DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
10903 New Hampshire Avenue
Silver Spring, MD 20993

October 12, 2017

MEETING MINUTES

Swedish Match North America, Inc.
Attention: Gerard Roerty, Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

FDA Submission Tracking Number (STN): TC0002533

Dear Mr. Roerty:

Please refer to the September 13, 2017, meeting held to discuss your Modified Risk Tobacco Product Applications (MRTPAs) under section 911(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the following products:

STN	TOBACCO PRODUCT NAME
MR0000020	General Loose
MR0000021	General Dry Mint Portion Original Mini
MR0000022	General Portion Original Large
MR0000024	General Classic Blend Portion White Large – 12 ct
MR0000025	General Mint Portion White Large
MR0000027	General Nordic Mint Portion White Large – 12 ct
MR0000028	General Portion White Large
MR0000029	General Wintergreen Portion White Large

A copy of the official minutes is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions please contact Rachel Forche, Regulatory Health Project Manager, at (240) 402-2729.

Sincerely,

Benjamin Apelberg -S

Digitally signed by Benjamin Apelberg -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000588076, cn=Benjamin Apelberg -S
Date: 2017.10.12 17:55:26 -04'00'

Benjamin Apelberg, PhD
Director
Division of Population Health Science
Office of Science
Center for Tobacco Products

Enclosure: Meeting Minutes

Food and Drug Administration
Center for Tobacco Products
10903 New Hampshire Avenue
Silver Spring, MD 20993

MEETING MINUTES

FDA Submission Tracking Number:	TC0002533
Meeting Minutes Issue Date:	October 12, 2017
Meeting Date and Time:	September 13, 2017 1:00 PM – 2:00 PM ET
Meeting Format:	Teleconference
Meeting Category:	MRTPA
Applicant Name:	Swedish Match North America, Inc. (SMNA)
Meeting Requestor:	Gerry Roerty, Vice President, General Counsel & Secretary
Product Name:	See above
Received Meeting Information Package:	June 27, 2017
Preliminary Reponses Sent:	September 11, 2017

I. MEETING ATTENDEES

FDA Attendees

Benjamin Apelberg, PhD, Director, Division of Population Health Science (DPHS)
Joanne Chang, PhD, Epidemiologist, DPHS
Blair Coleman, PhD, Epidemiologist, DPHS
Karen Cullen, PhD, Epidemiologist, DPHS
Stephanie Durkin, Team Lead, Division of Regulatory Project Management (DRPM)
LTJG Rachel Forche, MPH, Regulatory Health Project Manager (RHPM), DRPM
Ranjeeta Gupta, MA, MPH, RHPM, DRPM
Sarah Johnson, PhD, Social Scientist, DPHS
Antonio Paredes, MA, MS, Statistics Team Lead, DPHS
Alex Persoskie, PhD, Social Scientist, DPHS
LCDR Lana Rossiter, PhD, Branch Chief, DRPM
Cindy Tworek, PhD, Social Science Team Lead, DPHS

SMNA Attendees:

Patricia Ensor, Senior Advisor, Kantar Health
Ian McKinnon, Chief Research, Kantar Health
Steve Seiferheld, Director of Marketing Research, SMNA
Jim Solyst, Vice President, Federal Regulatory Affairs, SMNA

II. BACKGROUND

Swedish Match North America, Inc (SMNA) submitted a meeting request on June 27, 2017, to discuss Modified Risk Tobacco Product Applications (MRTPAs) under section 911(d) of the FD&C Act. The objective of this meeting was for SMNA to present and receive feedback on documents developed for the consumer observational research. On July 10, 2017, FDA issued a letter granting the meeting request. The meeting information package was submitted by SMNA on June 27, 2017. On September 11, 2017, FDA provided preliminary responses to the questions within the SMNA meeting information package.

III. OBJECTIVES

The meeting information package containing objectives, agenda, specific questions, and meeting attendees was received on June 27, 2017. As described in the meeting information package, the following objectives and outcomes were expected by SMNA attendees:

1. Ensure that the Center for Tobacco Products (CTP) understands the SMNA work to-date and the proposed path forward, and that CTP is in agreement with the approach presented.

2. Receive useful comments and suggestions from CTP on two foundational documents developed for the consumer observational research:
    a. Protocol for the General snus MRTP Consumer Research Observational Study
    b. Questionnaire associated with the Protocol for the Observational Study

IV. DISCUSSION

General FDA Response

Based on our preliminary review of the materials you submitted, we have the following initial comments about the proposed study. The comments are not indicative of all the issues that may be identified if we reviewed the study within the context of a complete submission of an MRTPA. In addition, please be aware that it is a review issue whether the study results and data provided within your MRTPAs are adequate to support modified risk claims under section 911.

Industry Submitted Questions and FDA Response

Question 1

Swedish Match has provided primary and secondary objectives related to the consumer research. In support of the objectives, Swedish Match has provided research hypotheses meant to be directly addressed by survey data and statistical

analysis. We request that CTP comment on the objectives and hypotheses. Of particular interest:

a. Have we omitted any topics deemed essential by CTP for successfully obtaining MRTP?
b. Are all hypotheses easy to understand and interpret by CTP?

FDA Response

(a) Your research question, as stated in your protocol (p. 6), is to determine how proposed modified risk claims, their execution elements, and types of media impact the perceptions and intentions of various cohorts of U.S. adult consumers. It is appropriate for the study to focus on the effects of the proposed modified risk claims on U.S. adult consumers' intentions and perceptions of health risk from using the proposed MRTPs. However, in addition to the claims themselves, you propose to investigate whether additional elements (warnings, flavor, and media formats) also impact consumers' intentions and perceptions. We have concerns about whether these latter questions are pertinent to address in the current study as they appear not to directly inform your MRTPAs. This is discussed more below. We also note that consumer understanding of the claims, which you do include in your objectives (see below), are important to include as part of the research question.

We note that your primary and secondary objectives do not appear to align with your research question. As stated in your protocol (pp. 6-7), your primary objectives are to assess intentions and compare pre- and post-exposure perceptions of risk. Completing these objectives would not seem to answer your research question, which is to understand how the proposed claims *impact* intentions and perceptions. Answering your research question entails having a comparator group in the analysis, for example, by either (1) comparing perceptions and intentions among people who have been exposed to the claims to the perceptions and intentions of people who have not been exposed to the claims, or (2) comparing the change in perceptions and intentions among people who have been exposed to the claims to the change in perceptions and intentions among people who have not been exposed to the claims.

Your primary objectives also include assessing understanding and believability of the MRTP claims, and consumer ability and willingness to comply with instructions for use. These are appropriate objectives. Assessing consumer understanding of the MRTP information is one of the primary ways a study like this can inform an MRTPA. Objective III covers this topic. However, it is unclear from your protocol and questionnaire how you will operationalize understanding," including how you will define and measure it. We provide more comments on this issue in response to your Question 12.

You have a set of secondary objectives pertaining to the effects of warning labels and flavors on intentions (p. 7). Unless there is a clear rationale for why these objectives are important to your MRTPAs, we do not consider that these objectives will provide relevant information for your MRTPAs. Additionally, your protocol contains no hypotheses related to these objectives. Moreover, as discussed below in response to Question 2, designing the study to address these secondary objectives may have overly complicated the study in a way that we believe would detract from its ability to address the research question. You may want to consider simplifying the study design to focus on the effects of the proposed claims on perceptions and intentions and how those effects differ based on consumer cohorts.

(a) Your hypotheses (pp.13-14), like your objectives, do not appear to align with your research question of determining the *impact* of the proposed claims on people's perceptions and intentions. Rather, your hypotheses appear to be focused on evaluating the absolute levels of perceptions and intentions after people view an advertisement. For example, Hypothesis 7 is that "Never or former tobacco/nicotine users will not plan to use *General Snus*™ in the next 30 days after exposure to the *General Snus*™ advertisement." An example of an alternative hypothesis that would better align with your research question may be, "Among never tobacco users, there will be no difference in intentions to use *General Snus*™ in the next 30 days between those who view a *General Snus*™ advertisement with vs. without the proposed modified risk claim." If the study randomly assigns people to view an advertisement with vs. without the claim, then statistical differences in post-exposure intentions between the two groups can be attributed to the *impact* of the modified risk claim, which may more clearly answer part of the research question you have posed.

Furthermore, as the protocol lacks details on how the study outcomes will be operationalized, we are unable to determine how these hypotheses will be analyzed (page 23 of the protocol points the reader to Section 5.2 for details on the outcomes of behavioral intentions and perceptions of risk; however, this section does not appear to have been included). It is important for us to understand these hypotheses so that, in turn, we can understand *how* the hypotheses will be tested (e.g., which statistical tests, using which measures) and what results you would consider supportive of your applications. For example, in Hypothesis 7 noted above ("Never or former tobacco/nicotine users will not plan to use *General Snus*™ in the next 30 days after exposure to the *General Snus*™ advertisement"), we do not know how you will define "will not plan to use." In this case and others, it is unclear whether you will make comparisons between an experimental condition and a control condition (i.e., conditions in which people view advertisements with or without the proposed claims, respectively). It is also unclear when and how the pre-post measures will be used. Relatedly, in your hypotheses, you refer to a "*General Snus*™ advertisement," but you do not specify whether the ads contain modified risk claims (i.e., experimental conditions) or not (i.e., control condition). It is

important to make this explicit. These details would be important to linking your study design to your research question.

As stated above, we think the study and analyses may be more informative if they were to focus on comparisons of study outcomes among people who view advertisements with vs. without the proposed modified risk claims. This would provide information about whether and how viewing the ads with the proposed claims changes people perceptions, intentions, and/or understanding regarding the product. Further, it would be informative to determine whether viewing the ads with the proposed claims has different effects on study outcomes depending on their tobacco use status, as this will help us understand whether providing the modified risk claims would increase the likelihood that users of more harmful products would switch to the proposed MRTPs but not increase the likelihood that other people would try or use the proposed MRTPs.

It is also possible to evaluate the impact of the proposed claims in a repeated measures, pre- vs. post-exposure study design. However, doing so may be more complex because the *change* in study outcomes between the pre- and post-exposure assessment has to be compared with the *change* in study outcomes in a control (no claim) condition. In a repeated measures, pre- vs. post-exposure study, it is still necessary to make comparisons with a control condition in order to (1) parse out the effect of the modified risk claim from the effect of the rest of the advertisement, and (2) control for any effects of repeatedly assessing the study outcome variables.

Specific comments on hypotheses: In addition to the issues described above, below we note specific comments for your consideration on your hypotheses:

Comment on Hypotheses 1 and 2: In your set of behavioral intentions items, you include: "interest in finding out information about", and "interest in looking for *General Snus*™ in a store where the participant usually shops". We assume these items were designed to assess interest in the product (i.e., presumed precursors to purchase or trial). This concept is addressed in the third item assessed: "interest in trying *General Snus*™ if they find it in their store." Given that the former are presumed precursors—and not directly of interest in their own right—we suggest these items may not be that informative to your evaluation of MRTP claims (or your applications). In light of the number of hypotheses you have, it may be to your benefit to simplify, and to eliminate these items which are less directly informative.

Comment on Hypothesis 3: How will "not be interested" be defined or operationalized?

Comment on Hypotheses 4-6: How will "interested in trying" be established? How would this hypothesis be supported? Are you hypothesizing that participants will be more interested after seeing an advertisement with the proposed claim, compared to those in the control condition?

We are unclear why you plan to combine all current tobacco/nicotine users into a single group. In your MRTPAs, you argued that an MRTP marketing authorization for these products would benefit population health by encouraging cigarette smokers to switch completely to your proposed MRTPs. If your rationale for the proposed MRTPAs still focuses on current cigarette smokers, it seems prudent to consider a hypothesis specific to smokers, per se. One potential method would be to examine the impact of exposure to the proposed claims among: current cigarette smokers, current smokeless tobacco users, former smokers, and never users of any tobacco product.

Comment on Hypothesis 7: How is "will not plan to use" in the next 30 days defined?

Comment on Hypotheses 8 and 9: Consider further specifying the following: "Some" could be any number; if two participants indicated likelihood of switching/dual use, would you consider this to be supportive evidence for your hypotheses?

Comment on Hypotheses 10-12: Is the hypothesis that the MRTP claim will *not* reduce intentions to quit? Consider clarifying.

Comment on Hypothesis 13: Does "may suffer" mean any response other than "no chance"? This needs to be specified. Currently, this could be interpreted such that essentially any response option on the scale could be supportive.

Comment on Hypotheses 14-18: Consider clarifying. It is unclear how these will be operationalized and tested. It is unclear if this is based on a comparison with the control condition, some absolute value on the scale (relative harm items), or using a pre-post comparison – with either the absolute or relative harm items?

Comment on Hypotheses 19-21: How are these outcomes defined and how would they be supported? (Compared to what?)

Additional comments pertaining to the Statistical Analysis Plan

Section 7.10 of the protocol states that a formal Statistical Analysis Plan (SAP) is to be developed to accompany the protocol; this is recommended. To facilitate FDA review, it is important that the SAP is a self-contained, in-depth exposition of all statistical procedures that form the basis for the quantitative assessment of the data to be generated from the study. Consider writing the SAP in a manner that the proposed statistical procedure associated with the statistical analysis of the data can unambiguously be replicated by reviewers at CTP. For example, it is

important that the SAP specify how the statistical analysis is driven by the design and objectives of the study. Based on our review of the protocol, the following items are provided for your consideration to be discussed clearly and in-depth in the SAP:

- It is not clear from the protocol whether the sampling strategy is clustered across panels. The same number of participants are to be selected for each of the five cohorts defined in Table 1; however, it is not clear from the protocol how many individuals are to be selected from each of the four panels. That is, if the objective is to ensure participation from all four panels, what is the strategy to achieve that objective? How are panels treated for the purpose of statistical inference?

- On page 9 the protocol states that "A representative sample… will be drawn….. In addition, the invited sample will be derived using probabilistic sampling." However, no information is provided in the protocol on the strategy leading to a representative sample or a probabilistic sampling scheme. For example, are you proposing to draw a representative sample from all panels? Are you proposing to implement a probability sampling strategy? On page 9 of the protocol, you are proposing to select panelists based on the size of "desired quotas," and it is not clear how the probabilistic nature of sampling relates to these quotas. Since these items are important in informing statistical inference, it is recommended that you discuss them in-depth in the SAP.

- It is not clear what you mean by hypothesis testing in section 6.3 of the protocol. For example, are you proposing to statistically test the 21 hypotheses outlined on page 13-14? For hypothesis testing, it is recommended that you state each hypothesis in the form of a null (H_{0}:) and alternative hypothesis (H_{1}:). It is important that the rationale for the selection of any statistical procedure for hypothesis testing be clearly specified in the SAP; including the rationale for or against multiplicity adjustment.

- It is important that the SAP discuss how the study design and sampling inform the statistical analysis of the data to be generated from the study. This is important in relation to statistical inference. For example, if you are planning to generalize statistical inference (external validity) to a population other than the participants of the study, then consider discussing how such generalization is possible based on the design of the study and the statistical analysis of the data.

Additional Discussion

SMNA stated that they may have overcomplicated what they produced. They want to ensure they are correctly understanding FDA's thoughts on an appropriate study design. SMNA brought up the alternative of using a monadic approach, using multiple cells if they have several claims – one cell for each claim, along with one cell representing a control.

FDA stated that this experimental design is appropriate given that the critical question is the impact of a particular modified risk claim upon some outcome. FDA recommended that SMNA consider randomizing participants to conditions which could include a control (no claim) condition, and one (or more) claim conditions. Claim conditions would be compared to the control condition to assess the impact of each claim on understanding, perceptions, and intentions. It is important that at least some of the study's hypotheses involve comparing the responses of participants who saw a claim to those of participants who did not.

FDA also recommended that SMNA consider the tobacco use groups they intend to study. FDA noted that their applications are focused on a comparison between their products and cigarettes, so it would make sense to have a group of current cigarette smokers to examine as a subgroup, rather than a group of current users of multiple tobacco product types. SMNA expressed their concern in omitting things that would later be of benefit. SMNA stated that they want to be comprehensive and acknowledge re-initiation from former users and asked whether it would line up with the expectations or guidance from the MRTP perspective if they were to add in a cohort of former smokeless users, bearing in mind that their claims are comparing cigarette smoking to snus usage. SMNA stated that their groups would then include current and former cigarette users, current and former smokeless users, and never users of tobacco.

FDA understands this rationale but expressed the notion that it is not possible to study every possible combination. FDA stated that there is not a set criteria of what the "right" groups to study are; rather, they are looking for a justification of why these are the appropriate groups to examine. As FDA has laid out in the guidance, never and former users are of particular interest because it helps FDA understand the population as a whole. FDA expressed that SMNA's proposed incorporation of smokeless tobacco groups is reasonable. FDA noted that although SMNA may not intend to communicate information about the relative harms of this product compared to other smokeless products, this is a population of current tobacco users who may be more likely to use this product. FDA cautioned SMNA that as they incorporate additional user categories, they are increasing the scope and breadth of the study, so it is important to choose areas of focus and interest. FDA recommended articulating a case of why a given group is of interest; e.g., if one group is more likely to switch to SMNA's product.

SMNA brought up their plans to have a video and a pamphlet for additional messaging and inquired whether FDA would want to see both or one of these mediums tested. SMNA stated that the video and pamphlet messaging are designed to be as consistent as possible regarding the information contained. FDA asked a clarifying question to understand whether the video and pamphlet will be used in addition to making claims on the packages, and SMNA responded that the package claim was not adequate, so to maximize the message penetration, print and video media needs to be utilized as well.

FDA stated that ideally, they would like to see everything tested, as different media formats may differ and affect how claims are received; however, realistically, SMNA should examine the costs and benefits of inclusion of additional factors in the study. FDA recommended that SMNA consider simplifying the design and selecting one medium that would be representative of how their marketing plan would be implemented overall. FDA recommended SMNA consider limiting participants' exposure to one stimulus so that participants do not have to repeat all the questions multiple times, compromising the data quality. FDA recommended that SMNA provide a rationale for why the selected stimulus is a good representation of how they plan to use the modified risk claim in their marketing.

SMNA inquired if FDA acknowledges using market research panels as a customary way of conducting online research, or if they have any concerns regarding the use of panels.

FDA stated that the use of online panels is prevalent and that FDA wants to be able to understand where the participants come from, how they are sampled, what populations they represent, just as they would do in any other study where a study sample is recruited and used to learn about a larger population.

SMNA confirmed that they will speak with Kantar Health to ensure that panel information is provided.

FDA asked if SMNA understood FDA's written responses regarding how to treat the smokeless tobacco warning labels in their study. FDA recommended that for external validity, SMNA consider including all four of the warnings and rotate them randomly. SMNA responded that they understand and agree with the recommendation.

SMNA noted that in the preliminary response letter, FDA commented on the content of two of the intentions questions, namely, "interest in learning more about snus" and "interest in looking for it in a store". SMNA asked whether FDA sees value in studying consumer mindset.

FDA responded that they understand interest may lead to seeking out information about a product, which may lead to intention to use. However, ultimately, FDA prioritizes intention to use, as that is most proximal outcome to use behavior.

Question 2

Swedish Match has elected to utilize statistical experimental design to collect data and build analytical models that will calculate the impact of stimuli and product elements. We will utilize appropriate statistical analysis to identify the ability of stimuli to affect consumer perception on General Snus. Does CTP wish to comment on the usage of experimental design within this project?

FDA Response

We agree that an experimental design is appropriate in this situation because your research question concerns the impact of the proposed MRTP claims on people's perceptions, understanding, and intentions. An experimental design, wherein exposure of claims can be experimentally manipulated, with the inclusion of a control condition, provides data to examine the causal impact of the claims.

However, we have some questions and concerns regarding the particular approach you've proposed: the Full Profile Conjoint discrete choice design. This type of design is typically used to determine the relative importance of different attributes on consumer choice or product ratings. It is particularly useful for understanding the tradeoffs that consumers are willing to make among competing product attributes (e.g., a car's gas mileage, safety rating, spaciousness, and price). In this case, the attributes are the claims, warning label variants, flavors, and media formats. However, as part of your MRTPAs, it is unclear why you are testing the differential effects of the attributes other than the proposed claims. Testing the effects of each proposed claim makes sense; you may be considering several options for your claims, and this type of study could help you select or identify the best one(s). However, it is unclear why the study is evaluating the effects of the other attributes such as flavors and warning label variants. In any case, the study design does not appear to align with your research question related to your proposed modified risk claims.

Importantly, the study design appears to be over complicated for the intended purpose, which may have undesirable consequences. Of particular concern is the burden that this study will place on each participant, and the assumption that participants will be able to persist through multiple readministration of the survey questions. Specifically, participants will be shown four different ad exposures. After each exposure, participants will be asked a very large number of questions (up to approximately 90, it appears), and this will be repeated for each of the four advertising exposures. In addition, people will be asked questions prior to and following these sets of questions, further adding to the

respondent burden. You estimate that the survey will take approximately 30 minutes for never users and 45 minutes for all other users. In general, for surveys administered to an online panel, we could expect that data quality may be reduced because of respondent fatigue when the survey length exceeds approximately 20 minutes. This could be exacerbated when questions are repetitive. With these considerations in mind, consider simplifying the study design such that each participant would be asked a fewer number of questions.

At our last meeting for these MRTPAs on March 22, 2017 (TC0002213), we agreed that a study would become very complicated if you tried to evaluate whether the effect of the proposed claims vary based on every aspect of the products and ad design. Our goal at that meeting was to convey to you that we did *not* expect a study to examine all of the multiple factors and their independent effects. We did suggest that your study stimuli include all required warning label variants (i.e., to help ensure the study's external validity), and we suggested that your analyses could control for the warning label but did not have to separately examine and evaluate the impact of each warning label variant on study outcomes. Given the myriad potential combinations of products and ad features (i.e., SKUs differing in product quantity, form, and flavor; different ad design elements), it would be appropriate to select test stimuli that are representative of your proposed MRTPs and how they will actually be marketed, and to test the effects of the proposed claims in the context of those products and ad features. To that end, we suggested you consider describing your marketing plan and how the ads used as stimuli are in fact representative. You did not provide any explanation of the stimuli referenced here (pamphlet and video)—for instance, how they relate to the marketing plan or what they are; nor did you provide explanation for your selection of the two flavors.

In conclusion, we are unclear why you have chosen this design. From our perspective, the design may be unnecessarily complicated and may cause respondent fatigue and attrition. Exposing each participant to multiple ads with varying design elements and claims, in an effort to conduct a full profile conjoint study of various attributes (e.g., warning labels, flavors), may detract from the study's ability to answer the research question: to examine the impact of the proposed claims on intentions, perceptions, and understanding, and to understand if the impact varies depending on tobacco use status in such a way that authorizing the proposed claims will benefit population health. We believe this could be accomplished with a simpler design. In addition, some of the ambiguity regarding the relationship between your study objectives and study design may account for the confusion surrounding the study hypotheses; these study elements are all interrelated.

Additional Discussion

SMNA accepted FDA's response; discussion regarding study design is incorporated above.

Question 3

Does CTP have any concerns or comments regarding our intended approach to cognitively testing the survey instrument?

FDA Response

Your intention to perform cognitive testing of the survey instrument prior to data collection appears appropriate. We can only provide this general assessment based on the overview you provided about your plan. As noted above, the adequacy of any data submitted is a review issue. Note: In your protocol, you mention that cognitive testing would be used to validate your instrument. We want to clarify that cognitive testing is not a means for measure validation. Rather, as you state, the cognitive testing can inform your instrument refinement by identifying "any potential problems with how consumers understand, interpret, and answer each survey question"; and inform your message development by providing "input into the clarity, understandability, and interpretation of the stimuli" (p.19).

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 4

Does CTP consider this protocol to adequately address the topic of manipulation checks?

FDA Response

We consider a manipulation check an important element of an experimental study as it provides information regarding whether participants noticed the manipulation (i.e., whether they saw the MRTP claim). Such a check may be particularly useful in a study conducted online, given that participation does not take place in a controlled environment free from external distractions. From our review of your materials, the manipulation check entails all participants being exposed to two ads (held constant across participants and conditions)—using "holdout" cards—and then answering questions to determine if they correctly recall the two ads. This exercise precedes, and is separate from, the actual (target) stimuli exposure. This is not what we would consider a manipulation check. In contrast, the manipulation check we describe necessarily follows the stimulus exposure and entails a question or two to ascertain whether participants indeed viewed the ad

and/or noticed the claim (that is the subject of the subsequent outcomes measures). For instance, this might take the form of a question assessing recall of some aspect of the ad (or the claim itself). For instance, in the protocol, an item like this follows the exposure (C1); this kind of item, tailored for the target stimuli (per condition), could serve the purpose of a manipulation check.

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 5

Swedish Match utilized traditional statistical power analysis to identify appropriate sample sizes, taking perhaps a conservative approach in assuming two-tailed hypothesis testing (while pre-stated hypotheses tend to be one-tailed in nature). We have also included oversampling of respondents under age 25 and at or above the legal tobacco age in their respective states. Does CTP have any opinions regarding sample size and oversampling of high-risk populations?

FDA Response

The information provided on page 25 of the protocol may not be sufficient for us to assess the sample-size calculation in relation to the design and objectives of the proposed study. For example, what is the relation of the effect size = 0.02 to the objectives of the study; and why is this a conservative effect? Note also that the calculations seem to be more relevant to a continuous variable and you are proposing to conduct a statistical analysis based on a multinomial logistic regression approach. Thus, it is not clear how this information incorporates the complexities associated with the DCE into the calculation of sample size.

Calculation of sample size is based on criteria controlling Type I & II error, design and objectives of the study, and the statistical analysis of the data to be generated from the study. When describing any approach to sample size calculation, it is important to discuss it in relation to the design and objectives of the study: the primary variable to form the basis for sample size calculation, the test statistics, the null and alternative hypothesis, and Type 1 & II error. For example, when many hypotheses are to be tested, it is important to discuss why the sample size calculation provides sufficient power to confirm an effect associated with each of the hypotheses. When historical data is used to justify a particular sample size, it is important to discuss the relationship between the proposed study and the historical studies. For example, how do the design and objective of the historical studies relate to those of the proposed study?

It is important that the SAP include an in-depth discussion on sample size calculation, including the rationale for the choice of statistical procedure for calculation of sample- size and how the features of the design and objectives of

the study are incorporated into the sample size calculations. Note that if the features of a selected study design cannot be incorporated into a sample size calculation, then it is important to provide a rationale as to why a particular sample size is sufficient to provide valid statistical inference based on the design and objectives of the study.

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 6

Swedish Match has used cohort definitions driven by examples utilized in other government studies and academic literature. Examples of studies reviewed include PATH, NCI HINTS, and the Tobacco Use Supplement to the Census' population survey. Does CTP feel our cohort definitions align with the literature and its own considerations?

FDA Response

As noted above in response to Question 1, we suggest carefully considering the most appropriate populations of interest based on the stated objectives and hypotheses (see one potential method noted above to examine: current cigarette smokers, current smokeless tobacco users, former smokers, and never users of any tobacco product). In review of the populations of interest provided in the current study protocol, several questions remain as to (a) how the products used to define "tobacco/nicotine users" were selected and if there will be a sufficient sample size of users of various products (e.g., cigarettes), (b) how various thresholds for tobacco product use were determined, and (c) how you will avoid overlap between user groups based on the definitions provided.

First, "tobacco/nicotine users" are defined in the protocol as "cigarettes, e-cigarettes and/or other vaping devices, moist snuff, chewing tobacco, and snus." However, the study protocol lacks clear justification for the inclusion of these products, and a rationale for why you selected only a subset of tobacco products versus users of any tobacco product (e.g., cigars and hookah). Furthermore, it is unclear if you intend to recruit a sufficient sample size of users of each product type in order to test study hypotheses among sub-types of tobacco users (e.g., cigarette smokers). In order to assess the impact of the claims on different types of tobacco product users (i.e., cigarette smokers versus smokeless tobacco users) the study would need to be powered appropriately to understand how users of different products respond to the proposed claims. Note, if you decide to recruit users of specific products (as suggested above), we recommend maintaining a category of "never tobacco users" including never users of any product.

Second, although cut-points have been established in the scientific literature for cigarettes and smokeless tobacco products, currently there is not an established cut-point for a lifetime threshold for e-cigarette products. Therefore, a rationale should be provided for the selected lifetime threshold being used to distinguish never and former users of "e- cigarettes and/or vaping devices." Similarly, it is not clear based on the study protocol why a past 30 day use measure was selected to define current vs. former use—indeed, a measure of current use on "every day", "some days", or "not at all" is also assessed in the study questionnaire, but is only used in the definition of current tobacco/nicotine users and not applied in the context of never or former tobacco/nicotine users—which is a standard measure for distinguishing current vs. non-current adult tobacco users in national surveys.

Additionally, according to the cohort definitions provided in the study protocol, there appears to be areas of potential overlap whereby the cohorts would not be mutually exclusive. Specifically, to be designated as a "former tobacco/nicotine users" a respondent could report having ever used a product but not in the past 30 days; and in the "never tobacco/nicotine users" cohort a respondent could also have ever used a product (just not having met a lifetime threshold) and not used the product in the past 30 days. It is unclear based on the cohort definitions how these types of respondents would be distinguished.

Additional Discussion

SMNA stated that they strive to use existing literature and trusted sources (e.g., national surveys) to drive their operational definitions for user groups, and they asked FDA if they view any studies or surveillance systems as more or less beneficial to augmenting their approach.

FDA stated that while they think it's reasonable to use national surveys to help inform decisions about definitions and thresholds, there are no set recommendations for what definitions to use or not use; furthermore, FDA recommended that SMNA consider making decisions on appropriate measures based on the stated goals of the study and the populations of interest. FDA noted that definitions of tobacco use may vary across studies, and it is not always consistent across products.

SMNA noted that they use the measure of "every day," "some days," or "not at all" to assess current tobacco use. SMNA asked FDA if they have a specific way of defining when someone becomes a "former user."

FDA responded that this again depends on the fundamental question of interest and that it can be defined differently in different studies.

SMNA noted that they also could not find well-established definitions for e-cigarette use.

FDA responded that SMNA should articulate a justification for defining use or users in a certain way and how this relates to their hypotheses. FDA recommended building off work that has been done as well as considering how it relates to the specific context of the objectives and hypotheses of their study.

Question 7

Does CTP concur with the inclusion and exclusion criteria of the study?

FDA Response

Generally, the stated inclusion and exclusion criteria seem appropriate; however, it is unclear why an individual would be excluded for being aware of *General Snus*™. Unless you have a compelling reason for excluding people who are aware of *General Snus*™, we would recommend against doing so as it may make the population less representative of potential users. Furthermore, based on the study questionnaire those who decline to answer questions relating to demographic characteristics (i.e., gender, race/ethnicity, education) appear to be excluded from the study, yet this exclusion is not described in the summary of inclusion/exclusion criteria.

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 8

The protocol provides a section on strengths and limitations of the chosen research methods. Does CTP have any thoughts regarding the project strengths and limitations?

FDA Response

On several occasions throughout the protocol, you made reference to the Population Assessment of Tobacco and Heath (PATH) study and other national studies that utilize complex survey designs. However, it is not clear from the protocol what information from these population studies is being used to inform the design of the proposed study. The protocol discussed a probability sampling approach to the proposed study; however, the protocol does not include a description of a probability sampling strategy. Are you proposing to emulate the sampling design of the PATH study in your study? Or are you using the PATH study to fill quotas associated with the demographic characteristics? It is important to thoroughly discuss how external well-designed population surveys are being used in the design of your study.

The proposed study design is based on sampling participants from four panels; and therefore if a proper probability sampling strategy is implemented to sample participants, then it seems that the population to be the basis for statistical inference consists of members of the four panels. If you are planning to make statistical inference to the U.S. population, then it is important to discuss in the SAP how the proposed study design achieved that. For example, provide a rationale as to why a frame developed from these four panels provides the desired coverage in relation to the U.S. population.

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 9

Throughout the questionnaire, Swedish Match has used question formats and scales driven by examples utilized in other government studies and academic literature. Examples of studies reviewed include PATH, NCI HINTS, and the Tobacco Use Supplement to the Census' population survey. We have also made extensive use of the Juster Scale, a well-established scale particularly effective in measuring future behavioral intent. Does CTP wish to comment on any of our question or scale choices?

FDA Response

We appreciate your referencing existing federal surveys in the design of your own instrument. Based on the information you provided, below we provide several comments for your consideration on measures listed in the questionnaire:

- Perceived risk: It may be preferable to separate the "don't know" response option from the scale rather than adding it on the end of the scale. Also, the question about the health risks of using *General Snus*™ compared to various other products (C3) is complex. We acknowledge that this complexity may be unavoidable. However, we suggest that, during cognitive testing, you assess whether people accurately understand what the item is asking them to do and how to use the response scale to provide their rating.

- Behavioral intentions: Your use of the Juster Scale for measuring likelihood of future behaviors appears appropriate. We note that your Juster Scale includes percentage labels (e.g., 90%) in addition to the verbal labels (e.g., "Almost sure") and frequency labels (e.g., "[9 chances in 10]"). The Juster Scale that we have previously seen does not include the percentages. Rather, those are replaced with the integers 0-10. Unless you have data supporting the validity of replacing the integers with percentages, we suggest using the

integers, as typically used. Also, if you have data or prior analyses showing the validity of the Juster Scale in predicting rates of tobacco product purchase or use, provide them in your application. We also provide comments on the content of some of your Juster Scale items above in response to Question 1 (notes on hypotheses).

- Understanding: In response to Questions 1 and 12, we comment on the construct of understanding. Based on your hypotheses, it seems that you plan to assess understanding based on responses to the risk perception items (absolute, relative, or some combination?). As discussed below (Q12), it will likely also be useful to develop items tailored to the specific content of the MRTP claims you develop, in order to assess the extent to which participants understand that information in particular.

- Intention to quit using cigarettes and moist snuff: We are not familiar with the item you propose to use to assess intentions to quit (Item A4). An item that has shown initial validity in terms of scaling participants' future likelihood of attempting to quit smoking cigarettes is the Motivation to Stop Scale (MTSS; see doi: 10.1016/j.drugalcdep.2012.07.012).

- Extraneous items: Given the long length of the questionnaire, we encourage you to eliminate any items that you do not have plans to analyze. For example, potential candidates for elimination may be Items S7 (awareness of various tobacco product types) and A3a (interest in switching to a hypothetical less harmful product).

Additional comments or clarifying questions:

- It is unclear to us what purpose the following items serve: A10, B5, B6, and S14 (given that the cohort definitions are derived from S13 and S13a).

- S13 – Chantix is not a nicotine product; we suggest removing it from the question wording to avoid confusion.

- The following items may exceed the limits of what consumers can predict about their own future behavior: C5, C6, C6a, and C6b. In addition, the scale for 6a is confusing. If a scale like this is used, consider reordering items to progress from no use to increasing use.

- C13 – Suggest removing the introductory phrase "Based on the information you just reviewed about General Snus…" because it is leading; this question is not directly about the ad, therefore there does not appear to be a need to directly reference it.

- C16 – These items assess believability. Are we correct in assuming these items will be tailored to match the actual claims to which the participant is exposed? (Or is this a standalone to assess the believability of these claims, in particular?).

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 10

Does CTP feel that Swedish Match has adequately addressed the topic of pregnancy within the questionnaire? i.e. Do you see any need to further probe how pregnant women might utilize General Snus while pregnant?

FDA Response

The inclusion of S16 in the screener to ascertain information on pregnancy seems appropriate and sufficient for the purposes of this study. This question alone could be used to assess if there is a difference in propensity to use *General Snus*™ as well as risk perceptions of snus versus other tobacco products among women who are pregnant (or intend to become pregnant) compared to those who are not.

The addition of items C17-C19 may be unnecessary for the purpose of understanding if there are any differences in intentions for product use and perceptions of risk among pregnant women versus those who are not pregnant or trying to get pregnant; and moreover, may raise concerns with IRB review of the questionnaire (particularly item C19), which may imply that pregnant women should consider switching to *General Snus*™ instead of quitting.

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 11

Our baseline stimuli, still in development, will provide an objective yet comprehensive background on General Snus - its origin, product attributes, ingredients, etc. The study stimuli will then add in only the MRTP-related messaging and warnings, in order to provide a clean read of pre- vs. post-effect of the MRTP information. Does CTP agree with this approach?

FDA Response

Our understanding is that you intend to show the baseline stimuli (basically a primer on *General Snus*™) to all participants, across all conditions, prior to showing them the advertisements with or without MRTP information. We have concerns about this approach. You state that, by first showing people the baseline stimuli, the study will be able to provide a "clean read" of the effect of providing the MRTP information. Our concern with this approach is that, after viewing the baseline stimuli on *General Snus*™, participants in the study will no longer be representative of members of the U.S. population who would be exposed to your modified risk claims if your MRTPAs are authorized. Presumably, after viewing the baseline stimuli, participants will know more about the origin, product attributes, and ingredients of *General Snus*™ than they did when they began the study. We cannot predict how this would affect their perceptions or understanding of the modified risk information they view later, but presumably the baseline stimuli will indeed have some effect on participants. Thus, by including the baseline stimuli, we believe you would reduce the generalizability of the study results to the U.S. population, many of whom may not know about these aspects of *General Snus*™. For purposes of external validity, we suggest that the study participants should approximate the U.S. population in terms of their awareness and knowledge of *General Snus*™. In doing so, the results of the study may provide a more accurate understanding of how the proposed modified risk information would affect U.S. consumers. If you are interested in ensuring that people understand what snus is, we suggest considering adding a preamble that defines, for the purpose of the questionnaire, the product that will be the subject of subsequent questions (an approach used in other survey studies like the PATH Study).

Additional Discussion

SMNA accepted FDA's response; no discussion occurred.

Question 12

In the original General Snus MRTP application, Swedish Match did not meet CTP expectations with regard to measuring respondent ability to comprehend and interpret stimuli. Does CTP see this questionnaire as being adequate in that regard?

FDA Response

In your initial study, you assessed subjective understanding, asking participants how well they understood the information. We see that you've dropped this question from the questionnaire, and that appears appropriate. Objective III addresses consumer understanding. However, it is unclear from the information submitted, how exactly understanding is operationalized, including how it is

defined and measured. We note that several of the hypotheses include the word "understand" (i.e., hypotheses, 13-18).

Whereas the draft MRTPA Guidance names particular beliefs of interest that such a study might address (e.g., beliefs about the risk of the product compared to quitting tobacco all together), we note it is important that measures of understanding be tailored to address the specific claim you are requesting to use. That is, the study may include items to assess the degree to which participants understood the information conveyed by the modified risk claim itself. Because we do not yet know your claims, we cannot tell how well you are assessing the information they convey. However, from the information provided in the protocol, it is unclear if the study will adequately assess understanding. Thus, we suggest you consider the need to develop survey measures to assess understanding of the claims that you develop; and these will necessarily depend on the specific content of those claims. As you develop your assessment of understanding, here are some additional considerations:

You may want to use more than one type of measure, including items that can be scored as "correct" or "incorrect." These measures could include assessing:

- the extent to which participants understand the health risks that are reduced when using the product as intended;
- the extent to which they understand that other health risks are <u>not</u> reduced when using the product as intended; and
- the conditions of using the product that are required to achieve reduced risk.

We recommend you consider providing information that can speak to the validity of your measures of understanding—i.e., to demonstrate that participants who correctly answer the questions are doing so because they understand the modified risk information, rather than because they can guess the correct answer without even viewing the modified risk information. For example, this could involve: including a control group of participants who do not see the modified risk information, so that comprehension scores can be compared between groups to determine whether it was higher among people who saw the information; or pretesting the comprehension questions, including people who do not see the modified risk information, to assess variability in participant responses.

<u>Additional Discussion</u>

SMNA acknowledged that they did not adequately demonstrate consumer comprehension of the claim. They asked FDA if they could tailor questions to each claim and ask questions that are more like quiz questions. For example, one

claim would list the conditions for which there is a lower risk by using snus versus cigarettes; the hypothesis is that people in the test cell should be able to more accurately provide information than those in the control cell. SMNA wanted FDA to confirm if they have interpreted the feedback correctly.

FDA stated that SMNA's interpretation is correct and reflects the response FDA provided to Question #12. FDA did not want to suggest that the risk perception items should be replaced by the understanding items, but rather that the items are complementary.

SMNA concurred with FDA's statement and stated that during the qualitative work leading up to this, they attempted to differentiate between understanding, believing, and being motivated by something. SMNA suggested that first they want to know if participants at least understand the information, and then they will evaluate if participants believe what they are being told with risk perception information. SMNA stated they are not looking to eliminate or replace questions (e.g., the risk perception items).

FDA encouraged the use of cognitive testing and carefully designing measures for understanding. SMNA stated that the cognitive testing portion of this process is being taken very seriously.

SMNA stated that they will reevaluate the study design and variables and keep FDA's priorities in consideration when developing surveys.

Question 13

Are there any other sections of the questionnaire on which CTP wishes to comment?

FDA Response

In addition to the notes above (Question 9), below are additional comments and/or questions for your consideration related to the questionnaire:

- Length: With the current design, participants will repeat the full set of items in the conjoint exercise (Section C) four times (i.e., after each advertisement exposure). This raises concerns about the effects of multiple claim exposures. Also, as noted above, it may degrade data quality and cause attrition because of participant fatigue. We encourage you to consider these costs when deciding whether or not to proceed with your current study design.

- Debriefing: Consider stating explicitly: (a) there are no safe tobacco products; (b) the claims about products they have viewed (for those in experimental conditions) have not been authorized by the FDA, the agency that regulates tobacco products.

- In the section on Data Quality, your protocol states the following: "In addition, respondents with clearly inconsistent responses during the conjoint exercise will be removed and replaced from the main study." It is unclear what this means (how are "inconsistent responses" identified?). It is important to have a clear, justifiable rationale for any removal of participants.

Additional Discussion

SMNA explained that despite their best efforts to recruit participants who will be quality respondents, there are some people who will take the survey simply to receive compensation and will not take it seriously. SMNA refers to those people as "inconsistent respondents" and historically has removed or replaced them.

FDA suggested that since the data collection is web-based, SMNA could build in checks against inconsistent responses. FDA recommended that SMNA consider clearly articulating how they clean and analyze the data. FDA noted that there should be a pre-specified approach to dealing with those issues as they arise, and that additionally, the way SMNA develops the instrument could be improved to minimize the possibility of inconsistent responses.

ADDITIONAL FDA COMMENTS

Based on the discussion and feedback FDA provided during this meeting, as SMNA revises their protocol, if they choose to, they may submit a new meeting request in accordance with the Guidance, "Meetings with Industry and Investigators on the Research and Development of Tobacco Products."

V. ATTACHMENTS

Handouts/Presentations
No handouts/presentations were provided during the meeting.