designed message is subject to null effects if exposure is insufficient.

Figure 2. *Lung cancer risk: Mean absolute risk perception scores associated with using only Copenhagen Snuff daily and with only smoking cigarettes daily, at post-test, by tobacco user group, test condition only.*



In conclusion, although consumers may overestimate the absolute risk of lung cancer from using the product, these findings suggest that participants accurately understand that lung cancer risk is *lower* in a person who exclusively uses Copenhagen Snuff than in a person who exclusively smokes cigarettes. Given the salience of lung cancer as a smoking-related risk and the considerable portion of smokers who do not understand the different risk posed by the proposed MRTP compared to cigarettes, even for this particular health effect, provision of the modified risk information to consumers will enable consumer understanding and ultimately benefit population health, particularly as they will be exposed many more times to the message in real life.

Overall Perceptions of Health Risks: Next, in assessing whether consumers will understand the modified risk information in the context of total health, an important consideration is that consumers do not perceive the proposed MRTP as having no risk.

Participants were asked to rate the likelihood that a person who only uses Copenhagen Snuff daily would experience a negative impact to their health, using an 11-point scale with the endpoints *0% Extremely unlikely* and *100% Extremely likely*. Across tobacco user groups assigned to the test condition, mean ratings at post-test ranged from approximately 61% to 85%. (Ratings were very similar at pre-test.) The applicant's statistical analyses showed that the proposed modified risk claim had no significant effect on perceptions of overall risk except for one group: LA-24 (i.e., young adult) nonusers of tobacco had statistically significantly lower risk perceptions of Copenhagen Snuff at post-test (80.5%) compared to pre-test (81.6%) (t = -3.96, $\rho < 0.001$, d = 0.28), though perceived likelihood remained very high and the magnitude of change was quite small.

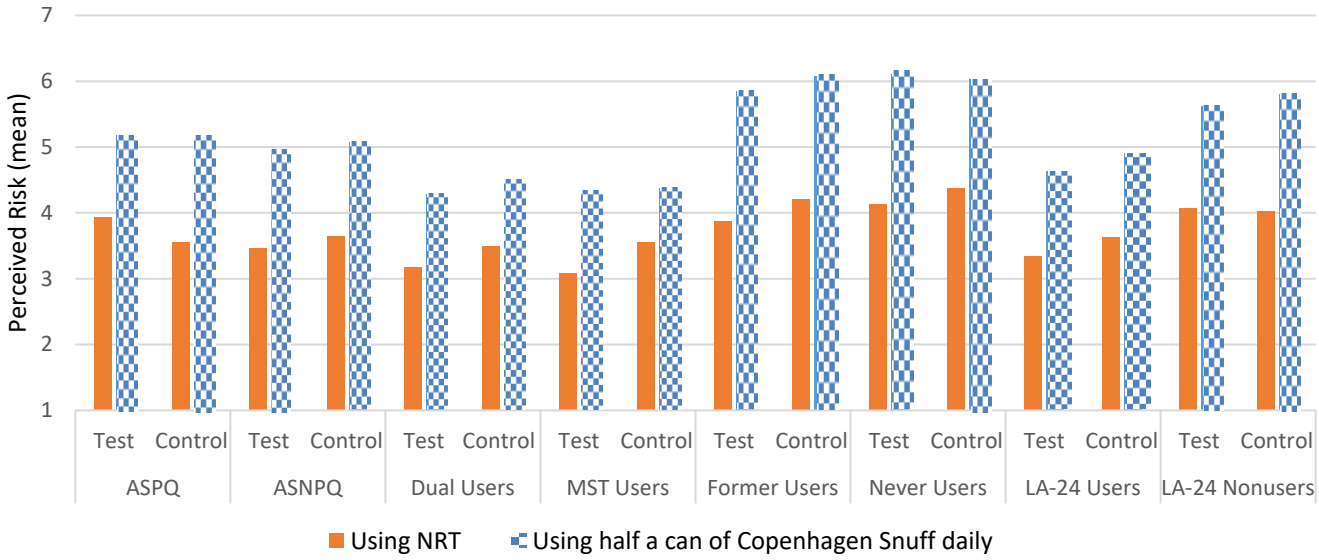
In general, these findings suggest that, after seeing the advertisement with the modified risk claim participants accurately perceived that using the proposed MRTP daily is likely to negatively impact health. This finding supports the conclusion that consumers will understand that the proposed MRTP is not harmless.

Perceptions of Health Risks Compared with Smoking Cessation and NRT Use: To assess whether consumers will adequately understand the modified risk information in the context of total health, I also considered whether the proposed claim may mislead people into thinking that using the product would present lower health risks compared to using NRT or compared to quitting all tobacco.

At post-test, participants rated the risk of using half a can of Copenhagen Snuff daily as higher than the risk of using NRT (Figure 3). This was true across all tobacco user groups and both study conditions. Similarly, at post-test, all user groups rated using half a can of Copenhagen Snuff daily as riskier than quitting all tobacco, as well as never using tobacco products. Post-test ratings did not appear to differ from pre-test ratings, suggesting that the claim did not affect these perceptions.

These data suggest that even with a modified risk claim, consumers have an appropriate understanding that using the proposed MRTP is more harmful to health than using NRT, completely quitting all tobacco use, or never using tobacco products.

Figure 3. *Mean absolute risk perception scores associated with using Copenhagen Snuff and with using NRT, at post-test, by tobacco user group and study condition.*



Note: *Perceived risk was rated on a scale from 1 (not at all risky) to 7 (very risky).*

Limitations:
Our assessment of the individual health risks of the product, as described above, concludes that the reduction in lung cancer risk described in the claim is substantiated for those who switch completely from cigarettes and use the proposed MRTP exclusively, as proposed by the applicant. Therefore, a component of understanding the claim in the context of total health is understanding how to use the product. A limitation of the CCI study is that it did not evaluate participants' understanding of how to use the proposed MRTP to attain the risk reduction purported in the claim; in other words, the CCI study did not directly assess the extent to which consumers understood that they must switch completely to the proposed MRTP. I would have liked the applicant to directly assess this given that this is critical to obtaining the full benefit of this proposed MRTP. However, the claim itself provides specific and clear language regarding who the product is for (with a call out to smokers) and directs potential users that they can reduce their lung cancer risk by "switching completely." FDA has previously authorized the marketing of another MRTP with the same language and has required that consumer understanding of the need to switch completely be tested in PMSS for that MRTP as well as another.

In examining this study overall, the Social Science review identified two limitations of the study method that could affect interpretation of the study results: the pre-post quasi-experimental design and the lack of a direct manipulation check. First, the review notes that pre-test-post-test designs, while scientifically appropriate in some situations, may have the disadvantage of potentially introducing testing effects and, in particular, make any potential effects of the claim harder to detect. On the other hand, another study used a similar design to examine the effects of reduced risk claims on consumer risk perceptions of tobacco that detected significant effects (Popova & Ling, 2014). It is difficult to know to what extent this particular study design element affected results. For instance, was this study a situation where individuals would have had such self-presentation concerns about consistency, and if so, is it likely they would be able to remain consistent in their answers given the large number of items, many of which had fairly wide response scales? However, because this methodology has been used in similar studies and is

a common study design, we believe the findings are valid; if anything, the applicant may have found fewer null effects had they used a post-test only design.

Second, a manipulation check could have been informative as it would have allowed the applicant to analyze results for only those participants who confirmed receipt of the manipulation. FDA recommends a manipulation check, which determines whether the manipulated factor (such as a modified risk claim) was noticed by the participants as intended. Such an assessment is important for evaluating internal validity of the study. For instance, if the manipulation check reveals that participants did not notice the modified risk claim, then this could account for a failure to find effects on the study outcomes. Although the study did not include a manipulation check administered directly following exposure to the ad, the claim recognition item does provide insight into the fact that there was a portion of participants who appeared not to attend to the claim.

In summary, the Social Science review concluded that the CCI study evidence suggests consumers generally understood the modified risk claim and its significance in the context of total health. Although the claim did not significantly affect risk perceptions, participants accurately rated that lung cancer risk is lower in a person who exclusively uses Copenhagen Snuff than in a person who exclusively smokes cigarettes. Importantly, consumers were not misled by the claim to think that the product poses no risks or poses lower risks relative to NRTs or quitting all tobacco. However, the Social Science review also notes that the study findings are subject to limitations—namely with the pre-post design—and notes that the claim may have effects in the real world not reflected in the study findings.

As TPL, I agree with the Social Science conclusion that the findings suggest consumers have an appropriate understanding of the proposed modified risk claim. As described in the Executive Summary, I concur with the Social Science review's perspective on a number of limitations in the applicant's CCI study and believe there were ways to have strengthened the study design. However, as noted earlier in this review, despite these limitations, I believe the applicant has met the statutory requirements for basic understanding of modified risk: participants understand that the proposed MRTP causes harm and that it is more harmful than quitting or NRT and the label directs users that they must switch completely to derive the benefits of the claim (in this case, a reduced risk of lung cancer relative to cigarettes).

I also agree that, though I would have liked the applicant's CCI study to provide more exposure to the claim at different time points, it is likely the findings from this study do not reflect the full real-world impact of the claim, which are likely to happen over a period of time as the idea gains more credibility and general awareness among the public. Thus, the findings likely underestimate the potential impact of the claim on consumers' perceptions. In the CCI study, most participants' perceptions of the risks of the product were unaffected by exposure to the claim, whereas with repeated exposure, it is likely more consumers would revise their beliefs regarding the relative risks of these products to bring them more in line with the scientific evidence. In turn, this increased believability of the claim, would allow a more informed choice of tobacco products and potentially lead to switching to this proposed MRTP.

3.3.2 Social Science Support for TPL Deficiency

At my request, Social Science examined the data submitted by the applicant in response to Deficiency #1 to evaluate if the proposed MRTP, with its new name and advertising, still supports appropriate consumer understanding of the proposed modified risk claim and its significance in the context of total health. The applicant submitted a (b) (4) that assessed whether (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

.

The (b) (4) findings suggest (b) (4)

(b) (4)

Taken together, Social Science concluded (b) (4)

As TPL, I find that Deficiency #1 was adequately addressed (b) (4)

postmarket surveillance studies (PMSS).

3.3.3 Conclusions: Consumer Understanding

Overall, the CCI study (b) (4) provided sufficient evidence to support appropriate consumer understanding of the proposed modified risk claim and its relative significance in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products. After seeing the advertisement with the modified risk claim, participants understood that the absolute risk of developing lung cancer is lower in a person who exclusively uses the proposed MRTP daily than in a person who smokes cigarettes daily. Participants also understood that using the proposed MRTP is risky to health, and that someone who only uses the proposed MRTP daily would likely experience a negative impact to their health. Finally, participants understood the risk of using the proposed MRTP is greater than that of using NRT, quitting all tobacco, and never using tobacco products.

Although the CCI (b) (4) support appropriate consumer understanding, the CCI study findings in general suggest that the modified risk claim had little or no impact on participants' perceptions. However, it is possible these results underestimate the potential impact of the claim — even from a brief exposure — on consumers' perceptions and intentions related to the MRTP. As the Social Science review noted, it's possible the null findings are an artifact of the study design: biased responses resulting from the pre-post design, or a failure of the manipulation (i.e., a proportion of participants did not view or notice or read the claim). An alternate explanation, as discussed at length by TPSAC, is that a one-time exposure is simply limited in the impact it can have on perceptions—particularly when the message may not be consistent with pre-existing beliefs, as discussed in the Social Science review. It would have been ideal if the applicant had conducted a manipulation check and required multiple exposures. That said, as described earlier, even with multiple exposures in a study, it would be difficult to replicate the real-world impact of the claim, which is likely to happen over time as the idea gains more credibility and general awareness among the public.

The study did not assess participants' understanding that a user must completely switch to the product (from cigarettes) in order to reap the benefit, nor did the study assess perceptions of the risk of dual use or partial switching. These outcomes are relevant because, as described above in Section 3.2.2.2, risk reduction is expected for smokers who switch completely—but not for those who continue to use both products. While this is an important limitation in the consumer understanding data, it is mitigated by the fact that the claim itself directs potential users that they can reduce their risk by "switching completely". Still, I agree with the Social Science review suggestion that the extent to which consumers understood that the proposed MRTP must be used exclusively and that dual users should switch completely should be monitored in postmarket surveillance as has been the case in previous MRTP authorizations.

In addition, Social Science examined (b) (4)

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3.4 Likelihood of Use and Impacts to Population

This section examines the potential benefits and harms of the proposed MRTP to the health of the population as a whole taking into account the impacts to users and non-users. This determination considers the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the MRTP and the increased or decreased likelihood that persons who do not use tobacco products will start using the MRTP. This section will review the evidence provided by BCP, Epidemiology, Social Science, and Statistics reviews.

3.4.1 Impacts to Users

3.4.1.1 Behavioral and Clinical Pharmacology

The BCP review utilized the Altria Client Services LLC (ALCS) Clinical Study and the peer-reviewed scientific literature to examine use behaviors and topics associated with abuse liability such as topography, dependence, subjective effects, and the pharmacokinetics of the proposed MRTP.

The ALCS Clinical Study was a within-subjects laboratory study that compared the nicotine pharmacokinetics and subjective effects of a test moist snuff tobacco product "produced to the identical specifications as for the Copenhagen Original Fine Cut Snuff product marketed on or before February 2007" with participants' usual brand of cigarettes and Nicorette Fresh Mint nicotine polacrilex gum (4

mg). Participants in this study were 24 smokers (≥ 10 menthol or non-menthol cigarettes per day for at least 1 year), ages 21-65 who were non-daily users of "original," "natural," "regular," or similarly flavored MST products (≥ 20 uses during lifetime, but not used every day in previous 30 days) with no use of Nicorette Fresh Mint gum in the previous 3 months.

The BCP review examined the pharmacokinetics associated with the proposed MRTP and focused on the rate of increase in plasma nicotine concentration because the rate affects abuse liability, such that a faster rate of increase results in greater abuse liability. In the ALCS Clinical Study, the rate of absorption suggests that the proposed MRTP may have lower abuse potential than usual brand cigarettes and similar or greater abuse potential than Nicorette gum. The literature related to nicotine and MST products corroborated the clinical study's findings. The rate of nicotine absorption from MST is slower than cigarettes, and it is similar to that of nicotine gum and nicotine lozenges; however, more nicotine is typically delivered by MST than cessation aids (e.g., Benowitz et al., 1988; Kotlyar et al., 2007).[8]

Abuse liability is not determined based solely on plasma nicotine data, but also relies on subjective effects. In the ALCS clinical study, for items related to subjective effects such as craving and sensory impact, use of cigarettes was higher than use of Nicorette gum or the proposed MRTP. This suggests that the abuse potential of the test MST product may be lower than that for usual brand cigarettes and similar to or higher than the abuse potential of Nicorette gum among cigarette smokers under conditions of brief exposure. The scientific literature on positive subjective effects validated the study results. Subjective effects of ST products are similar to or greater than those associated with FDA-approved cessation aids and less than those associated with cigarettes.

Another topic related to use of the proposed MRTP is topography, which refers to how a person uses a tobacco product in terms of quantity and duration of use. Topography data from multiple sources, including the ALCS Clinical study, show that the dip duration of "Copenhagen" and other moist snuff products is approximately 40 minutes, dip size is roughly 2 g, average dips per day is between six and nine, and MST products are typically used 22-28 out of 30 days among current users. No evidence of intentional or unintentional product misuse was reported in the ALCS Clinical Study, and limited reports of misuse were observed in the literature.

While dependence was not assessed by the ALCS study, some evidence suggests tobacco cessation rates are higher among ST users than in cigarette smokers, indicating that ST users may be less dependent relative to cigarette smokers. For example, in a systematic review of tobacco cessation studies, higher rates of cessation were observed among ST users assigned to control conditions (19.1% – 33%) than cigarette smokers assigned to control conditions (9.8% - 11.2%; Fagerström & Eissenberg, 2012). Another study reported that the quit rate among exclusive ST users was three times higher than the quit rate among exclusive smokers (35% vs. 11.3%) in a sample of over 15,000 respondents who participated in a longitudinal survey in 2002 and 2003 (Zhu et al., 2009). Overall, evidence from the scientific literature suggests it may be less difficult for ST users to quit using their tobacco products than cigarette smokers.

The BCP review notes several ALCS Clinical Study limitations. One limitation is that the study utilized a test product identical to Copenhagen Classic Snuff but did not add the proposed claim to the packaging, so it is unknown how the proposed MRTP would impact users relative to the study outcomes. Furthermore, study participants were regular cigarette smokers with previous experience using moist snuff tobacco products. Thus, the study provided no information about use patterns in daily ST users or

[8] One product in the studies was labeled "Copenhagen," but the applicant did not specify that it was the proposed MRTP.

smokers with no history of MST use. Third, no measures of dependence were assessed. All told, this reduces the generalizability of the study.

In summary, the BCP review concluded that the MRTPA had adequate information to draw conclusions regarding clinical studies examining abuse liability:

- The abuse liability associated with the proposed MRTP is equal to, or greater than, some FDA-approved cessation aids (e.g., nicotine gum) and no use of tobacco products
- The risk of addiction associated with use of the proposed MRTP may be lower than the risk of addiction with cigarette smoking

As TPL, I agree with BCP's findings and interpret the evidence to suggest that the proposed MRTP may confer a lower risk of addiction than cigarettes, but a greater risk of addiction than cessation aids or quitting suggesting that the level of satisfaction may still be sufficient to encourage smokers to completely switch. While pharmacokinetics should not be affected by the claim, I note that all data evaluated in the BCP review were collected from participants who were not exposed to the modified risk claim.

3.4.1.2 Epidemiology

The Epidemiology review is based on the applicant's secondary analysis of national survey data and internal, unpublished secondary analysis of national survey data both specifically regarding Copenhagen Snuff Fine Cut as well as published long-term observational epidemiological evidence. The published literature addresses ST use and health effects overall, which informs the current review given that the applicant was a market leader during the time the studies were conducted.

In the current marketplace, ST use among adults in the National Health Interview Survey (NHIS) was 2.4% with 5.9 million total estimated users (Creamer et al., 2018). This is consistent with Population Assessment of Tobacco and Health (PATH) Wave 5 (2018/19) data, which also found a prevalence of any ST product use among adults of 2.4%. Use of non-snus ST is more common among males, non-Hispanic whites, adults living in nonurban areas, and adults ages 25-49 (Cheng et al., 2017). Data from the 2021 National Youth Tobacco Survey found that the prevalence of reported current ST use was 1.2% (95% CI: 0.8-1.6) for high school students and 0.6% (95% CI: 0.4-0.9) for middle school students. NYTS results from 2021 cannot be directly compared to results from 2019 and 2020 due to differences in data collection methodology (Park-Lee, Ren et al. 2021, Gentzke, Wang et al. 2022). These data are concordant with the 2019 Youth Risk Behavior Survey, which found that 3.8% of high school students reported ST use (Creamer et al., 2020). However, rates vary by rurality, with rates of ST use among rural adults and youth twice as high as those in urban areas (Buettner-Schmidt et al., 2019).

Epidemiology examined patterns of use of any Copenhagen product using data from PATH Wave 5. FDA's analysis of past 30-day non-light ST users (i.e., those who reported using ST more than ten times in their lifetime and last used ST within the past 30 days) found that nearly four in ten youth (ages 12-17; 38.3%), roughly half of young adults (ages 18-24; 52.7%), and nearly a third of adults 25 and older (30.6%) reported using a Copenhagen product as their brand usually or most recently used.

Copenhagen users reported consuming the product on 26.3-28 days in the past month. Copenhagen users consumed, on average, 0.57 cans on those days compared to 0.56 cans, on average, among all MST users. Among Copenhagen Snuff Fine Cut users who were exclusive users, the average number of cans used on days used was 0.56, compared to 0.60 among exclusive total MST users overall.

The Epidemiology review also examined patterns of transitions around dual use and complete switching in the current marketplace. Studies from the observational literature find that complete switching from exclusive cigarette smoking to exclusive ST use is low, in the range of 0.3% to 4.9% (Tam et al., 2015; Anic et al., 2018; Chang, Levy & Meza, 2018). Dual users are most likely to continue dual use of both products (44.3% in a 4-year period), but if they completely switch, more dual users move to exclusive cigarette use (27.0% in a 4-year period) than to exclusive ST use (17.4%). A recent 2021 report by Jackson et al. using data from PATH Study Waves 3 (2015/16), 4, and 5 indicates that very few people who smoke cigarettes transition to ST, either for dual use or exclusive use (Jackson, Ren et al. 2021). Among exclusive smokers at PATH Study Wave 3, only 1.6% (95% CI: 1.3-2.1) transitioned to dual use with an ST product and only 0.1% (95% CI: 0.1- 0.2) switched to exclusive ST use at PATH Study Wave 4. Of the dual users at Wave 3, 7.6% (95% CI: 4.4-10.6) transitioned to exclusive ST use at Wave 4. The majority of exclusive cigarette smokers who transitioned to dual use at Wave 4 continued smoking cigarettes at Wave 5, either as dual users or as exclusive cigarette smokers. The conclusions of this article align with previous research indicating that switching from cigarette smoking to ST is uncommon (Tam, Day et al. 2015, Chang, Levy et al. 2018). This recent study was also concordant with other studies including a systematic review and found that dual users were more likely than exclusive smokers to switch to exclusive ST use (Zhu et al., 2009; Tam et al., 2015), with estimates ranging from 4.9% to 17.4%.

Examining data on dual use specific to the applicant's product but without modified risk information, Wave 4 of the PATH study found that approximately 16.7% of Copenhagen users also used cigarettes (i.e., dual use) in the past 30 days, which equates to about 67,000 U.S. dual users. These estimates for the percent of past 30-day cigarette use in Copenhagen users are lower than the 30% and 40% of overall MST dual users found in the ALCS and in PATH studies (at Wave 1 and Wave 4), respectively, suggesting that a much larger proportion of Copenhagen users do not use cigarettes relative to other brands of MST. In addition, PATH analyses showed dual Copenhagen users reported smoking fewer cigarettes on days they smoked (11.0) than did MST users overall (16.2), though tests of statistical significance were not conducted. Furthermore, among Copenhagen dual cigarette users the average number of cans used on days used was 0.59, compared to 0.44 among MST dual cigarette users overall. Taken together, while there is a smaller proportion of dual users of Copenhagen relative to other brands, they use more of their Copenhagen product and smoke fewer cigarettes relative to other brands, which may indicate a greater chance of success in complete switching to Copenhagen than with other MST brands. Therefore, among users who may benefit from the proposed MRTP, dual users of ST and cigarettes, and especially the 67,000 dual users of Copenhagen, might be likely to view and find the claim relevant and are a particularly important target population for the proposed MRTP were it to be authorized.

In conclusion, Epidemiology found sufficient evidence to describe the current behavioral patterns of use for the proposed MRTP and found that while ST use is low, the proportion of ST users using Copenhagen products in the current marketplace is large and roughly one in six of those users also smokes cigarettes.

As TPL, I agree with these conclusions and note that the dual users of the proposed MRTP are among the users most likely to benefit from the proposed MRTP were it to be authorized.

3.4.1.3 Social Science

The Social Science review examined the potential impact of the proposed MRTP on users by examining the applicant's CCI study. In the study, the pre-test and post-test questionnaires assessed participants' behavioral intentions to try, use, dual use, and switch to Copenhagen snuff. Each of these outcomes was assessed with multiple items using a response scale ranging from 1 (strongly disagree/definitely not) to

6 (strongly agree/definitely). In addition, participants were asked about intentions to quit smoking (yes/no) and intentions to quit all tobacco (yes/no).

Overall, the results showed that levels of interest among current users is low to moderate (Table 4). In general, there were no significant differences[9] between conditions (or from pre- to post-test) suggesting the claim did not influence intentions. On average, among smokers, ratings of intentions were low. When exposed to the claim, adult smokers (ages 25 and older) not planning to quit reported intentions below the scale midpoint for intentions to try (*M* = 2.48), use (*M* = 2.34), or switch (*M* = 2.09) to Copenhagen.[10] Similarly, for LA-24 (i.e., young adult) tobacco users, the means were a bit higher, but still below the midpoint for intentions to try (*M* = 3.24), use (*M* = 3.20), or switch (*M* = 2.73). Notably, dual users of any ST product and cigarettes had the highest levels of intentions to try (*M* = 4.54) and use (*M* = 4.32) the product; however, among this group, intentions to dual use (*M* = 4.3) were higher than intentions completely switch (*M* = 3.5).

Table 4. *Unadjusted mean scores for intentions to try, use, switch, and dual use Copenhagen Snuff, at pre-test and post-test, among adult tobacco users.*

Group	Condition	Intentions to Try [a]		Intentions to Use [a]		Intentions to Switch[a]		Intentions to Dual Use	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
ASPQ	Control	2.43	2.30	2.31	2.20	2.19	2.11	2.19	2.06
	Test	2.40	2.36	2.29	2.25	2.16	2.11	2.15	2.05
ASNPQ	Control	2.54	2.46	2.41	2.31	2.08	2.06	2.33	2.22
	Test	2.49	2.48	2.32	**2.34***	2.02	2.09	2.24	2.23
MST Users	Control	4.36[b]	4.35[b]	4.27	4.18	Not asked			
	Test	4.49[b]	4.37[b]	4.22	4.16				
Dual Users	Control	4.51[b]	4.38[b]	4.22	4.13	3.33	3.27	4.19	3.97

[9] This analysis yielded only one statistically significant result: intentions to use Copenhagen Snuff were higher among ASNPQ who viewed the advertisement with the claim, compared to those who viewed the advertisement without the claim ($F = 9.15$, $\rho = 0.003$, $eta^2 < 0.01$). However, the magnitude of the change was so small that given the context of the other findings both for intentions to use across user groups as well as other metrics for the ASNPQ group, this finding was not seen as meaningful.

[10] These smokers represent adult smokers who reported planning to quit. Scores were within a 0.2 difference relative to smokers who were not planning to quit.

	Test	4.59[b]	4.54[b]	4.43	4.32	3.51	3.51	4.32	4.15
Tobacco Users LA-24	Control	3.19[b]	3.13[b]	3.15	3.10	2.63	2.62	2.91	2.82
	Test	3.31[b]	3.24[b]	3.23	3.20	2.73	2.73	3.02	2.96

[a]Composite measure
[b]Represents only those MST Users (43%), dual users (42%), and tobacco users LA-24 (70%) who were not current Copenhagen Snuff users.
*****Denotes statistical significance. After Bonferroni adjustment, *p*-values < 0.008 were considered to be statistically significant.
Note. Response scale ranging from 1 (strongly disagree) to 6 (strongly agree).

Finally, the results showed that viewing the advertisement with the claim versus without the claim did not significantly impact intentions to quit smoking. Therefore, there is no indication that the marketing of the proposed MRTP would adversely impact the likelihood of quitting tobacco among those who planned to do so.

Social Science concluded that these findings show that exclusive smokers are unlikely to completely switch to Copenhagen Snuff, and that while dual users are more likely than exclusive smokers to completely switch to the proposed MRTP, they are more likely to continue to dual use rather than switch completely. These findings are consistent with the use patterns currently observed in the U.S. population, described by Epidemiology: complete switching from exclusive cigarette smoking to exclusive ST use is low among U.S. consumers, and dual users of MST and cigarettes tend to continue dual using, with transitions from dual use to exclusive smokeless use being relatively uncommon.

As TPL, I generally agree with the conclusions of Social Science. However, my interpretation of these findings also accounts for the limitations of the CCI study discussed in Section 3.3 with regard to consumer understanding. In particular, just as I interpreted the CCI study to underestimate the potential impact of the proposed MRTP on consumer understanding and product perceptions given the entrenched beliefs about the product category; here, too, I expect it may take time and multiple exposures to reach and influence users who could stand to benefit. Still, I expect that the ultimate proportion of smokers who are likely to completely switch to this proposed MRTP is small, yet, for those smokers who are open to ST, this proposed MRTP has the potential to significantly reduce their risk. The CCI study results support that the group most likely to adopt the proposed MRTP would be current ST users. Taken together, dual users of ST products and cigarettes are most likely to benefit from the proposed MRTP. In addition, a real-world, targeted marketing campaign is likely to repeatedly expose these users to the message, which over time further increases the likelihood they would switch completely. While intentions did not change substantially between pre- and post-test nor for those viewing the claim or not, given the one-time exposure to the claim, it is unlikely to have changed people's beliefs or motivations. However, with repeated exposure to the claim that would be seen in real world circumstances, and particularly for dual users who showed more interest than other groups in trying, using, and switching, the proposed MRTP has the potential for population health benefit. Thus, while the universe of people who will benefit from this MRTP is modest, given that the claim has been substantiated and the risk for nonusers to initiate tobacco use due to the MRTPA is quite low (see Section 3.4.2), there will be a net benefit to population health, and the modified risk information will enable consumers to make a more informed choice about their tobacco use.

3.4.2 Impacts to Non-users

This section will address the potential impact of authorizing the proposed MRTP on non-users. Non-users include youth, young adults, and adults older than age 25. The impact to youth was examined by Epidemiology using secondary analysis of national datasets as examined by the applicant and FDA. The impact to non-user young adults and adults over age 25 was examined by Social Science using the applicant's CCI study.

3.4.2.1 Epidemiology

Youth are considered a vulnerable population of non-users because youth who initiate with Copenhagen Snuff Fine Cut and other ST products are at risk of developing sustained addiction to tobacco products. Epidemiology used the applicant's analysis of national data as well as literature to examine the likelihood of use among youth. In 2021, data from NYTS showed that the prevalence of reported current ST use was 1.2% (95% CI: 0.8-1.6) for high school students and 0.6% (95% CI: 0.4-0.9) for middle school students. As noted above, NYTS data from 2021 cannot be directly compared to results from past years (2019 and 2020) (Park-Lee, Ren et al. 2021, Gentzke, Wang et al. 2022). NYTS 2021 data also showed that past 30-day use of any ST product was lower than use of electronic cigarettes, cigars, or cigarettes, equal to hookah, but higher than traditional pipe (Gentzke et al., 2022). Recent analyses of the 2020 NYTS report a linear decrease in ST product use among high school students from 7.9% in 2011 to 3.1% in 2020 and among middle school students from 2.7% to 1.2% (Gentzke et al., 2020). These rates vary substantially by rurality with rural youth, who view ST use as normative and as a personal choice with social benefits, using ST at roughly twice the rate of urban youth (Buettner-Schmidt et al., 2019).

Looking specifically at Copenhagen products, in the ALCS analysis of data from the National Survey on Drug Use and Health (NSDUH), Copenhagen (no sub-brand specified) was commonly used (no proportion provided) among youth ST users during 2002-2014. Contrarily, the applicant's analysis of PATH Wave 1 Study data found that only 1.5% of youth ages 12-17 who reported using ST more than ten times in their lifetime and last used ST within the past 30 days used "Copenhagen Snuff" as the type of Copenhagen product usually or most recently used. However, when expanding the analysis to any Copenhagen product, consistent with NSDUH, FDA found that 40.8% reported Copenhagen as their usual or most recent brand used in Wave 1. This estimate was similar in Wave 5 with 38.3% of youth citing Copenhagen as their usual or most recently used brand. The discrepancy in the applicant's analysis and FDA's analysis is likely due to the way in which the applicant analyzed the data, specifically using only responses in which youth specified "Copenhagen Snuff" and excluding youth who responded that they used "Copenhagen" in general. In the context of PMSS, the applicant would need to ensure that the participants in their studies can reliably identify that they are using the proposed MRTP, which will have a new sub-brand name (i.e., Copenhagen Classic Snuff), as opposed to Copenhagen brand products overall. Moreover, the applicant will need to ensure that participants can distinguish between Copenhagen Classic Snuff and other sub-brands such as Copenhagen Snuff Fine Cut. This may be challenging in a national study such as PATH and may be more likely to occur in smaller, focused studies.

Examining young adults, another vulnerable population, the applicant found that 1.9% of young adult (ages 18-24) current established ST users (defined as: "has ever used the product fairly regularly and now uses every day or some days") used Copenhagen Snuff as their last brand used or usual brand, compared to 9.4% of adult established users ages 25 and older. However, when FDA ran internal analyses of PATH Wave 5 and examined all Copenhagen products, the trend was reversed; half of young adults (52.7%) reported Copenhagen as their most recent or usual brand as compared to a third of adults ages 25 and older (30.6%). This is notable in light of the new Tobacco 21 law because the

Copenhagen brand now has a much larger market share among young adults not of legal age to purchase tobacco.

While some studies have suggested that youth who use ST products may be more likely to subsequently initiate tobacco products that present higher levels of individual risk such as cigarettes (Haddock et al., 2001; Severson, Forrester, & Biglan, 2007; Soneji et al., 2015; Tam et al., 2015; Tomar, 2003; Watkins, Glantz, & Chaffee, 2019), other studies in youth and young adults have found no association (O'Connor et al., 2005; Kozlowski et al., 2003; Timberlake, Huh, & Lakon, 2009).

It is concerning that nearly 40% of youth and about half of young adults that used ST recently and have used more than 10 times in their life, reported Copenhagen as their usual or most recent brand in PATH Wave 5. Nevertheless, youth use of ST is quite low (1.3% in 2020) and has been decreasing for a decade (Gentzke et al., 2020) suggesting a likely low overall impact of an authorization on youth. As explained below, careful placement of advertising of the proposed MRTP to prevent exposure to youth and young adults under the age of 21 is warranted, as are stringent postmarket surveillance requirements of impacts to users under age 21 were the proposed MRTP to be authorized.

3.4.2.2 Social Science

The MRTPA did not contain any data for nonsmokers or former smokers regarding initiation. The applicant relied on evidence from its CCI, which was reviewed by Social Science. Results from the CCI study showed that non-users, including former users, never users, and young adult nonusers of tobacco products, had virtually no intentions to try nor use the proposed MRTP (*M*s = 1.2-1.4; 1.2-1.4). The modified risk claim neither increased intentions to try nor use the proposed MRTP among these groups. In addition, evidence suggests youth initiation of ST is expected to be low (<2%) (Miech, 2016). However, these data are in the absence of marketing a product as lower risk. There is no direct evidence to determine how the proposed claim would affect youth non-users. FDA is aware of one published study evaluating the impact of a modified risk claim about snus on youth, which found that a modified risk claim impacted risk perceptions among youth and adults similarly but affected susceptibility to use the product only among adults (El-Touhky et al., 2018). Though this study did not examine the same modified risk claim nor MST, the ST sub-category of the proposed MRTP, it is still potentially informative. While the CCI data suggesting that non-users are unlikely to want to try the proposed MRTP are encouraging, given that lower risk perceptions can predict tobacco use initiation, and ST initiation, specifically (Chafee et al., 2019), it is possible that exposing youth and young adult non-tobacco users to the proposed MRTP could increase their risk of initiating use, especially if they are in an area with higher ST use in those groups (i.e., rural areas).

In summary, the Epidemiology and Social Science reviews concluded that the MRTPA contained adequate information on the impact to non-users with respect to the following:

- Epidemiologic literature showing relatively low use of ST amongst youth, though use is higher in rural youth, especially males
- Intentions data suggesting very low intentions of use amongst non-users

As TPL, I agree that in the current marketplace, there is not a large overall risk of non-users – including youth – initiating tobacco use using the proposed MRTP. Paired with the small group of smokers and dual users that may switch to the MRTP, there stands to be a modest population health benefit. However, given the association between risk perceptions and initiation there is a potential risk of any MRTP to youth and young adults. In addition, there is a larger risk of initiation for rural youth, especially males. In addition, the large (and increasing for youth) market share of Copenhagen products among youth and young adults supports a greater measure of caution. Accordingly, if authorized, the proposed

MRTP marketing must be targeted to maximize exposure to intended users, and prevent exposure among unintended users, particularly youth and young adults under the age of 21.

3.4.3 Population Modeling

The applicant developed its own model, the ALCS Cohort Model, for population modeling to examine the total difference in all-cause mortality of a hypothetical cohort comparing a base scenario (i.e., current market conditions where there is no authorized MRTP) and a modified scenario (i.e., the proposed MRTP receives a modified risk granted order). Though validated for both sexes, the current MRTPA's model only includes males, due to the historically low prevalence of ST use among women.

3.4.3.1 Statistics

Overall, the Statistics review assessed the modeling approach as a reasonable tool to determine the potential effect that authorization of the proposed MRTP would have on the population. No statistical concerns were identified regarding the step-by-step model development approach, nor the validation and programming code associated with the model. Inputs were calculated based on results of the CCI study. However, some limitations were identified. First, transition probabilities (e.g., initiation, switching, cessation, relapse) for both cigarettes and the proposed MRTP and their association with mortality rates are kept constant over the five-year modeling period. This likely obscures some changes that could occur in shorter periods, such as quitting and relapsing within a two-year period. Second, the Linked Mortality Analysis is based on a small number of deaths among ST users, which could lead to greater variability and bias in the estimates. Third, estimates of differences in tobacco use behaviors with the proposed MRTP from CCI study data were generally not statistically significant with very small differences, even though these estimates are used as model inputs. Fourth, the model did not account for users of other STs completely switching to or dual using with the proposed MRTP, which further underscored the need to receive additional information from the applicant regarding product characterization. Thus, while Statistics was comfortable with the modeling approach, there were concerns about the inputs used for the model. As with other population models, the outputs vary based on the inputs, and this application contained considerable uncertainty around the inputs.

3.4.3.2 Epidemiology

For a cohort of one million males, the applicant's model determined that, by age 73, there would be 1,120 more survivors with the proposed MRTP in the marketplace. The model found that the transition producing the greatest benefit was cigarette smokers switching to exclusive ST use, which led to 425 more survivors. The model also found that non-smokers who initiate tobacco use using the proposed MRTP instead of smoking led to 393 additional survivors. The transition producing a significant detriment was cigarette smokers who would have otherwise quit smoking switching to ST use (63 fewer survivors). Based on CCI findings, the applicant estimated that initiation of MST use by never tobacco users would actually decrease by 5% with authorization of the product with the proposed modified risk claim because intentions to use and try the proposed MRTP decreased from pre- to post-test (non-significantly). This input led to a very small population health benefit (10 additional survivors). Epidemiology also noted that estimates of differences in tobacco use behaviors were derived from the CCI study, and data were generally not statistically significant, even though these estimates are used as model inputs. Given the small number of additional survivors relative to the uncertainty in the parameters used as inputs, it is possible that with more robust and certain parameters, the number of survivors could shift in either direction.

With that caveat in mind, overall, Epidemiology noted an expected population health benefit from current cigarette smokers who would otherwise continue smoking switching to exclusive use of the proposed MRTP and from adult non-tobacco users who would otherwise initiate cigarette smoking instead initiating use of the proposed MRTP. Though there would be some harm from non-users who would not have initiated now using the proposed MRTP and smokers who would have quit switching to the proposed MRTP, the applicant estimated that authorization of the product with the proposed modified risk claim would result in 7,500 additional survivors in the U.S. native-born male population after a follow-up period of 60 years.

In summary, the Epidemiology and Statistics review concluded that the MRTPA contained adequate population modeling with respect to the following:

- The step-by-step model development approach and the validation and programming code
- The model itself
- The finding that the proposed MRTP would result in modest population health benefit

However, both disciplines noted the concerns around the inputs used and recognize that a model is only as good as the inputs.

As TPL, I agree with the conclusion that the population modeling tools and approach were appropriate. However, a significant limitation is that many behavioral inputs into the model were derived from non-statistically significant findings in the CCI study, which led to considerable uncertainty regarding the model and its findings. While the applicant's population health model indicates that the proposed MRTP would yield modest health benefits for the population, the results of the population model are dependent on the behavioral inputs and would therefore differ (and could even show a net negative impact) if the behavioral inputs were different. Because of this, I assigned minimal weight to the population model, and instead relied on other findings such as consumer understanding of the claim in the CCI study and the broader literature on tobacco use behavior to reach conclusions about the population health impact.

3.4.4 Conclusions: Impact to the Population

Currently, ST use in the U.S. is low, but dual use with cigarettes among the product class is substantial. Patterns of switching indicate that the likelihood of completely switching from either exclusive cigarette or dual use to exclusive ST remains quite low. Though the applicant's CCI study corroborated the current patterns by demonstrating low to moderate levels of interest in using the proposed MRTP among those who stand to benefit (i.e., smokers and dual users), this must be examined in the context of misperceptions about the relative harms of ST relative to cigarettes also shown in the CCI study. In addition, although it is unlikely that a one-time exposure would significantly change perceptions and then intentions in general, a real-world, targeted marketing campaign is likely to repeatedly expose these users to the message, which over time, further increases the likelihood they would switch completely.

The CCI study demonstrated that the level of interest in using the proposed MRTP among those who stand to benefit most—current smokers—is relatively low, and the addition of the modified risk claim did not affect this. On the other hand, current dual users of an ST product and cigarettes expressed more interest in the product. As might be expected, these results suggest greater appeal to current users already using a product in the category of the proposed MRTP, rather than the average smoker. Certainly, ST products do not universally appeal to users of other tobacco products. Accordingly, it is

likely that this proposed MRTP would appeal to a minority of smokers—those who are open to the category of ST. Appealing to that group of smokers and persuading them to completely switch to a less harmful alternative presents an opportunity to benefit population health.

In examining whether the proposed MRTP provides a strong enough subjective effect and sensory experience to encourage complete switching, I found that the abuse liability for the proposed MRTP is greater than use of FDA-approved cessation aids, but lower than that associated with cigarette smoking. This suggests that for those tobacco users who wish to reduce their tobacco-related risks, but do not wish or are not able to quit altogether, the proposed MRTP is a viable alternative.

The group that the proposed MRTP may be most likely to impact is current dual users who could reduce their individual risk by switching completely. It is notable that current dual-use Copenhagen users appear to consume more of their Copenhagen product daily and smoke fewer cigarettes daily than do dual users of other ST products, suggesting that dual users of the applicant's products may have an easier time with switching to exclusive use of the proposed MRTP (since the balance of the use of the two products may be weighted more toward Copenhagen use) than dual users of other ST products. Overall, by enabling people who smoke to switch completely, the proposed MRTP would benefit population health. Taken together, these findings provide support that the proposed MRTP would increase exclusive use of Copenhagen Classic Snuff among adult tobacco consumers who would benefit from complete switching, including both smokers and dual users of cigarettes and ST. As noted earlier, likewise, the applicant's population health model indicates modest health benefits for the population. However, due to behavioral inputs into the model from non-significant findings in the CCI study, I assigned minimal weight to this evidence in my decision making.

Regarding the impact to non-users, national estimates suggest that use of ST among youth is low (1.3%) and is declining over time and that the likelihood of initiating on an ST product is low. However, this varies by rurality with rural youth use of ST at roughly twice the rate of urban youth (Buettner-Schmidt et al., 2019). While Copenhagen appears to be perhaps the most popular brand among youth who use ST, the applicant's CCI study showed that non-users (including young adults) had virtually no intentions to try or use the proposed MRTP. Overall, this suggests a low risk for vulnerable groups in granting an MRTP marketing authorization. However, given the association between risk perceptions and initiation, and ST initiation, specifically (Chafee et al., 2019), there is a potential risk of any MRTP to youth. Accordingly, if authorized, MRTP marketing must be targeted to maximize exposure to intended users and prevent exposure among unintended users, particularly youth, especially given the popularity of the applicant's brand among youth.

Overall, as the TPL, I find that the evidence on likelihood of use suggests that the proposed MRTP will benefit population health.

4. Environmental Impact

A finding of no significant impact (FONSI) was signed by Luis Valerio, PhD, ATS, on October 25, 2022. The FONSI was supported by an environmental assessment prepared by FDA on October 24, 2022.

5. Conclusions and Recommendation

5.1 Statutory Requirements for Authorization

On March 20, 2018, on behalf of USSTC, ALCS submitted an MRTPA for its Copenhagen Classic Snuff tobacco product (GF1200194).

The application requested authorization under Section 911(g)(1) of the FD&C Act to market the product with the following risk modification claim: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer."

For FDA to issue a risk modification order under Section 911(g)(1) of the FD&C Act, FDA must determine that the applicant has demonstrated that the proposed modified risk tobacco product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- 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.

In accordance with Section 911(g)(4) of the FD&C Act, in evaluating the benefit to health of individuals and of the population as a whole under Section 911(g)(1) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Furthermore, FDA requires that the advertising and labeling of an MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products (section 911(h)(1) of the FD&C Act).

5.2 Conclusions: Scientific Evidence

My review of the scientific evidence integrated various threads regarding the proposed MRTP and its potential effects on health and tobacco use behavior. I undertook this assessment to determine whether the MRTPA met the statutory requirements listed above.

Based on the original MRTPA (MR0000192), I recommended sending a deficiency letter to the applicant to address insufficient information across eight deficiencies identified by the disciplines of Engineering, Chemistry, Toxicology. This letter was sent on March 26, 2021. The deficiencies identified by Engineering, Chemistry, and Toxicology requested information needed to adequately characterize the product and determine whether it could be manufactured consistently in order to draw final conclusions about the individual health risks of the product (including risks relative to other ST products) and, ultimately, the benefit to the population as a whole. (b) (4)

(b) (4)

In response to the Deficiency Letter, in MR0000199, the applicant addressed all eight deficiencies. (b) (4)

(b) (4) Based on its review of this information, Social Science concluded that (b) (4) . As mentioned earlier, the extent to which consumers understand that the proposed MRTP must be used exclusively and that dual users must switch completely should be monitored in postmarket surveillance.

Deficiencies #2-7 requested information to aid in FDA's determination of whether the applicant can manufacture its product consistently and to allow full product characterization to be able to make definitive conclusions regarding our assessment of the risk from the proposed MRTP compared to the risk from other ST products. In response, the applicant provided the requested test data; manufacturing and processing components such as steps, controls, and SOPs; manufacturing and testing protocols; ingredient information; method validation summaries; and HPHC information. The applicant's responses addressed the deficiencies in an acceptable manner to Engineering, Chemistry, and Toxicology. As TPL, I agree with the conclusions of Engineering, Chemistry, and Toxicology regarding the responses to these deficiencies, and find that the product can be manufactured consistently and can now be fully characterized. Therefore, the HPHC data initially submitted by the company is valid and can be analyzed as was submitted and a definitive assessment of risk of the proposed MRTP relative to other ST products could be undertaken.

Deficiency #8 requested that the applicant provide scientific evidence and rationale about how exposure to HPHCs in ST 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, particularly in comparison to other ST products. In MR0000199, the applicant stated that because the vast majority of the marketplace was MST, the appropriate comparison for HPHCs was other MST products. Epidemiology confirmed this assertion and therefore, Chemistry and Toxicology determined this comparison was a reasonable approach and compared HPHCs to levels in other MST products. Therefore, the portion of the deficiency related to dry snuff, loose leaf, and Swedish snus is resolved. As TPL, I agree with this approach to compare the proposed MRTP to the MST category.

Toxicology used an offsetting analysis that focuses on HPHC increases and decreases that are analytically non-equivalent between two tobacco products. Through this approach, Toxicology determined that higher levels of some HPHCs relative to the MST category were offset by the lower levels of other HPHCs. Specifically, utilizing median HPHC levels as recommended by Statistics, lower levels of NNK and

free nicotine offset the higher levels of BaP and cadmium from a carcinogenic perspective. Further, Toxicology determined that non-cancer toxicities resulting from potential exposure to higher levels of BaP and cadmium as compared to other MST products were not a concern due to values remaining below the reference doses established by the Environmental Protection Agency (EPA). Therefore, Toxicology felt this deficiency was appropriately addressed and had no further toxicological concerns.

As TPL, I concur that all deficiencies have been adequately addressed by the applicant. With these deficiencies addressed, I was able to fully assess the individual health risks, and therefore, the benefit to the population as a whole.

In examining claim substantiation and the risks to individual health of the proposed MRTP, the applicant used data from the ST product category and bridged to the proposed MRTP, which is an acceptable approach given the robust body of longitudinal epidemiologic literature on STs and the applicant's market share during the time period of these studies. When comparing ST use to cigarette smoking, ST use poses lower risks of certain health outcomes. Specifically, those who completely switched from cigarettes to ST had generally lower risks for lung cancer, heart disease, oral cancer, and stroke.

FDA also examined the proposed MRTP compared to use of other tobacco products, including other ST products, and to never use. In comparison to never use of tobacco, use of ST exposes users to HPHCs and poses health risks. Based on authoritative reviews and meta-analyses, ST has been demonstrated to be a cause of oral, esophageal, and pancreatic cancer world-wide. In addition, numerous studies have shown that ST use can cause addiction as well as reproductive and developmental toxicities.

Overall, I find that the claim has been substantiated: switching completely to the proposed MRTP from cigarettes will confer a lower risk of lung cancer. This is also consistent with TPSAC's evaluation of the evidence. The evidence also suggests that switching completely to the proposed MRTP would lower HPHC exposure as well as reduce risk of morbidity and mortality for several other diseases relative to smoking.

In examining consumer understanding, the CCI study, although limited in several ways, provided basic evidence to support appropriate consumer understanding of the proposed modified risk claim and its significance in the context of total health. After seeing the advertisement with the modified risk claim, participants understood that using the proposed MRTP is risky to health, and that someone who only uses the proposed MRTP daily would likely experience a negative impact to their health. Participants also understood that the absolute risk of developing lung cancer is lower, but not eliminated, in a person who exclusively uses the proposed MRTP daily than in a person who smokes cigarettes daily. Finally, participants understood that using the proposed MRTP is not less risky than using other MST products, and that the risk of using the proposed MRTP is greater than that of using NRT, quitting all tobacco, and never using tobacco products. Although the CCI study findings in general suggest that a one-time exposure to the claim did not significantly affect risk perceptions, and I would have liked to have seen multiple exposures in the study and an assessment of the dose-response relationship, it is likely the findings do not reflect the full real-world impact of the claim once consumers are exposed to the claim repeatedly and over time with credible and substantiated information; thus, these findings likely underestimate the potential impact of the claim on consumers' perceptions.

The limitation that the study did not assess participants' understanding that a user must completely switch to the product (from cigarettes) in order to reap the benefit is mitigated by the fact that the claim itself directs potential users that they can reduce their risk by "switching completely." Still, the extent to

which consumers understand that the proposed MRTP must be used exclusively and that dual users must switch completely should be monitored in postmarket surveillance.

In examining the likelihood of use and impacts to the population, Epidemiology examined current use behavior, patterns of use, intentions to use, and modeling. Currently, ST use in the U.S. is low, but dual use with cigarettes among the product class is substantial. Patterns of switching indicate that the likelihood of completely switching from either exclusive cigarette or dual use to exclusive ST remains quite low. Though the applicant's CCI study corroborated the current patterns by demonstrating low to moderate levels of interest in using the proposed MRTP among those who stand to benefit (i.e., smokers and dual users), this must be examined in the context of misperceptions about the relative harms of ST relative to cigarettes also shown in the CCI study, as noted above. With the repeated exposure to the modified risk claim that would occur if the proposed MRTP were to be authorized, that may lead to the desired effect: moving users of combustible products to a product with modified risk.

The CCI study demonstrated that the level of interest in using the proposed MRTP among those who stand to benefit most—current smokers—is relatively low, and the addition of a one-time exposure to the modified risk claim did not affect this. On the other hand, current dual users of an ST product and cigarettes expressed more interest in the product. As might be expected, these results suggest greater appeal to current users already using a product in the category of the proposed MRTP, rather than the average smoker. I note that because these are group means, they do not reflect variability within the group; this is particularly relevant when considering a consumer product about which people will naturally vary widely in terms of interest. Certainly, ST products do not universally appeal to users of other tobacco products. Accordingly, it is likely that the MRTP would appeal to a minority of smokers—those who are open to the category of ST. In examining whether the proposed MRTP provides a strong enough subjective effect and sensory experience to encourage complete switching, BCP found that the abuse liability for the proposed MRTP is greater than use of FDA-approved cessation aids, but lower than that associated with cigarette smoking. This suggests that for those tobacco users who wish to reduce their tobacco-related risks, but do not wish or are not able to quit altogether, the proposed MRTP is a viable alternative. With targeted marketing toward cigarette smokers of brands of the applicant's parent company, there is a large segment of current smokers who may receive direct marketing materials regarding the proposed MRTP, which may present them with new information about the relative lung cancer risk. Appealing to that group of smokers and persuading them to completely switch to a less harmful alternative presents an opportunity to benefit population health.

As mentioned previously, the group that the proposed MRTP may be most likely to impact is current dual users who could reduce their individual risk by quitting cigarettes but continuing to use the proposed MRTP, thereby switching completely. Perhaps unsurprisingly, current dual users of smokeless products reported the highest mean levels of intentions to use the product. I expect that the MRTP will influence some proportion of these users to stop smoking and use the product exclusively, which would significantly reduce their individual risk and help benefit the population health. Given the brand's market share and the over (b) (4) dual users of Copenhagen, this is a particularly ripe population who would benefit from the proposed MRTP. In addition, it is notable that dual-use Copenhagen users consume more of their Copenhagen product daily and smoke fewer cigarettes daily than do dual users of other ST products, suggesting that dual users of the applicant's products may have an easier time switching to exclusive use of the proposed MRTP as the balance of the use of the two products may be weighted more toward Copenhagen use than dual users of other ST products.

Regarding the impact to non-users, specifically to youth, national estimates suggest that use of ST among youth is low (2.3%) and is declining over time and that the likelihood of youth initiating tobacco

use with an ST product is low. However, this varies by rurality with rural youth use of ST at roughly twice the rate of urban youth (Buettner-Schmidt et al., 2019), a concern substantial enough that the FDA's Real Cost Campaign has a series of ads targeted at rural youth use of ST with the tag line "smokeless doesn't mean harmless." While Copenhagen appears to be perhaps the most popular brand among youth who use ST, the applicant's CCI study, though it did not include youth, showed that non-users (including young adults) had virtually no intentions to try or use the proposed MRTP. However, given the association between risk perceptions and initiation, there is a potential risk of any MRTP to youth. Accordingly, if authorized, MRTP marketing should be targeted to maximize exposure to intended users, and prevent exposure among youth, especially given the popularity of the applicant's brand among youth ST users.

Taken together, these findings provide support that the proposed MRTP would increase exclusive use of Copenhagen Classic Snuff among adult tobacco consumers who would benefit from complete switching, including both smokers and dual users of cigarette and ST products while posing a low risk of initiation to non-users of tobacco, including youth. Overall, by enabling people who smoke to switch completely, the proposed MRTP would benefit population health

In conclusion, I conducted a thorough scientific review of the information contained in the MRTPA, and considered the recommendations from TPSAC, comments, data, and information submitted to FDA by interested persons, and other scientific information identified by the agency from other sources. After examining the totality of evidence across scientific reviews, I found that the proposed modified risk claim is scientifically accurate: smokers who switch completely to the proposed MRTP will have a lower risk of lung cancer. Furthermore, the data support a benefit to population health through reductions in overall morbidity and mortality associated with the use of the proposed MRTP, relative to cigarette smoking, that would not be offset by nonusers initiating with the product nor users of other ST products switching to the proposed MRTP. Although the CCI study findings suggest that a one-time exposure to the claim did not significantly affect risk perceptions, this is likely due to widespread and persistent misperceptions of the product as more harmful than it is relative to cigarettes and the several study design limitations. Importantly, the applicant did demonstrate that consumers have an appropriate understanding of the MRTP as not harmless and more harmful than NRT or quitting. An authorization of the proposed MRTP would allow for multiple exposures to credible and substantiated information over time in real-world settings. This will allow those tobacco users most likely to switch completely to receive information that will help combat those misperceptions and enable them to choose an MRTP.

5.3 Recommendation for the Risk Modification Order Request

With respect to the risk modification order request, I find that the proposed MRTP, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and 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. Therefore, I recommend issuing a Modified Risk Granted Order (MRGO) to the applicant.

Section 911(h)(4) of the FD&C Act requires an MRTP order to be for a specified time period. I recommend authorization for a period of five years. Although this review has found that the product will benefit the health of the population as a whole, that determination may change over time as a function of how the product is actually used by consumers. Therefore, monitoring use of the product that is the subject of this application in terms of uptake, dual use, and complete switching is required. Postmarket surveillance and studies (PMSS) (refer to Appendix 1 for requirements to be conveyed to the applicant) must include an assessment of MRTP users' behavior and understanding at multiple time points as well as a computational model using data from users' behaviors as inputs to demonstrate a continued

benefit to population health. A five-year period is a reasonable amount of time for trends in use behavior to emerge to evaluate in postmarket surveillance and studies and assess whether the standard continues to be met and whether the order should be renewed.

Section 911(h)(5) of the FD&C Act enables the Secretary to require that an MRTP, for which an applicant obtained an order under subsection (g)(1), comply with requirements relating to the product's advertising and promotion. Under this Section, I recommend that the MRGO include the advertising and promotion requirements listed in Appendix 2, including requirements related to (i) annual reporting of certain advertising and marketing information; (ii) notifications related to the product's labeling, advertising, and marketing; and (iii) additional conditions for marketing. Based on my review and a consult by the Office of Health Communication and Education, these requirements are necessary to my conclusion that permitting the marketing of the proposed MRTP will benefit the population as a whole. Regarding the reporting of certain advertising and marketing information in point (i) above, I considered whether to recommend requiring the applicant to submit their reports to FDA annually vs. more frequently, such as every 6 months. Several factors led me to conclude that annual reports would be sufficient. The proposed MRTP is a pre-existing tobacco product that has been on the U.S. market for many decades, being granted pre-existing status by FDA in 2012. It is a traditional loose MST product with an established user base and brand, no characterizing flavor, and no evidence of novel features that appear likely to rapidly generate youth interest in the product. Based on my evaluation, annual reporting would be appropriate for the proposed MRTP.

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7. Appendices

Appendix 1: Required Postmarket Surveillance and Studies (PMSS)

Under Section 911(i)(1) of the FD&C Act, FDA must require postmarket surveillance and studies for any product for which an applicant received an order under 911(g)(1) in order to: "…determine the impact of the order issuance on consumer perception, behavior, and health, to enable the Secretary to review the accuracy of the determinations upon which the order was based, and to provide information that the Secretary determines is otherwise necessary regarding the use or health risks involving the tobacco product."

I. PMSS Content

MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the tobacco product that is the subject of this order (hereinafter, the MRTP), as actually used by consumers, continues to benefit the health of the population as a whole is likely to be driven by use behavior. Therefore, monitoring use of the MRTP in terms of uptake, dual use, and complete switching is required. In particular, your PMSS must assess the extent to which new users of the MRTP were non-users of tobacco products, smokers, or other tobacco product users before initiating the MRTP, and the extent to which such new users of the MRTP become exclusive users or dual users with cigarettes or other tobacco products, including other smokeless tobacco (ST) products, over time. Relatedly, such surveillance must include an ongoing assessment of consumers' understanding of the claim and perceptions of the MRTP. In particular, PMSS must assess the extent to which users of the MRTP understand that, to reduce their risk of lung cancer as described in the modified risk claim, they must switch from smoking cigarettes to using the MRTP exclusively. To adequately assess these impacts, you must conduct PMSS that include assessing users' behavior and consumer understanding at multiple time points.

In addition, FDA has determined that assessing the impact of your MRTP order on uptake of the product requires surveillance of MRTP sales and distribution, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting MRTP sales and distribution in the U.S. by major metropolitan areas and channels where the MRTP is sold (e.g., convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops). Your annual PMSS report must include:

- U.S. sales and distribution of the MRTP by quarter since the granting of your modified risk granted order (for the initial reporting period) or the previous reporting period (for all reports that follow), including, total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas and channels where the product was distributed and sold during the reporting period (e.g., convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops).
- A brief synthesis and summary of the sales and distribution data for the initial reporting period or the previous reporting period (for all reports that follow), including annual and quarterly growth rate (percent change) in total U.S. sales and distribution of the MRTP since this Order was issued.
- All Universal Product Codes (UPCs) used for the MRTP when selling or distributing it in the U.S.

MRTP Use and Health Risk – Adverse Experiences

In order for FDA to determine whether the MRTP, as actually used by consumers, continues to benefit the health of the population as a whole, your PMSS must include ongoing surveillance of all adverse experiences associated with the use of the MRTP. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported adverse experiences for the tobacco product, which includes a listing of all adverse experiences during the reporting period and a cumulative list, including all serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the product including nature, frequency, and potential aggravating factors.

For purposes of this reporting under this order, *serious adverse experience* means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening condition or illness;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of this reporting under this order, *unexpected adverse experience* means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the MRTPA (including the results of human subject investigations) and other relevant sources of information, such as postmarket reports and studies;
- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

Surveillance of New Research Study Findings on the MRTP and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the MRTP, as actually used by consumers, continues to benefit the health of the population as a whole, your PMSS must include surveillance of new research study information about the MRTP and consumer perception, behavior, or health. In particular, your PMSS protocol must include procedures for monitoring and assessing findings both in your own studies (i.e.,

studies conducted by you or on your behalf) and in publications including any new scientific data (published or otherwise) regarding the MRTP and consumer perception, behavior, or health. Your annual PMSS report must include:

- A summary of significant findings about the tobacco product from research studies conducted by you or on your behalf, whether or not such studies were specifically required under this order.
- A summary of significant findings in publications not previously reported and full copies of the articles. This must include any new scientific data (published or otherwise) on the MRTP and consumer perception, behavior, or health.

Modeling the Impact of the MRTP on Population Health

In order for FDA to determine whether the MRTP continues to benefit the health of the population as a whole, your PMSS must include computational modeling of the impact of the MRTP on population health. Such modeling must incorporate data and information collected through PMSS, including the percentage of former smokers who start using the MRTP; the percentage of current smokers who start using the MRTP and become dual users; the percentage of current smokers who switch completely to the MRTP; the percentage of youth and young adults below the federal minimum age of sale who start using the MRTP; the percentage of individuals who start using the MRTP and then initiate or re-initiate combusted cigarette smoking; the percentage of other tobacco product users, including a specific breakout for other ST products, who start using the MRTP and become dual users; and the percentage of other tobacco product users, including a specific breakout for other ST products, who switch completely to the MRTP. Postmarket modeling must incorporate the latest information on acute and long-term health effects of using the MRTP relative to combusted cigarette smoking in order to assess the short and long-term population health impacts of the marketing. Your annual PMSS report must include:

- A description of the methodological approach used in the model;
- A copy of the model or its underlying code, such that FDA can independently run and verify the model inputs and outputs;
- A description of all model inputs, including the justification for input values and how they were derived from postmarket data and information; and
- A summary of the modeling results and their implications for assessing whether the MRTP continues to benefit the health of the population as a whole.

II. Submitting PMSS Protocols and Reports

Within 30 days of receiving this notice, you must submit complete protocols for your PMSS as required under section 911(i)(2) of the FD&C Act. Label your submission clearly as a "PMSS Protocol," and reference your MRTPA Submission Tracking Number (STN). If you have more than one protocol, each protocol should be a separate submission. If applicable, each protocol should include the name(s) of the principal investigator(s) and materials that demonstrate the relevant professional credentials and training that qualify them to lead the study. Within 60 days of receipt of the protocol(s), FDA will determine if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol(s) will result in collection of the data or other information that FDA designates as necessary to protect public health, pursuant to section 911(i)(2) of the FD&C Act. FDA will notify you of and provide opportunities to address, any

deficiency in the submission. If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly. For protocol amendments that are administrative in nature (e.g., corrections in punctuation or titles), the amended protocol must be received by FDA within 30 days of the update. For protocol amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology, etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval.

As part of the requirement to conduct PMSS, you must initiate and conduct your PMSS per timeframes established in your protocols and approved by FDA. Note that for PMSS that involve human subjects, the anticipated start date for each study must account for the time required for securing IRB approval, as needed. In addition to specifying the start date, your protocols must contain timelines for completion of major study milestones including, as applicable, the start and completion of participant recruitment, initiation of data collection (per wave, if applicable), completion of data collection, analysis, and report writing. If you deviate from these timelines, we request that you report the deviation within 30 days to FDA.

Section 911(i) of the FD&C Act requires that the results of PMSS be submitted on an **annual basis**. These reports must be identified as “PMSS Report” and reference the MRTPA STN for each report. The PMSS Report must indicate the beginning and ending date of the period covered by the report and must include accomplishments since the last reporting period. For quantitative updates on studies in progress (e.g., participant accrual), reports should describe both interim (since the last reporting period) as well as cumulative (since study initiation) accomplishments. The PMSS Report describing studies in progress must describe the status of PMSS, including, as applicable the status of recruitment, data collection, and analysis; a summary of the study milestones achieved and any deviations from the agreed upon timelines in the protocol; a summary of protocol amendments; and a summary of any preliminary analyses conducted. Once a study is completed, the PMSS Report should include the complete final study report.

Appendix 2: Advertising and Promotion Requirements

I. Recordkeeping and Retention

Under section 911(h)(5) of the FD&C Act, these risk modification orders require you to establish and maintain the following records:

- Records pertaining to the product's labeling, advertising, marketing, and/or promotion – whether conducted by you, on your behalf, or at your direction – including:
  - Specimens of all labeling (including all labeling variations, such as those reflecting different required warnings), labels, inserts/onserts, instructions, and other accompanying information;
  - Copies of all advertising, marketing, and/or promotional materials published, disseminated to consumers, or for use in engaging or communicating with consumers;
  - Copies of any formative research studies conducted among any audiences in the formation of the labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the product, and including copies of the stimuli used in testing;
  - Copies of any consumer evaluation research studies conducted among any audiences to determine the effectiveness of labeling, advertising, marketing, and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the product, and including copies of the stimuli used in testing;
  - Copies of any contractual agreements regarding the creation and/or dissemination of the product's labeling, advertising, marketing, and/or promotional materials, including for example, in print media, online or through digital platforms (e.g., social media and mobile applications), such as influencers, bloggers, and ambassadors, on your behalf, or at your direction;
  - Copies of all advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including any:
    - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
    - Targeting of specific adult audiences by age-range(s), including young adult audiences, ages 21-24, and other demographic and/or psychographic characteristics that reflect your intended target audience;
    - With respect to individuals under the federal minimum age of sale of tobacco products, actions taken to restrict youth-access and limit youth-exposure to the product's labeling, advertising, marketing, and/or promotion;
    - Use of owned, shared, and/or paid social media to create labeling for, advertise, market and/or promote the products;
    - Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the product;
    - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the product was demonstrated and how access will be restricted to individuals at or above the federal minimum age of sale of tobacco products; or
    - Use of public-relations or other communications outreach to create labeling for,

advertise, market, and/or promote the product;

- Copies of all records pertaining to media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), and all post-launch delivery-verification reports submitted to you from an accredited source, by channel, by product, and by audience demographics; and
- Policies and procedures for real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products, including documentation of such monitoring activities and implementation of corrective and preventive measures.

II. Annual Reporting

Under section 911(h)(5) of the FD&C Act, this order requires that you submit the following reports to FDA on an annual basis, beginning twelve months from the date of this order. For each twelve-month reporting period, these annual reports must include:

- A cover letter that includes the following text in your subject line: **ANNUAL REPORT for MR0000108**. The cover letter should include the STN, static product ID if applicable, and corresponding tobacco product name, applicant name, date of report, and reporting period.
- Records pertaining to the product's labeling, advertising, marketing, and/or promotion – whether conducted by you, on your behalf, or at your direction – including:
  - A summary of all formative research studies conducted among any audiences in the formation of new labeling, advertising, marketing, and/or promotional materials, not previously submitted, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the product, and including the findings of these studies and copies of the stimuli used in testing;
  - A summary of all consumer evaluation research studies conducted among any audiences, not previously submitted, to determine the effectiveness of labeling, advertising, marketing, and/or promotional materials and shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the product, and including the findings of these studies and copies of the stimuli used in testing; and
  - A summary of the creation and dissemination of the product's labeling, advertising, marketing, and/or promotional materials including a list of all entities involved and a description of their involvement, including a description of contractual agreements with such entities.
- A description of the implementation of all advertising and marketing plans – whether conducted by you, on your behalf, or at your direction – not previously submitted, including strategic creative briefs and paid media plans, by channel, and the details, dollar amount(s) and flighting of such plans, by channel, including a description of any:
  - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;

  - Targeting of specific group(s) by age-range(s), including young adults, ages 21-24, and other demographic or psychographic characteristics that reflect the intended audience(s), including the source(s) of such data;

  - With respect to individuals under the federal minimum age of sale of tobacco products, actions taken to restrict access to the product and limit exposure to the product's labeling, advertising, marketing, and/or promotion;
  - Use of owned, earned, shared, or paid media to create labeling for, advertise, market, and/or promote the product;
  - Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, and/or promote the product;
  - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the product was demonstrated and how access was restricted to individuals at or above the federal minimum age of sale of tobacco products; or
  - Use of public-relations or other communications outreach to create labeling for, advertise, market, and/or promote the product; including the original date such plans were first used and the date they were discontinued, and a description of all changes to such plans since the last periodic report, by channel;
- An analysis of the actual delivery of advertising impressions, by channel, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), not previously submitted. This analysis must be verified against post-launch delivery-verification reports for paid media submitted to you or entities working on your behalf or at your direction from an accredited source;
- A summary of media tracking and optimization, by channel and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products, and including a summary of implementation of any corrective and preventive measures, not previously submitted;
- All final printed labeling (including all variations, such as those reflecting different required warnings) not previously submitted (e.g., if previously submitted under section 905(i) or previously submitted at the last reporting period and no changes were made, please list the date and manner of submission), including the date the labeling was first disseminated and the date when the labeling was discontinued, and a description of all changes to the labeling. The labeling must include all the panels and be presented in the actual size and color with legible text. The labeling must include labels, inserts/onserts, instructions, and any other accompanying information or materials for the product; and
- All final full-color advertising, marketing, and/or promotional materials, published, disseminated to consumers, or for use in engaging or communicating with consumers not previously submitted (e.g., if previously submitted under 905(i) or previously submitted at the last reporting period and no changes were made, please list the date and manner of submission), along with the original date such materials were first disseminated and the date they were discontinued, and a description of all changes to the materials. The materials must be legible, include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5" x 11" piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the advertisement does not allow for text to be read easily, the complete text must be provided separately and clearly referenced. Digital media, such as videos and animations must be submitted in a format that FDA is able to open and review.

III. Notifications

Under section 911(h)(5) of the FD&C Act, this order requires that as of the authorization date of your modified risk order, and for a period of six months starting with the initial dissemination of the marketing materials for the MRTP, you submit the following notifications of your marketing plans and materials to FDA and all other labeling, advertising, marketing, and promotion. This notification must be received by FDA at least 30 days prior to dissemination, which includes but is not limited to the publication, dissemination to consumers, or use in engaging or communicating with consumers of such materials.

This 30-day notification requirement to submit the product's labeling, advertising, marketing, and/or promotional materials and plans in advance of their use is not for pre-approval – that is, FDA is not requiring that it review and approve such materials or plans before they may be used. Rather, such advance notification will provide FDA timely access to such materials and plans and, if needed, allow FDA to provide advisory comments, including any concerns about their possible impact on youth appeal and tobacco use initiation and on the finding that continued marketing of your product will benefit the health of the population as a whole. You may begin disseminating the materials 30 days after the notification is received by FDA.

Each 30-day notification must include:

- A single submission with a cover letter that includes the following subject line: **30-DAY NOTIFICATION for MR0000108**. The cover letter should include the STN and corresponding tobacco product name, applicant name, date of notification, and planned dissemination date;
- Full-color copies of all such labeling, advertising, marketing, and/or promotional materials for the product, Copenhagen Classic Snuff. The materials must include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5" x 11" piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the material does not allow for text to be read easily, the text may be provided separately and referenced. Digital media, such as videos, must be submitted in a format that FDA is able to open and review.
- All advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the details, dollar amount(s) and flighting of such plans, by channel and by product, including any plans to:
    - Use competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;
    - Target specific group(s) by age-range(s), including young adults, ages 21-24, and other demographic or psychographic characteristics that reflect your intended audience(s), including the sources of such data;
    - With respect to individuals below the federal minimum age of sale of tobacco products, actions taken to restrict access to the product and limit exposure to the product's labeling, advertising, marketing, and/or promotion;
    - Use owned, earned, shared, or paid media to create labeling for, advertise, market, and/or promote the product;

- Use partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, and/or promote the product;
- Conduct consumer engagements – whether by you, on your behalf, or at your direction – including events at which the product will be demonstrated and how access will be restricted to individuals at or above the federal minimum age of sale of tobacco products; and/or
- Use public-relations or other communications outreach to create labeling for, advertise, market, and/or promote the product.

IV. Additional Conditions for Marketing

Under section 911(h)(5) of the FD&C Act, this order requires you to:

- For any of the product's labeling, advertising, marketing, and/or promotion appearing in your **owned digital properties** (e.g., your company-owned, consumer-directed, product-branded website(s) and/or mobile applications)– whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, at the first point of access to such properties, to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at or above the federal minimum age of sale of tobacco products.
- For any of the product's labeling, advertising, marketing, and/or promotion appearing in any **shared digital properties** (e.g., your product-branded social media accounts, pages and associated content; content promoting your product on your behalf disseminated through another entity's social media accounts) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of the available site-, platform- and content-(e.g., post, video) specific age-restriction controls (e.g., age-restrict an entire product-branded account and all associated content disseminated through such account; ensure age-restriction of a specific video disseminated by an influencer promoting the product on your behalf through the influencer's account), at the first point of access to such properties, to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at or above the federal minimum age of sale of tobacco products.
- For any of the product's labeling, advertising, marketing, and/or promotion appearing in **paid digital media** (e.g., paid digital banner advertisements for the product running on another company's website; paid advertising for the product running in social media; paid distribution of influencer content; paid advertising in streaming/Over-The-Top video programming; paid advertising in streaming/internet radio content) – whether conducted by you, on your behalf, or at your direction:
  - Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to precisely target delivery of such labeling, advertising, marketing, and/or promotion to only individuals who are at or above the federal minimum age of sale of tobacco products. Such targeting must use only first- and/or second-party age-verified data, where:
    - "First-party" age-verified data is data owned by you (e.g., your customer registration data collected via site traffic to your company-owned website; data you use in direct marketing to your adult smoking customers) that you have age-verified through independent, competent, and reliable data sources; and
    - "Second-party" age-verified data is first-party data owned and age-verified by another competent and reliable entity (e.g., another company's first-party user registration data)

to which you have access. Such data must be age-verified by the second party.
    - "First-party" and "second-party" data does not include data obtained from data aggregators who categorize consumers based on trackable activities and inferred interests (e.g., internet search terms, video interactions, browsing history, purchasing behaviors) to create demographic and psychographic profiles marketers may use to enhance audience targeting. Such data is not considered age-verified and can only be used in combination with first- and/or second-party age-verified data.

- Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies (e.g., using an embedded tracking pixel in all digital advertising) – whether conducted by you, on your behalf, or at your direction – to **track and measure actual delivery of all advertising impressions**, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region). Such monitoring requires real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products. Such monitoring also requires post-launch delivery verification reports for paid media be submitted to you or entities working on your behalf or at your direction from an accredited source.
- For any use of **partners, influencers, bloggers, and/or brand ambassadors** to create labeling for, advertise, market, and/or promote the product – whether conducted by you, on your behalf, or at your direction – disclose to consumers or viewers, via the use of statements such as "sponsored by [firm name]" in such labeling, advertising, marketing, and/or promotional materials, any relationships between you and entities that create labeling for, advertise, market, and/or promote the product, on your behalf, or at your direction.

The requirements above are intended to help ensure that the MRTP, as actually used by consumers, will continue to benefit the health of the population as a whole. Limiting youth initiation of the product and, relatedly, youth exposure to advertising and marketing materials for the product are important factors in the population health benefit analysis. Accordingly, FDA also recommends limiting youth exposure to any of the tobacco product's labeling, advertising, marketing, and/or promotion appearing in print media publications.

After receiving authorization, the determination of whether the MRTP, as actually used by consumers, continues to benefit the health of the population as a whole is likely to be driven by use behavior. An uptake in youth initiation and use of the product would have a significant negative impact on the population health benefit analysis. To help ensure that your product, as actually used by consumers, continues to benefit the health of the population as a whole, we strongly recommend that you take measures to limit youth initiation and use of the product, beyond limiting advertising and promotion as required in this order. For example, we strongly recommend you adopt the following measures related to all digital sales of your product:

- For any **digital sales** – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, to prevent the sale of the product to individuals who are under the federal minimum age of sale of tobacco products.

Relatedly, we request that you submit the following information to CTP on an annual basis:

- A summary of the implementation and effectiveness of any policies and procedures regarding verification of the age and identity of purchasers of the product.
- A summary of the implementation and effectiveness of any policies and procedures regarding restrictions on youth access to the product.

We remind you that if FDA can no longer make the determination that your product, as actually used by consumers, will benefit the health of the population as a whole, FDA must withdraw the modified risk order, after an opportunity for an informal hearing. See under section 911(j)(1) of the FD&C Act. Although adopting the measures above is not in itself a guarantee that the product will continue to benefit the health of the population as a whole, it is an important step in helping to ensure that there are no grounds for withdrawal of your order.