



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
9200 Corporate Boulevard
Rockville MD 20850-3229

June 25, 2014

REC'D JUN 30 2014

R.J. Reynolds Tobacco Company
c/o RAI Services Company
Attention: James E. Swauger, Ph.D., DABT, Vice President – Regulatory Oversight
401 N. Main Street
Winston-Salem, NC 27102

Submission Tracking Number (STN): TC0001068

Dear Dr. Swauger:

Please refer to your meeting request to discuss your planned submission of a Modified Risk Tobacco Product Application (MRTPA) under section 911 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act).

A copy of the official minutes of the meeting, held on May 29, 2014, is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LTJG Khadar Diria, M.S., Regulatory Health Project Manager, at (240) 402-0094.

Sincerely,

Digitally signed by Conrad J. Choiniere -S
Date: 2014.06.25 09:15:08 -04'00'

Conrad J. Choiniere, Ph.D.
Director
Division of Population Health Science
Office of Science
Center for Tobacco Products

Enclosure: Meeting Minutes



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
9200 Corporate Boulevard
Rockville MD 20850-3229

Meeting Date and Time: May 29, 2014, 1:00 PM – 2:00 PM EST
Meeting Format: Face-to-face
Meeting Category: MRTTP
Submission Tracking Number: TC0001068
Applicant Name: RAI Services Company
Meeting Requestor: James E. Swauger
Product Name: N/A
Received Meeting Information Package March 20, 2014
Preliminary Comments Sent: May 27, 2014
Meeting Attendees:

FDA Attendees:

Antonio Paredes, M.S., Statistician, Office of Science (OS)
Benjamin Apelberg, Ph.D., Branch Chief, Epidemiology, OS
Cathy Backinger, Ph.D., Deputy Director for Research, OS
Cindy Tworek, Ph.D., Acting Branch Chief, Social Science, OS
Conrad Choiniere, Ph.D., Director, Division of Population Health Science, OS
Daryll Miller, M.A., Senior Regulatory Health Project Manager, OS
Dorothy West, M.P.H., Special Assistant to Office Director, OS
Gilberto Ramos, Consumer Safety Technician, OS
Glen Jones, Ph.D., Deputy Director, Regulatory Science, OS
Khadar Diria, M.S., Regulatory Health Project Manager, OS
Karen Somers, Ph.D., Director, Advisors and Consultant Staff; Acting Director, Division of Regulatory Project Management, OS
Kimberly Benson, Ph.D., Chief, Division of Nonclinical Science, OS
Matthew Holman, Ph.D., Director, Division of Product Science, OS

Applicant Attendees and Representatives:

Geoffrey Curtin, Ph.D., Senior Director, Regulatory Oversight
James Swauger, Ph.D., DABT, Vice-President, Regulatory Oversight
Michael Borgerding, Ph.D., Senior Director, RJRT Research and Development
Mitchell Neuhauser, Managing Counsel, Regulatory

1.0 BACKGROUND

On March 20, 2014, FDA received correspondence from RAIS requesting a meeting and based on the statement of purpose, objectives, and proposed agenda, FDA granted the meeting request.

This meeting was held to discuss RAIS's planned submission of a Modified Risk Tobacco Product Application (MRTPA) under section 911 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for all CAMEL SNUS Brand Styles. Specifically, the applicant plans to discuss the type of epidemiological study data necessary for successful filing of an MRTPA for all of the CAMEL SNUS brand styles, including requirements for pre-market demonstrations relative to

consumers' comprehension and perceptions of MRTP messaging materials; specific requirements for successful filing of an MRTPA with regard to Section 911(d)(1), Section 911(d)(4), Section 911(d)(5), and Section 911(g)(1) of the FD&C Act; and the scope of studies and data considered pivotal for evaluating an MRTPA under section 911(g)(1) of the FD&C Act.

On May 27, 2014, FDA provided preliminary draft responses to RAIS's questions posed in the meeting request correspondence received on March 20, 2014.

2.0 DISCUSSION

FDA has responded to RAIS's questions below under the subheadings "FDA Response." A summary of additional discussion that occurred during the meeting is captured under the subheading "Discussion During Meeting." The text outside of these subheadings consists of background explanation and questions from RAIS. FDA's use of this language should not be construed as FDA's adoption of or agreement with the text drafted by RAIS. The comments are not indicative of all the issues that may be identified if FDA reviewed the studies within the context of a complete submission of an MRTPA.

Industry Submitted Questions and FDA Response:

1. **RAIS intends to submit an application seeking a "risk modification order" distinguishing each of the CAMEL SNUS brand styles from combusted cigarettes currently for sale in the U.S. market. RAIS believes that the submission of an inter-category MRTP application is consistent with Section 911 of the Tobacco Control Act, as well as the Agency's current thinking on this issue. Does CTP Agree?**

FDA RESPONSE: FDA agrees that an "inter-category" comparison is consistent with Section 911 of the FD&C Act. However, FDA's assessment of whether it is appropriate to issue an order to allow the marketing of a product as an MRTP will depend on the type of comparisons proposed in the MRTPA, the strength of the evidence to support those comparisons, and the impact that those comparisons will likely have on consumer perceptions, comprehension, and behavior.

Discussion During Meeting:

RAIS Clarifying Question: Are "behaviors" appropriately addressed in terms of likelihood of use among current, former and never tobacco users determined by attractiveness studies?

FDA suggested that abuse liability or actual use studies could be used to assess behaviors related to using the products, particularly after being exposed to the modified risk marketing. RAIS stated that given these products are already in the market, they have been collecting data on behaviors using a number of surveys. One of the surveys includes information down to the brand and style level, so RAIS can study the questions about tobacco consumption behaviors among users in the U.S. RAIS stated that the information they have about consumption patterns will provide data about real-world product use that may not be gleaned from studies that focus on

attractiveness, perception, and behavioral intentions. RAIS stated that the surveys they conduct do not collect any information about perception of risk of their products.

2. **Per Section 911(g)(1) of the Tobacco Control Act and current draft guidance for industry (“Guidance for Industry: Modified Risk Tobacco Product Applications”, issued March 2012), issuance of a “risk modification order” requires that the applicant provide evidence to demonstrate that the product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, as well as 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.**

Accordingly, RAIS believes that epidemiological studies are necessary for the Agency to evaluate an application submitted under Section 911(g)(1) of the Act. Does CTP Agree?

FDA RESPONSE: There is currently no requirement for the submission of any particular types of studies in order for the Agency to evaluate an application submitted under Section 911(g)(1) of the FD&C Act (risk modification order). A range of scientific studies and analyses could be conducted for an MRTPA so that FDA can determine whether the criteria for issuance of an order under section 911(g) of the FD&C Act have been satisfied. We think that applicants seeking a risk modification order can submit human studies that show the product’s use will result in a significant reduction in harm and the risk of tobacco-related disease to individual tobacco users. Examples of such studies include observational epidemiological studies, such as cohort or case-control studies, or randomized clinical trials, in which tobacco users (such as smokers) are randomly assigned to switch to a potential MRTP or continue using their usual tobacco product to assess differences in the risk of clinical endpoints.

Discussion During Meeting:

RAIS Clarifying Question: What would FDA consider as suitable and appropriate clinical endpoints for assessing differences in current and potentially modified risk tobacco products?

FDA stated that, at present, FDA does not have a list of endpoints. FDA asked RAIS to provide, if they have any, scientific evidence of support for any endpoint that they select, such as biomarkers for disease risk that have been validated as an endpoint to show that harm is reduced.

3. **Assuming that epidemiological studies are necessary and based on the plain language of Section 911 of the Tobacco Control Act, RAIS does not believe that brand style-specific epidemiology is required to support an application seeking a “risk modification order” distinguishing each of the CAMEL SNUS brand styles from combusted cigarettes currently sold in the U.S. market. Does CTP agree?**

FDA RESPONSE: FDA agrees that it is not necessary for epidemiological studies used to support an MRTPA to focus solely on each specific, uniquely identified product that is the subject of the application. However, in applying this evidence to support an MRTPA for a specific product, you should provide evidence demonstrating how the product under study and the product that is the subject of the application are comparable in terms of characteristics that may influence disease risk. This may include, but is not limited to, differences in product design, product chemistry, package type and size, portion size, labeling, flavor, exposure to harmful and potentially harmful constituents (HPHC), and factors that may influence product use behavior.

Discussion During Meeting:

RAIS Clarifying Question: Would FDA intend that the potential influence of characteristics such as package size/type, portion size, labeling and flavor be addressed based on behavioral outcomes?

FDA recommended that RAIS provide as much evidence as possible to show that RAIS products are comparable to Swedish products in terms of risk factors. FDA asked RAIS to provide information regarding the product constituents that contribute to risk of disease. The applicant stated that the use patterns between RAIS products and Swedish products are similar in terms of daily exposure, epidemiology data, and toxicants. FDA asked the applicant to provide such data.

RAIS Clarifying Question: Please verify that evidence suggested by FDA “demonstrating how the product under study and the product that is the subject of the application are comparable in terms of characteristics that may influence disease risk” is limited to publically available information, as well as information available by inspection or testing of a product when the applicant is not the manufacturer of the product.

FDA confirmed RAIS’s understanding of the information FDA is suggesting be submitted. Such evidence includes the survey data that RAIS discussed earlier in the meeting.

4. **During the past several decades, snus product have replaced combusted cigarettes as the predominant form of tobacco used among Swedish tobacco users; during this same period, there has been a significant reduction in harm from tobacco-attributable disease among individual tobacco users, as well as a substantial benefit to the health of the population as a whole (*i.e.*, taking into account both users and non-users of tobacco products).**

RAIS believes that all of the CAMEL SNUS brand styles are low-nitrosamine, Swedish-style snus products. Furthermore, RAIS believes that the available Swedish epidemiological studies evaluating the risks for smoking and tobacco-related diseases are relevant and sufficient for the Agency to evaluate an

application submitted for all of the CAMEL SNUS brand styles under Section 911(g)(1) of the Act. Does CTP agree?

FDA RESPONSE: The sufficiency of any particular study or set of studies cannot be assessed outside of the context of a full application. However, the available Swedish epidemiological studies on the health risks of Swedish snus may be relevant to support an MRTPA for Camel Snus products, provided you submit evidence that demonstrates that your products are comparable to the products under study in terms of the characteristics that may influence disease risk. As discussed previously, this may include, but is not limited to, differences in product design, product chemistry, package type and size, portion size, labeling, flavor, exposure to HPHCs, and product use behaviors (e.g., amount and frequency of use).

Your submission should also demonstrate whether and how the findings from populations and locations outside of the U.S. may be applicable to the U.S. population. You should provide information regarding how you extrapolated the results of studies on Swedish snus products in Sweden, or other countries, to estimate the public health impact of the marketing of Camel Snus on the U.S. population. These impacts include, but are not limited to, individual health outcomes that occur in both intended and unintended consumers of the product, abuse liability, risk of dependence, likelihood of tobacco product use initiation (particularly among vulnerable populations, such as youth), likelihood of tobacco product use cessation, and likelihood of multiple tobacco product use. You should also provide an assessment of how those impacts may be influenced by cultural, environmental, legal, and institutional differences between the two countries.

Discussion During Meeting:

RAIS Clarifying Question: RAIS intends to provide information on Swedish-style snus use in Sweden, current use of CAMEL SNUS in the U.S. and likely use patterns for CAMEL SNUS as an MRTP; is FDA suggesting that additional information will be necessary to demonstrate relevance of the Swedish epidemiological studies?

FDA recommended that RAIS provide a study showing that Swedish style snus are similar to RAIS snus products in terms of use patterns among users in the U.S. and Sweden. In addition, FDA stated that RAIS should consider differences in product pricing, marketing strategies, and other differences when inferring impacts on the US population.

5. **RAIS believes that information on product design and composition (i.e., tobacco product type, tobacco curing practice and manufacturing process), as well as evidence from comparative HPHC chemistry and in vitro testing are appropriate and sufficient to demonstrate that all of the CAMEL SNUS brand styles are Swedish-style snus products consistent with the snus products currently sold in the Swedish and U.S. markets. Does CTP agree?**

FDA RESPONSE: The sufficiency of any particular study or set of studies cannot be assessed outside of the context of a full application. However, you should submit information about product design, composition, package type and size, portion size, and labeling in your application. You should also provide comparative HPHC and *in vitro* testing data. If you are seeking to compare your products to combusted tobacco products, then we recommend that you also submit the HPHC and *in vitro* testing data for combusted tobacco products. If you are planning to rely on epidemiological data for Swedish snus to support your application, then we recommend that you also submit the HPHC and *in vitro* testing data for Swedish snus products. This data would be beneficial for determining whether the epidemiological data for Swedish snus can be extrapolated to your snus products.

When addressing the toxicology of your product, the acceptability of any studies submitted in your application is ultimately a review decision. When using this information in order to support the assertion that the US-sold product is comparable to the Swedish-style product, product design, composition, HPHC levels, and *in vitro* toxicology studies could be appropriate. Publicly available literature could also be used to address any toxicological differences that may arise from differences in product design and composition.

Toxicology information can be informative and supportive of modified risk claims. Nonclinical studies should be capable and sensitive enough to address the endpoints being evaluated.

Discussion During Meeting:

RAIS Clarifying Question: Could FDA explain the inclusion of packaging, portion size and labeling for demonstrating products are comparable?

FDA stated that there may be differences in packaging between the U.S. and Swedish products that lead to differences in product constituents. In addition, there may be differences in portion size and labeling between the U.S. and Swedish products that lead to different perceptions and behaviors. RAIS should address these issues in their marketing application.

- 6. RAIS intends to submit a single MRTP application for the six (6) styles of CAMEL SNUS currently sold in the U.S. market. Comparative HPHC chemistry and *in vitro* biology will be conducted for all products concurrently. RAIS requests confirmation that a single MRTP application that includes all six brand styles of CAMEL SNUS is appropriate.**

FDA RESPONSE: Regarding the organization of your submission, we agree with your proposal for a single MRTP submission as described; however, the content should be clearly identified and delineated as pertaining or not pertaining to each uniquely identified snus product. We recommend that you provide a single, combined cover letter and table of contents, across all products; however, the content should be clearly identified and delineated as pertaining or not pertaining to each

uniquely identified snus product. We highly encourage you to create a sample of your single MRTP submission and provide it to us for feedback prior to submission.

Discussion During Meeting:

RAIS Clarifying Question: Would a “submission content plan” be appropriate for meaningful review and comment by FDA?

FDA suggested that RAIS submit a shell of the submission for review. FDA will conduct a review to determine the appropriateness of the submission content plan. In addition, FDA recommended that RAIS submit two versions of each application, one that is redacted for trade secrets or otherwise confidential commercial information and one that is not.

7. **Per current draft guidance for industry regarding MRTP applications, the Agency has identified the following as recommended pre-market demonstrations relative to consumer comprehension and perception:**
- a. **The ability of consumers to understand the modified risk claims and the significance of the information in the context of one’s health;**
 - b. **Consumers’ beliefs about the health risk of using the product relative to other tobacco products, including those within the same class of products;**
 - c. **Consumer beliefs about the health risks of using the product relative to cessation aids; and,**
 - d. **Consumer beliefs about the risks of using the product relative to quitting all tobacco.**

RAIS understands that (a) above is meant to address consumer comprehension of the modified risk claim/information, and that (b) thru (d) above are meant to address consumer perceptions/interpretations of that information. Does CTP agree?

FDA RESPONSE: We generally agree with the interpretation as outlined; however, understanding the inherent risk of tobacco products will itself relate in many ways to items (b) thru (d) and can subsequently help to inform our understanding of how consumers comprehend the modified risk claim/information. In addition to consumer beliefs about the relative risks and benefits of using the tobacco product, we recommend that the data and information you provide address consumer comprehension and perceptions and include information about consumer beliefs of the absolute risks associated with using the tobacco product, i.e., Camel Snus.

Discussion During Meeting:

RAIS Clarifying Question: RAIS intends to submit information on the four recommended outcomes; is FDA advocating that information be collected on the benefits of MRTP use beyond those specified within the risk messaging? Also, FDA recommends that consumer beliefs of “absolute risks” associated with using MRTP be provided; would such information be in the form of for example, “How likely do

you think it is that a regular user of CAMEL SNUS would get lung cancer? Does the nature of the question depend on the proposed risk messaging?

FDA stated that there is no single best way to collect information on consumer perceptions; however FDA cautions that the collection of information is not too narrowly focused on b, c, and d. The FD&C Act does not provide a specific definition of the term “context of total health” as used in Section 911(h)(1). FDA recommends that studies examine whether there are misconceptions about the products. In the context of tobacco use, comprehension could include an assessment of consumer beliefs related to the various health risks from the product and how those risks compare to risks from the use of other tobacco products.

RAIS requested further clarification about what are FDA’s definitions of absolute risk and the likelihood of a regular CAMEL SNUS user developing lung cancer. FDA stated that there is no single established method for getting this information and that an example could be merely asking respondents whether or not the product poses a risk of cancer.

RAIS asked whether FDA advocates that RAIS explore comprehension that “goes beyond messaging”, meaning comprehension or beliefs that may extend beyond the information provided in the marketing, such as switching products to reduce the risk. FDA recommended that these studies provide information on potential unintended consequences such as a “halo effect”, i.e., beliefs that the product may also reduce the risk of diseases not mentioned in the marketing information. FDA recommended that RAIS get some insight as to whether or not halo effects exist and to what extent. RAIS indicated that they are gathering data related to potential halo effects.

8. **RAIS understands that (a) above is similar in intent and design to OTC label comprehension and self-selection studies in that the desired outcome is consumer clarity with regard to the meaning of the modified risk claim and application of that information to self. Does CTP agree?**

FDA RESPONSE: FDA believes that studies similar in design to OTC label comprehension and self-selection studies could provide useful information to inform our understanding of whether and how consumers comprehend the modified risk information, as described in (a). We believe that you may need to draw on several measures of comprehension and perception to fully assess how consumers read, understand, and interpret information about modified risk used in proposed product labels, labeling, advertising and marketing. This could also include comprehension related to the modified risk claim in terms of risk perceptions and/or perceptions of harm for product use, switching, initiation, and cessation across populations of product users and potential users, which may extend beyond the scope of the typical label comprehension or self-selection study.

Discussion During Meeting:

RAIS asked for clarification on what does FDA mean by the phrase “perceptions and/or perceptions of harm from product use, switching, initiation and/or cessation”?

FDA recommended that RAIS study whether users get the impression that products are free of risk or whether they understand that the reduction in risk occurs if they completely switch from cigarettes to SNUS products.

9. RAIS understands (b) thru (d) above indicate that a “risk modification order” from CTP to market all of the CAMEL SNUS brand styles under Section 911(g)(1) of the Tobacco Control Act will be issued only if the following three conditions are met:
- i. consumers perceive/interpret that using cigarettes presents greater health risks than using CAMEL SNUS products;
 - ii. consumers perceive/interpret that using CAMEL SNUS products is NOT a safer alternative than using cessation aids; and,
 - iii. consumers perceive/interpret that using CAMEL SNUS products is NOT a safer alternative than quitting all tobacco.

Does CTP agree?

FDA RESPONSE: Items (i)-(iii) above are relevant to the statutory standard for granting a (g)(1) order. However, in the absence of a complete application, we cannot say that meeting these three conditions would be necessary or sufficient for finding that a (g)(1) order would be appropriate. Please refer to our responses to earlier questions regarding other information that we recommend you supply in your MRTPA with respect to consumer comprehension and perceptions.

Discussion During Meeting:

RAIS accepted FDA’s preliminary response and no additional discussion occurred.

10. RAIS understands that pre-market recommended demonstrations, *i.e.*, (a) thru (d) above, are CTP’s interpretations of the statutory comprehension- and perception-related, population-level requirements. As such, RAIS’s intended analyses among potentially vulnerable populations represent secondary (versus primary) endpoints that will be informative, but are not required, for comprehension- and perception-related demonstrations. Does CTP agree?

FDA RESPONSE:

FDA has concerns with this approach. Your MRTPA should include a discussion of populations who may be particularly likely to use the product. This discussion would be useful in assessing potential impacts and determining appropriateness of study sample, which could or could not include potentially vulnerable populations. You should justify the appropriateness of participant samples in each study and how these samples contribute to the overall understanding of potential effects in the population as a whole. We recommend that studies conducted to support an MRPTA consider the population as a whole and employ oversampling of populations that are particularly likely to be affected, positively or negatively, by the marketing of the product. As

such, there may be certain products for which the impact on vulnerable populations may represent primary endpoints. In order for FDA to assess the potential effects of the marketing of the MRTP on both users and non-users, applicants should provide scientific justifications for the appropriateness of participant samples selected for each study and how they contribute to the overall understanding of potential effects in the population as a whole.

Discussion During Meeting:

RAIS Clarifying Question: RAIS intends to examine comprehension and perceptions among the population as a whole, as well as among current, former, never, likely quitters and experimenters; would FDA suggest additional populations for examination?

FDA stated that this approach is reasonable. FDA recommended that RAIS identify populations that may be susceptible to the modified risk marketing information and address those populations in their applications.

- 11. As previously noted, RAIS intends to submit a single MRTP application for the six (6) styles of CAMEL SNUS currently sold in the U.S market. Furthermore, comprehension-and perception-related testing will be conducted for all six styles concurrently (i.e., as a brand family). RAIS requests confirmation that this approach is appropriate.**

FDA RESPONSE: FDA believes that it is appropriate to conduct the studies for all six styles (unique products) concurrently. However, there may be aspects of the unique products that could have impacts on consumer perceptions of the product, which could directly affect consumer comprehension of the modified risk information. When determining if an MRTP order should be issued, FDA must also consider "the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application." FDA believes that consumer perceptions of the product, including the associated risks to health, will inform our understanding of whether consumers are likely to use the product. Therefore, if differences exist between brand styles (e.g., different flavors, package type and size, portion size) that could influence consumer perceptions and comprehension, then FDA recommends that the studies be sufficiently powered to detect potential differences in comprehension and/or perception between the various unique products.

Discussion During Meeting:

RAIS Clarifying Question: Does survey data on current tobacco use behaviors showing no differences based on brand styles address the issue? In addition, RAIS asked whether it is appropriate to provide the data from their survey.

FDA stated that the question cannot be answered without knowing the extent of RAIS survey data. However, FDA indicated that the survey data on use of the snus should be submitted.

Per Section 911 of the Tobacco Control Act and current draft guidance for industry, FDA expects the applicant to include, as part of its submission of “relevant” documents, all study reports, study protocols and raw data (in electronic format, where available, with instructions about its use). If any of this information is not available, the Agency expects the applicant to provide an explanation for the omission. To that end:

- 12. RAIS seeks guidance regarding those studies that would be considered pivotal (versus non-pivotal) for the Agency to evaluate an application submitted under Section 911(g)(1) of the Tobacco Control Act.**

FDA RESPONSE: FDA has not identified any particular set of studies as being considered “pivotal” or “non-pivotal” for an MRTPA. FDA recommends that you provide all study reports, data, and research to support your MRTPA. Additionally, you should provide an explanation regarding the appropriateness and applicability of information regarding a snus and/or combusted cigarettes product in support of an MRTPA. If you submit information regarding snus and/or combusted cigarettes in support of an MRTPA for your proposed product, we recommend that you conduct bridging studies that compare the two products in order to assess the applicability and relevance of that information for the MRTPA. Note that for any findings you submit that are relevant to the health effects of your proposed modified risk tobacco product, Section 911(d)(5) requires you to submit all documents relating to those findings, as described in our general response above.

Discussion During Meeting:

RAIS Clarifying Question: What is the meaning of FDA’s statement, “if you submit information regarding snus and/or combusted cigarettes in support of an MRTPA for your proposed product, we recommend that you conduct bridging studies to compare the two products in order to assess the applicability and relevance of that information for the MRTPA”?

FDA stated that RAIS should provide evidence to demonstrate that RAIS products are similar to Swedish snus, in terms of ingredient and constituent reporting, toxicological data, and surveys that show similarities. RAIS may also consider providing a study showing similarities and differences in Swedish snus and Swedish cigarettes compared to American snus and American cigarettes.

- 13. RAIS currently holds the view that the chemistry, mutagenicity and cytotoxicity studies are pivotal studies for a CAMEL SNUS MRTP application submitted under Section 911(g)(1) of the Tobacco Control Act (refer to study protocols, Attachments A-C, respectively). In addition, RAIS believes that pre-market determinations of consumer comprehension and perception are pivotal studies for a CAMEL SNUS MRTP application submitted under Section 911(g)(1) of the Act. Lastly, RAIS believes that the available Swedish epidemiology studies providing information on the comparative risks associated with using snus**

and/or combusted cigarettes provide pivotal data for a CAMEL SNUS MRTTP application submitted under Section 911(g)(1) of the Act. As such, RAIS intends to provide, where available, study reports, study protocols and raw data (in electronic format with instructions about its use). RAIS requests confirmation that this approach is appropriate.

FDA RESPONSE: See response to question 12. RAIS should provide, where available, study reports, study protocols and raw data for all studies included in the MRTPA.

Discussion During Meeting:

RAIS accepted FDA's preliminary response and no additional discussion occurred.

14. RAIS believes that all other studies are non-pivotal studies for a CAMEL SNUS MRTTP application submitted under Section 911(g)(1) of the Tobacco Control Act. As such, RAIS intends to provide, where available, study reports and study protocols for such studies; and, does not intend to provide raw data (in electronic format, with instructions about its use) for non-pivotal studies. RAIS requests confirmation that this approach is appropriate.

FDA RESPONSE: See responses to questions 12 and 13.

Discussion During Meeting:

RAIS accepted FDA's preliminary response and no additional discussion occurred.

15. If CTP holds the view that raw data in electronic format is required for both pivotal and non-pivotal studies, RAIS seeks clarification regarding any potential differences in the requirements for raw data in electronic format when a study is pivotal (versus non-pivotal) for the Agency to evaluate an application submitted under Section 911(g)(1) of the Tobacco Control Act. For example, does CTP expect a data dictionary for each non-pivotal study if data dictionaries do not currently exist?

FDA RESPONSE: FDA recommends that your MRTTPA include raw data in electronic format. A well-constructed data dictionary is an essential component of any submission in electronic format; we recommend the use of a data dictionary otherwise referred to as the *define file*. Without data definitions it is not possible to fully understand and analyze or review your data. Each of the following references provides information on issues associated with data to be submitted in electronic format, including data standards, such as the Study Data Tabulation Model of the Clinical Data Interchange Standards Consortium, and the development of *define files*:

[Data Standard at the FDA](#)

[FDA Draft Guidance: Providing Regulatory Submissions in Electronic Format - Standardized Study Data](#)

[FDA Draft Guidance: Study Data Technical Conformance Guide](#)

FDA recommends that data in electronic format be submitted following data standards, including a well-constructed *define file*. These steps will enhance our ability to more fully understand and characterize the evidence provided by each of the studies. The recommended data file format is SAS open transport using the SAS xport engine (data.xpt). When a data dictionary or *define file* does not exist, we recommend that you construct one using the best available information on the design and conduct of each of the studies.

Discussion During Meeting:

RAIS Clarifying Question: RAIS indicated that they plan to submit eCTD-formatted applications. How should RAIS organize the applications? RAIS proposed that they organize the applications according to scientific discipline and type of studies, such as the following sections: chemistry, in vitro biology, in vivo biology, clinical studies, and population level studies. However, RAIS stated that there are no “buckets” in the FDA outline to guide where these documents should be placed, thus requested a general confirmation.

FDA clarified that this is an appropriate way to organize the relevant documents. RAIS stated that, during their earlier interaction with FDA, they were directed to provide all draft reports of their clinical studies. RAIS stated they will provide final reports and include hyperlinks to earlier drafts of the reports. FDA concurred with the proposed approach.

- 16. Per Section 911(d)(1) of the Tobacco Control Act, the applicant is required to include in their MRTP application a description of the product and any proposed advertising and labeling. RAIS requests clarification regarding inclusion of proposed direct mail and/or website communication in the MRTP application. Specifically, RAIS seeks clarification regarding the scope and form of the information that should be provided in the application; and, whether such information should be provided in the same section as any proposed print advertising that communicates modified risk messaging.**

FDA RESPONSE: FDA recommends that studies test the impact of the modified risk information as they are likely to be seen by consumers in the marketplace. We recommend that you include as stimuli in your studies any appropriate direct mail and/or website communication, as consumers would view these in the marketplace related to the product. FDA notes that the results of a comprehension and/or perception study could be influenced by the nature and location of the stimuli and how that is presented to consumers in the marketplace.

Discussion During Meeting:

RAIS Clarifying Question: RAIS recognizes that testing of print advertising, direct mail and website communication will require electronic presentation of all stimuli; is this consistent with CTP’s current thinking? RAIS further stated that online is the best way to do survey data by testing a large number of people and providing a series of questions about comprehension and perception of the products.

FDA agreed that online testing is a good way to obtain comprehension, qualitative, and quantitative data. FDA recommended that RAIS perform qualitative work, such as conducting interviews, to probe more deeply into respondent reactions and comprehension of marketing materials. FDA stated that RAIS can use this information to inform the development of a comprehension study to uncover areas of misconceptions.

3.0 ACTION ITEMS

None

4.0 ATTACHMENTS

- RAI Services Company's PowerPoint entitled "MRTP Application for CAMEL SNUS Brand Styles"
- Camel Snus brochures which RAIS provided during the meeting

FDA Center for Tobacco Products
Office of Science
May 29, 2014



Meeting Agenda

- Meeting objective/key meeting outcomes (10 min)
- Use of existing epidemiological studies to provide information on potential for significant reductions in individual harm and benefit to population as a whole (10 min)
- Expectations regarding studies/analyses intended to demonstrate that CAMEL SNUS brand styles are Swedish-style snus products (*i.e.* comparative HPHC chemistry *in vitro* testing) (15 min)
- Pre-market studies/analyses intended to provide information on consumer comprehension and perceptions (15 minutes)
- Submission of study reports, study protocols and raw data from pivotal *versus* non-pivotal studies [Section 911] (10 min)



Key Meeting Outcomes

RAIS seeks confirmation/clarification regarding

- type(s) of epidemiological study data necessary for successful filing of an MRTP application for CAMEL SNUS brand styles [Section 911(g)(1)];
- requirements for pre-market demonstrations relative to consumers' comprehension and perceptions of MRTP messaging materials;
- specific requirements for successful filing of an MRTP application [Sections 911(d)(1), 911(d)(4), 911(d)(5) and 911(g)(1)]; and,
- scope of studies and data considered pivotal for evaluating an MRTP application [Section 911(g)(1)].



Rationale for Risk Modification Order

[Question 1] RAIS believes that submission of an inter-category MRTP application is consistent with Section 911, as well as the Agency's current thinking

[FDA] "inter-category" comparison is consistent with Section 911; an order allowing marketing of a product as an MRTP will depend on:

- type of comparison proposed
- strength of evidence to support the comparison
- impact the comparison will likely have on consumer perceptions, comprehension and behaviors

[clarifying question: are "behaviors" appropriately addressed in terms of likelihoods of use among current, former and never tobacco users, e.g., attractiveness study?]



Rationale for Risk Modification Order

[Question C] RAIS intends to submit a single MRTP application for six (6) styles of CAMEL SNUS currently sold in the U.S. market. Comparative HPHC chemistry and *in vitro* biology will be conducted for all products. Concurrently, RAIS requests confirmation that a single MRTP application that includes six brand styles of CAMEL SNUS is appropriate.

[FDA] agree with the proposal for a single MRTP application (as described); however, content should be clearly identified/delineated as pertaining/not pertaining to each uniquely identified product; highly encourage submission of a sample of the single application for further discussion.

[clarifying question: would a "submission content plan" be appropriate for meaningful review and comment by FDA?]



Epidemiological Studies

[Question 2] RAIS believes epidemiological studies are necessary for the Agency to evaluate an application submitted under Section 911(g)(1)

[FDA] notes requirement for human studies showing use of product will result in significant reduction in individual harm and risk for tobacco-attributable disease

- observational epidemiological studies (i.e., cohort, case-control)
- randomized clinical trials examining differences in clinical endpoints

[clarifying question: what would FDA consider as suitable and appropriate clinical endpoints for assessing differences in current and potentially modified risk tobacco products?]



Epidemiological Studies

[Question 3] RAIS *does not* believe brand style-specific epidemiology is required to support application seeking "risk modification order" distinguishing each of the CAMEL SNUS brand styles from combusted cigarettes currently sold in U.S. market

[FDA] not necessary for epidemiological studies to focus solely on each specific, uniquely identified product; *however*, the product under study and the subject of the application must be shown to be comparable for characteristics that may influence disease risk

- product design, product chemistry, package size/type, portion size, labeling and flavor
- exposure to HPHCs
- factors that may influence product use behavior



Epidemiological Studies

[Question 3; FDA] . . . the product under study and the subject of the application must be shown to be comparable for characteristics that may influence disease risk

[clarifying question: would FDA intend that the potential influence of characteristics such as package size/type, portion size, labeling and flavor be addressed based on behavioral outcomes?

Also, RAIS requests verification that evidence suggested by FDA "demonstrating how the product under study and the product that is the subject of the application are comparable in terms of characteristics that may influence disease risk" is limited to publically available information, as well as information available by inspection or testing of a product when the applicant is not the manufacturer of the product]



Epidemiological Studies

[Question 4] RAIS believes the available Swedish epidemiological studies evaluating risks for smoking and tobacco-related diseases are relevant and sufficient for the Agency to evaluate an application submitted for CAMEL SNUS brand styles under Section 911(g)(1)

[FDA] Swedish epidemiological studies on the health risks of Swedish snus may be relevant to support MRTP for CAMEL SNUS, provided products are shown to be comparable in terms of characteristics that may influence disease risk; should also provide evidence that findings from outside populations are applicable to the U.S. population

- health outcomes of intended and unintended consumers
- abuse liability and risk of dependence
- likelihood of initiation, cessation and dual/poly use



Epidemiological Studies

[Question 4; FDA] Swedish epidemiological studies on the health risks of Swedish snus may be relevant to support MRTP for CAMEL SNUS, provided products are shown to be comparable in terms of characteristics that may influence disease risk; should also provide evidence that findings from outside populations are applicable to the U.S. population

- health outcomes of intended and unintended consumers
- abuse liability and risk of dependence
- likelihood of initiation, cessation and dual/poly use

[clarifying question: RAIS intends to provide information on Swedish-style snus use in Sweden, current use of CAMEL SNUS in the U.S., and likely use patterns for CAMEL SNUS as an MRTP; is FDA suggesting that additional information will be necessary to demonstrate relevance of the Swedish epidemiological studies?]



Epidemiological Studies

[Question 5] RAIS believes information on product design and composition (*i.e.* tobacco product type, tobacco curing practice and manufacturing process), as well as evidence from comparative HPHC chemistry and *in vitro* testing are appropriate and sufficient to demonstrate that CAMEL SNUS brand styles are Swedish-style snus products consistent with snus products currently sold in the Swedish and U.S. markets.

[FDA] should submit information on product design, composition, packaging, portion size and labeling; also, comparative HPHC and *in vitro* testing data (including combusted tobacco and Swedish snus products)

to support the assertion that the U.S. product is comparable to Swedish snus, product design, composition, HPHC levels and *in vitro* testing could be appropriate

[clarifying question: could FDA explain the inclusion of packaging, portion size and labeling for demonstrating products are comparable?]



Comprehension and Perceptions

[Question 7] The Agency has identified the following as recommended pre-market demonstrations relative to consumer comprehension and perception.

- a) ability of consumers to understand modified risk claims and significance of information in context of one's health
- b) consumers' beliefs about health risks of using product relative to other tobacco products, including those within same class of products
- c) consumer beliefs about health risks of using product relative to cessation aids
- d) consumer beliefs about risks of using product relative to quitting all tobacco

[FDA] agree with RAIS's interpretation that (a) meant to address comprehension of modified risk claim/information and (b)-(d) meant to address perceptions/interpretations of that information

recommend that information be provided on consumer beliefs of absolute risks associated with using MRTP (i.e., CAMEL SNUS)



Comprehension and Perceptions

[Question 7, FDA] agree with RAIS's interpretation that (a) meant to address comprehension of modified risk claim/information and (b)-(d) meant to address perceptions/interpretations of that information

recommend that information be provided on consumer beliefs of absolute risks associated with using MRTP (i.e., CAMEL SNUS)

[clarifying question: RAIS intends to submit information on the four recommended outcomes; is FDA advocating that information be collected on the benefits of MRTP use beyond those specified within the risk messaging?

Also, FDA recommends that consumer beliefs of "absolute risks" associated with using MRTP be provided; would such information be in the form of, for example, "How likely do you think it is that a regular user of CAMEL SNUS would get lung cancer? Does the nature of the question depend on the proposed risk messaging?]



Comprehension and Perceptions

[Question 8] RAIS understands (a) above is similar in intent and design to OTC label comprehension and self-selection studies in that the desired outcome is consumer clarity with regard to the meaning of the modified risk claim and that application of that information to self

[FDA] believes studies similar in design to OTC label comprehension and self-selection studies could provide useful information on consumer comprehension

may require several measures of comprehension/perception to fully assess how consumers read, understand and interpret information about modified risk used in the proposed MRTP advertising; could include comprehension of claim in terms of *risk perceptions and/or perceptions of harm from product use, switching, initiation and/or cessation*



Comprehension and Perceptions

[Question 9] RAIS understands (b) thru (d) above to indicate that a risk modification order from FDA to market CAMEL SNUS brand styles under Section 911(g)(1) will be issued only if following three conditions are met

- ✓ consumers perceive/interpret that using cigarettes presents greater health risks than using CAMEL SNUS products
- ✓ consumers perceive/interpret that using CAMEL SNUS products is NOT safer alternative than using cessation aids
- ✓ consumers perceive/interpret that using CAMEL SNUS products is NOT safer alternative than quitting all tobacco

[FDA] above conditions are relevant for granting an order, but may not be necessary or sufficient (refer to earlier responses to questions)



Comprehension and Perceptions

[Question 10] RAIS intends analyses among potentially vulnerable populations represent secondary (versus primary) endpoints that will be informative, but are not required, for comprehension- and perception-related demonstrations

[FDA] some concerns with this approach; should include discussion (scientific justification) of populations that may be particularly likely to use the product (may or may not include potentially vulnerable populations)

recommend studies consider the population as a whole and employ oversampling of populations that are likely to be affected, positively or negatively, by the marketing of the product; there may be certain products for which the impact on vulnerable populations represents a primary endpoint

[clarifying question: RAIS intends to examine comprehension and perceptions among the population as a whole, as well as among current, former, never, likely quitters and experimenters; would FDA suggest additional populations for examination?]



Comprehension and Perceptions

[Question 11] RAIS intends to submit single MRTP application for six (6) styles of CAMEL SNUS currently sold in U.S. market. Furthermore, comprehension- and perception-related testing will be conducted for all six styles concurrently (i.e., as a brand family)

[FDA] believes it appropriate to conduct studies for all unique products concurrently; however, there may be aspects of the unique products that could impact consumer comprehension and/or perceptions differently (e.g., flavors, package type and size, portion size)

believes that consumer perceptions of the product, including associated risks to health, will inform understanding of whether consumers are likely to use product

[clarifying question: would survey data on current tobacco use behaviors showing no differences based on brand styles address issue?]



Comprehension and Perceptions

[Question 16] RAIS requests clarification regarding inclusion of proposed direct mail and/or website communication in MRTP application. Specifically, RAIS seeks clarification regarding scope and form of information that should be provided in application; and, whether such information should be provided in same section as any proposed print advertising that communicates modified risk messaging

[FDA] recommends that studies test impact of risk messaging as they are likely to be seen by consumers in marketplace; and, that studies include stimuli for direct mail and/or website communication

believes that results of comprehension and/or perception study could be influenced by nature and location of stimuli and how it is presented to consumers

[clarification: RAIS recognizes that testing of print advertising, direct mail and website communication will require electronic presentation of all stimuli; is this consistent with CTP's current thinking?]



Data Reporting Requirements

[Question 12] RAIS seeks guidance regarding those studies that would be considered pivotal (versus non-pivotal) for the Agency to evaluate an application submitted under Section 911(g)(1).

[FDA] studies not identified as being considered "pivotal" or "non-pivotal" for MRTP application; recommends that all study reports, data and research to support MRTP application be provided, coupled with explanation regarding appropriateness/applicability of information in support of MRTP

for any findings submitted that are relevant to the health effects of the proposed MRTP, Section 911(d)(5) requires submission of all documents relating to those findings

[RAIS requests clarification regarding the meaning of FDA's statement, "If you submit information regarding snus and/or combusted cigarettes in support of an MRTPA for your proposed product, we recommend that you conduct bridging studies to compare the two products in order to assess the applicability and relevance of that information for the MRTPA."]



Data Reporting Requirements

[Question 13] RAIS currently holds the view that the chemistry, mutagenicity and cytotoxicity studies are pivotal studies for a CAMEL SNUS MRTP application submitted under Section 911(g)(1), that pre-market determinations of consumer comprehension and perception are pivotal studies, and that the available Swedish epidemiology studies providing information on the comparative risks associated with using snus and/or combusted cigarettes provide pivotal data. As such, RAIS intends to provide, where available, study reports, study protocols and raw data (in electronic format with instructions about its use). RAIS requests confirmation that this approach is appropriate.

[FDA] addressed in response to question 12; should provide, where applicable, study reports, study protocols and raw data for all studies included in the MRTP application.



Data Reporting Requirements

[Question 14] RAIS believes that all other studies are non-pivotal studies for a CAMEL SNUS MRTP application submitted under Section 911(g)(1). As such, RAIS intends to provide, where available, study reports and study protocols for such studies; and does not intend to provide raw data (in electronic format with instructions about its use) for non-pivotal studies. RAIS requests confirmation that this approach is appropriate.

[FDA] addressed in responses to questions 12 and 13.



Data Reporting Requirements

[Question 15] If FDA holds the view that raw data in electronic format is required for both pivotal and non-pivotal studies, RAIS seeks clarification regarding any potential differences in the requirements for raw data in electronic format when a study is pivotal (versus non-pivotal) for the Agency to evaluate an application submitted under Section 911(g)(1) of the Tobacco Control Act. For example, does FDA expect a data dictionary for each non-pivotal study if data dictionaries do not currently exist?

[FDA] recommends that application include raw data in electronic format, and that a well-constructed data dictionary (*i.e.*, "define file") is an essential component of any submission in electronic format

when a "define file" does not exist, recommend one be constructed using best available information on design and conduct of each of the studies

[RAIS has additional questions on health-related documents and draft reports in the context of an eCTD-focused application.]



SWAP
THE SMOKE FOR
MORE
FREEDOM
& **LESS**
RISK



SNUS

WARNING: Smokeless tobacco is addictive.

4 SIMPLE main INGREDIENTS

Regular Large

2 POUCH sizes
(actual size)

5 FLAVORS

15 POUCHES PER TIN

CUSTOMIZE YOUR ENJOYMENT WITH UP TO 30 minutes OF FLAVOR PER POUCH

WHAT IS camel snus?

Camel SNUS (rhymes with "moose") is finely ground premium tobacco in a soft fleece pouch.

HOW IS IT DIFFERENT?

Many smokeless tobacco products, like dip and chew, are fermented loose tobacco. Sure, they're smoke-free, but they can get messy and require spitting.

Snus is different. It's smoke-free, mess-free and spit-free. Camel SNUS is heat-treated, not fermented, and crafted with four main ingredients: tobacco, water, salt and flavoring.

HOW DO I USE IT?

- **Pop** open the tin.
- **Slide** the pouch under your upper lip.
- **Taste** the real, premium tobacco.

You'll know the flavor is on its way when you feel a slight tingling.

SNUS

WARNING: Smokeless tobacco is addictive.

I'm a smoker. WHY WOULD I SWITCH?

No smoke means...

- No hassle.
- No lingering smoke smell.
- More freedom.
- Fewer carcinogens.
- Less risk for you and those around you.

Switching completely to Camel SNUS greatly reduces your risk of serious disease.



DISCOVER MORE @ snusnation.com*

no smoke = LESS RISK



Scientific studies have shown that Camel SNUS contains fewer carcinogens than cigarette smoke.



Switching completely from cigarettes to Camel SNUS significantly reduces your risk for lung cancer, respiratory disease, coronary heart disease and oral cancer.



Camel SNUS is smoke-free, so there are no secondhand smoke risks for those around you.

No tobacco product is safe. If you're a smoker concerned about the health risks from smoking, the best choice is to quit. But if you're not going to quit using tobacco products, you should think about switching to Camel SNUS.

Minors and pregnant women should never use tobacco products, and adults who do not use or have quit using tobacco products should not start.

If you want to quit using tobacco products, a good place to begin is talking to a health care provider. There are many programs, products and other resources available to help tobacco consumers quit. Information on quitting is also available on the websites of the American Cancer Society, the American Lung Association and the American Heart Association.

*WEBSITE RESTRICTED TO AGE 21+ TOBACCO CONSUMERS

SNU

WARNING: Smokeless tobacco is addictive.

1

15 mess-free
POUCHES OF
FINELY GROUND
PREMIUM
TOBACCO PER
TIN

2

easy and
DISCREET TO USE:
POP OPEN THE TIN, SLIDE
THE POUCH UNDER YOUR
UPPER LIP AND TASTE
THE REAL, PREMIUM
TOBACCO

3

no
LINGERING
smoke
smell



4

SMOKE-FREE.
SPIT-FREE.
HASSLE-FREE.

5

no smoke
means LESS
RISK FOR YOU
and THOSE
AROUND YOU

DISCOVER MORE @ snusnation.com*

SNUS

*WEBSITE RESTRICTED TO AGE 21+ TOBACCO CONSUMERS

**WARNING: Smokeless
tobacco is addictive.**

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Richardson, TX 75083-4039

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MAILING LIST, P.O. BOX 834049, RICHARDSON, TX 75083-4049. OR CALL 1-800-665-6381

MAILING RESTRICTED TO AGE 21+ TOBACCO CONSUMERS

1



DISCOVER THE MANY
REASONS TO SWITCH
TO camel snus.

Camel

WARNING: This product
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TOBACCO PER
TIN

2

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THE POUCH UNDER YOUR
UPPER LIP AND TASTE
THE REAL, PREMIUM
TOBACCO

3

NO
LINGERING
SMOKE
SMELL

WARNING: This product is not a



4

SMOKE-FREE.
SPIT-FREE.
HASSLE-FREE.

5

no smoke
means LESS
RISK FOR YOU
AND THOSE
AROUND YOU

no smoke = LESS RISK



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a safe alternative to cigarettes.



DISCOVER MORE @ snusnation.com*

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SNUS

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WARNING: This product is not a safe alternative to cigarettes.

4 SIMPLE MAIN INGREDIENTS

Tobacco + Water + Salt + Flavoring

Regular Large

2 POUCH SIZES (actual size)

CUSTOMIZE YOUR ENJOYMENT WITH UP TO **30** minutes OF FLAVOR PER POUCH

5 FLAVORS

15 POUCHES PER TIN

SNUS

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