Camel Snus MRTP Application

Tobacco Products Scientific Advisory Committee
September 13-14, 2018
Introduction and Overview

Michael Ogden, PhD
Senior Vice President, Scientific & Regulatory Affairs
RAI Services Company
Benefits of Advertising Camel Snus as an MRTP

- Smokers who switch completely to Camel Snus can greatly reduce their risk for four smoking-related diseases:
  - Lung cancer
  - Oral cancer
  - Respiratory disease
  - Heart disease
- Authorization of the proposed modified risk advertising is highly likely to yield a net public health benefit
An Important Consideration

• There is no one-size-fits-all approach to dramatically reduce the harm from smoking
  – Different types of reduced-risk products appeal to different people

• Clearing the proposed MRTP advertising for Camel Snus is a scientifically sound step to reduce tobacco risk
Presentation Topics

• Camel Snus history, product development and design
• Proposed modified risk advertising
• Scientific evidence that individual health risk is reduced when smokers switch to Camel Snus
• Consumer studies showing the proposed advertising will promote beneficial behavioral changes in smokers
• Statistical modeling indicating the population as a whole will benefit from the resulting risk reductions
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<td>Introduction and Conclusions</td>
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<td><strong>Kristin Marano, MPH, PhD, CPH</strong></td>
<td>Epidemiology</td>
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<td><strong>Saul Shiffman, PhD</strong></td>
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<td>Senior Scientific Advisor, Pinney Associates</td>
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<td>Professor of Psychology, Psychiatry, Pharmaceutical Sciences and Clinical Translational Science, University of Pittsburgh</td>
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<td><strong>Geoffrey Curtin, PhD</strong></td>
<td>Population Health Benefit for Camel Snus with Modified Risk Advertising</td>
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<td>Senior Director, Scientific &amp; Regulatory Affairs, RAI Services Company</td>
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Consumers need accurate information about the relative risks of products to encourage them to migrate to less harmful products.
Camel Snus Product Design

- Camel Snus is a spitless, pouch, smokeless tobacco product
- Designed to have risk-reduction characteristics of Swedish snus
  - Made with low-toxicant tobaccos
  - Has same basic formulation
  - Flavors adapted for American palate using common smokeless tobacco and food ingredients

Each tin contains 15 pouches
Camel Snus Production Process and Styles

• Production Process
  – Low toxicant, finely milled tobaccos
  – Mixed with water, salt and heat-treated
  – Buffered with pH-stabilizing solution, further heat-treated
  – Humectants and flavors added
Camel Snus Production Process and Styles

- **Production Process**
  - Low toxicant, finely milled tobaccos
  - Mixed with water, salt and heat-treated
  - Buffered with pH-stabilizing solution, further heat-treated
  - Humectants and flavors added
Camel Snus MRTP Messaging Topline

- Only seeking authorization for the specific modified risk messages and layouts submitted to the FDA
- Presents adult smokers with accurate, easily understood comparative risk information
  - No change to current product label or government smokeless tobacco warnings
- Subject to post-market surveillance
Overview of Print Advertisement

- Three versions/advertising executions developed through iterative process
- Important to present clear, accurate scientific information using appealing language and graphics easily understood by smokers
- The three versions are very similar, but there are some important differences
Overview of Print Advertisement

WARNING: This product can cause mouth cancer.

WHAT IS CAMEL SNUS?
- Camel SNUS (packets with “snus”) is finely ground premium tobacco in a soft, resealable pouch.
- Like all tobacco products, Camel SNUS contains nicotine and is addictive.

HOW IS IT DIFFERENT?
- Many smokeless tobacco products, like dip and clove, are fermented loose tobacco.
- Their nicotine content is higher, and they can cause jaw and gum pain.
- How is it different? It’s snus-free, easier to use and less messy.
- Camel SNUS is heat-treated, not fermented, and coated with fine, food-grade ingredients - tobacco, water, salt, and flavoring.

HOW DO I USE IT?
- Slide a pouch under your upper lip.
- Taste the real, premium tobacco.
- Dispose of the pouch in the trash when you are finished.

WARNING: This product can cause mouth cancer.

WHAT IS CAMEL SNUS?
- Camel SNUS (packets with “snus”) is finely ground premium tobacco in a soft, resealable pouch.
- Like all tobacco products, Camel SNUS contains nicotine and is addictive.

NO SMOKE = LESS RISK
- Scientific studies have shown that Camel SNUS contains less of the harmful chemicals than cigarettes.
- Camel SNUS is smoke-free, so there are no secondhand smoke risks for those around you.

WARNING: This product can cause mouth cancer.

NO SMOKE = LESS RISK
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WARNING: This product can cause mouth cancer.
Camel Snus MRTP Messages – 1st Panel

Introduces opportunity for adult smokers to reduce risk

Note cigarette crushed by snus tin

Maintains government warning

WARNING: This product can cause mouth cancer.
Camel Snus MRTP Messages – 2\textsuperscript{nd} Panel

- Describes product and use
- Emphasizes that Camel Snus ‘contains nicotine’ and ‘is addictive’
- Describes ingredients, sizes, flavors, quantity, and use duration

\textbf{WARNING:} This product can cause mouth cancer.
Key modified risk statement (variations among executions)

Additional benefits of switching

Balancing information

WARNING: This product can cause mouth cancer.
Camel Snus MRTP Messages – 3rd Panel

**NO SMOKE = LESS RISK**

- Smokers who switch completely from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.
- Scientific studies have shown that Camel SNUS contains less of the harmful chemicals than cigarette smoke.
- Camel SNUS is smoke-free, so there are no secondhand smoke risks for those around you.

**NO TOBACCO PRODUCT IS SAFE**

- Like all tobacco products, Camel SNUS contains nicotine and is addictive.
- Adults who do not use or have quit using tobacco products should not start.
- Minors and pregnant women should never use tobacco products.
- If you’re a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider.
- But if you’re not planning to quit using tobacco products, you should think about switching to Camel SNUS.

**WARNING:** This product can cause mouth cancer.
Variations in Key Modified Risk Statement – 3rd Panel

key modified risk statement (variations among executions)

‘Less harmful chemicals’

‘Smoke-free’ statement
**Variations in Key Modified Risk Statement – 3rd Panel**

**Execution 1**

Smokers who switch completely from cigarettes to Camel SNUS can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.

**Execution 2**

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer, oral cancer, respiratory disease and heart disease.

**Execution 3**

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease.
Camel Snus MRTP Messages – 3rd Panel

I’M A SMOKER. WHY SHOULD I SWITCH?

Switching to SNUS means...

- Less of the harmful chemicals found in cigarette smoke
- Less risk for you and those around you
- No lingering smoke smell
- Hassle-free tobacco

WARNING: This product can cause mouth cancer.
Camel Snus MRTP Messages – 3rd Panel

NO SMOKE = LESS RISK

Smokers who switch completely from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.

Scientific studies have shown that Camel SNUS contains less of the harmful chemicals than cigarette smoke.

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

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- If you’re a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider.
- But if you’re not going to quit using tobacco products, you should think about switching to Camel SNUS.

WARNING: This product can cause mouth cancer.
MRTP Advertising for Camel Snus

WARNING: This product can cause mouth cancer.
Epidemiology

Kristin Marano, MPH, PhD, CPH
Director, Scientific & Regulatory Affairs
RAI Services Company
Smokers who Switch Completely to Camel Snus Can Reduce Risk

• For smokers who switch completely, Camel Snus reduces risk:
  – Lung cancer
  – Oral cancer
  – Respiratory disease
  – Heart disease
Epidemiology Confirms Significant Risk Reductions Compared to Smoking

- Epidemiology is a scientific tool for assessing associations between exposure and disease risk
- Considerable epidemiological data exists regarding smokeless tobacco
- Scientific consensus that smokeless tobacco use presents significantly lower risks than cigarette smoking
- Data from U.S. and Sweden demonstrate lower risks for these four diseases
Smokeless tobacco use presents less risk of lung cancer, oral cancer, respiratory disease, and heart disease.
Two Large Cohorts

• U.S. Cancer Prevention Study II (CPS-II)
  – American Cancer Society
  – Over 500,000 males
  – Enrollment and follow-up
    • 1982-1988 (smokers); 1982-2000 (smokeless tobacco users); 1982-2002 (switchers)

• Swedish Construction Workers Cohort
  – Over 250,000 males
  – Enrollment and follow-up
    • 1969-1992
### U.S. Epidemiology Data Confirm Significant Reductions in Risks for All Four Diseases

#### Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II

<table>
<thead>
<tr>
<th>Disease</th>
<th>Smokers</th>
<th>Switchers</th>
<th>Smokeless Tobacco Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>23.3</td>
<td>2.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Oral Cancer</td>
<td>NR</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>10.9</td>
<td>3.2</td>
<td>10.6</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>10.9</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

- Solid bars = statistically significantly different versus never users of tobacco
- Open bars = not statistically significantly different versus never users of tobacco

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005
NR=Not Reported

Dashed line represents hazard ratio=1.0
U.S. Epidemiology Data Confirm a Significant Reduction in Risk for Lung Cancer

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II

- The risk for smokers is more than 20 times the risk for never users
- The risk for switchers is one fourth that of smokers
- The risk for smokeless tobacco users is one tenth that of smokers

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

Dashed line represents hazard ratio=1.0

Solid bars = statistically significantly different versus never users of tobacco
U.S. Epidemiology Data Confirm a Significant Reduction in Risk for Oral Cancer

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II

- Smokers
- Switchers
- Smokeless Tobacco Users

Hazard Ratio

0.0 1.0 5.0 10.0 15.0

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005
NR=Not Reported
Dashed line represents hazard ratio=1.0

“Epidemiologic studies of smokeless tobacco indicate that it increases the risk of oral cavity… [cancer], at least for some forms of smokeless tobacco. The associated risks … are less than the risk … from smoking.”
– US Surgeon General, 2014

- The risk for smokers is more than 10 times the risk for never users
- The risk for smokeless tobacco users is not different from never users
Swedish Epidemiology Data Confirm a Significant Reduction in Risk for Oral Cancer Including Switchers

Odds of Oral Cancer, Case-Control Study, Sweden
1980-1989, 354 incident cases

- The risk for switchers is ~half that of smokers
- The risk for snus users is ~half that smokers

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

CC-32
The risk for smokers is more than 10 times the risk for never users.
The risk for switchers is a third of that of smokers.
The risk for smokeless tobacco users is not different from never users.

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005
Dashed line represents hazard ratio=1.0

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco
U.S. Epidemiology Data Confirm a Significant Reduction in Risk for Coronary Heart Disease

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II

- The risk for smokers is ~3 times the risk for never users
- The risk for smokeless tobacco users is ~half that of smokers
- The risk for switchers is ~half that of smokers

Solid bars = statistically significantly different versus never users of tobacco

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005
Dashed line represents hazard ratio=1.0

CC-34
U.S. Epidemiology Data Confirm Significant Reductions in Risks for All Four Diseases

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II

<table>
<thead>
<tr>
<th>Disease</th>
<th>Smokers</th>
<th>Switchers</th>
<th>Smokeless Tobacco Users</th>
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<td>10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>2.8</td>
<td></td>
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</tbody>
</table>

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005
NR=Not Reported
Dashed line represents hazard ratio=1.0
Swedish Epidemiology Data Confirm Significant Reductions in Risks for Lung Cancer and Oral Cancer

Swedish Construction Workers

Smoking versus Snus Risk
~10x higher

Smoking versus Snus Risk
~3x higher

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

Luo et al. 2007
Swedish Epidemiology Data Confirm Significant Reductions in Risks for Respiratory Disease and Heart Disease

Swedish Construction Workers

- Smoking versus Snus Risk ~4x higher
- Smoking versus Snus Risk ~2x higher

Risk

- Respiratory Symptoms: Smokers 6.2, Snus Users 1.4
- Ischemic Heart Disease (Mortality): Smokers 3.3, Snus Users 2.0

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

Bolinder et al. 1992
Bolinder et al. 1994
U.S. and Swedish Epidemiology Data are Relevant to Camel Snus

- Lower exposure with Camel Snus than the smokeless tobacco products used during the epidemiology studies
  - Toxicants
  - Consumption
Corrected: Camel Snus Has Lower Levels of TSNAs than U.S. Smokeless Tobacco Products Used in Epidemiology Studies

Camel Snus has significantly lower TSNAs than historical U.S. smokeless tobacco products.


U.S. smokeless data from Djordjevic et al. 1993

NR=Not Reported

CC-39
Camel Snus has significantly lower TSNAs than historical Swedish snus products.


Swedish snus data from Österdahl et al. 2004
## Usage of Camel Snus is Less than Historical Usage of U.S. Smokeless Tobacco Products

<table>
<thead>
<tr>
<th></th>
<th>Camel Snus&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Historical U.S. Smokeless Tobacco Products&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td><strong>Average amount used/day</strong></td>
<td>3 – 5 g</td>
<td>7 – 20 g</td>
</tr>
</tbody>
</table>

U.S. Epidemiology Data Confirm Significant Reductions in Risks for All Four Diseases

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II

- **Lung Cancer**: Hazard Ratio 23.3
- **Oral Cancer**: Hazard Ratio 10.9
- **Chronic Obstructive Pulmonary Disease**: Hazard Ratio 10.6
- **Coronary Heart Disease**: Hazard Ratio 2.8

Smokers who switch completely from cigarettes to Camel Snus can greatly reduce their risks for lung cancer, oral cancer, respiratory disease, and heart disease.

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005
NR=Not Reported
Dashed line represents hazard ratio=1.0

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco
Clinical and Preclinical Research

Elaine Round, PhD
Senior Director, Scientific & Regulatory Affairs
RAI Services Company
Clinical and Preclinical Studies Fully Support the MRTP Advertising

- Clinical studies examined human use and exposure
- Preclinical studies compared Camel Snus to cigarettes
  - Cytotoxicity (lung cancer, oral cancer, respiratory disease, heart disease)
  - Mutagenicity (lung cancer, oral cancer)
  - Genotoxicity (lung cancer, oral cancer)
  - Animal studies (assess short and long-term effects for all four diseases)
- The entire body of clinical and preclinical evidence
  - Consistent with the epidemiological conclusions
  - Supports reduced health risks from Camel Snus compared to smoking
Several Clinical Trials Studied Camel Snus

- Eight RJRT studies with varying endpoint combinations
- Five additional published studies
- **Endpoints included:**
  - Product use
  - Nicotine pharmacokinetics
  - Mouth-level exposure
  - Biomarkers

Biomarkers, Not Chemistry, Provide Definitive Information about Exposure to Toxicants

- **Biomarkers**
  - **Measure**
    - Actual exposure to HPHCs, accounting for HPHC content
  - **Integrate**
    - Product chemistry
    - Product use
      - Amount used per day
      - Time used per day
      - Route of exposure
Increases in Product Content Do Not Translate Into Increased Exposure – Nicotine

*Values cited from FDA Briefing Document*
Increases in Product Content Do Not Translate Into Increased Exposure – Nicotine

*Values cited from FDA Briefing Document

CC-48
Comparison of Natural Adopters of Camel Snus to Exclusive Smokers

- Relevant natural adopter study groups
  - Cigarettes only, N=60
  - Camel Snus only, N=50
  - Non-tobacco users, N=59
Carcinogens: Camel Snus Use Results in Lower Exposure, Generally Similar to No Tobacco Use

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Carcinogens: Camel Snus Use Results in Lower Exposure, Generally Similar to No Tobacco Use

Solid bars = statistically significant difference versus smoking
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Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Generated during combustion
Carcinogens: Camel Snus Use Results in Lower Exposure, Generally Similar to No Tobacco Use.

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Present in tobacco

Generated during combustion
Carcinogens: Camel Snus Use Results in Lower Exposure, Generally Similar to No Tobacco Use

- 4-aminobiphenyl
- 2-aminonaphthalene
- o-tolidine
- Naphthalene
- Acrylamide
- Crotonaldehyde
- Benzene
- 1,3-butadiene
- Mutagens
- NNN
- NNK

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Respiratory Toxicants: Camel Snus Use Results in Lower Exposure, Similar to No Tobacco Use

- Naphthalene
- Acrolein
- 1,3-butadiene
- Hydrogen Cyanide

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Cardiovascular Toxicants: Camel Snus Use Results in Lower Exposure, Similar to No Tobacco Use

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Cardiovascular Toxicants: Camel Snus Use Results in Lower Exposure, Similar to No Tobacco Use

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Comparison of Natural Adopters of Camel Snus to Exclusive Smokers and Users of Camel Snus and Cigarettes

- **Natural adopter relevant study groups**
  - Cigarettes, N=60
  - Camel Snus only, N=50
  - Non-tobacco users, N=59
  - Cigarettes and Camel Snus, N=50
Carcinogens: Dual Use of Camel Snus and Cigarettes Does Not Increase Exposure

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Carcinogens: Dual Use of Camel Snus and Cigarettes Does Not Increase Exposure

- Solid bars = statistically significant difference versus smoking
- Open bars = no statistically significant difference versus smoking

Generated during combustion

Present in tobacco
Clinical Biomarker Results Show Reduced Toxicant Exposure When Cigarette Smokers Switch to Camel Snus

- Participants resided in clinic for the duration of 1-week study
  - Baseline smoking – 2 days
  - Product switch – 5 days
- Smokers were switched completely from cigarettes to:
  - Exclusive Camel Snus use, N=30
  - Abstinence from all tobacco and nicotine products, N=25
Carcinogens: Camel Snus Use Decreases Exposure, Similar to Abstinence

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Carcinogens: Camel Snus Use Decreases Exposure, Similar to Abstinence

Solid bars = statistically significant difference versus smoking
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Generated during combustion
Present in tobacco
Respiratory Toxicants: Camel Snus Use Decreases Exposure, Similar to Abstinence

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Naphthalene  Acrolein  Acrylonitrile  Ethylene Oxide  1,3-butadiene  Hydrogen Cyanide
Cardiovascular Toxicants: Camel Snus Use Decreases Exposure, Similar to Abstinence

Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking
Exclusive Camel Snus use exposes individuals to significantly lower levels of carcinogens, respiratory toxicants, and cardiovascular toxicants than cigarettes.
## All Preclinical Study Results Support Proposed MRTP Advertising

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Camel Snus</th>
<th>Cigarette Smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subchronic animal studies</strong></td>
<td>No toxicity</td>
<td>Histopathologic and inflammatory respiratory changes&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Chronic animal studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>No toxicity</td>
<td>Epidermal tumors&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 year</td>
<td>No tumors</td>
<td></td>
</tr>
<tr>
<td><strong>in vitro cytotoxicity</strong></td>
<td>Substantial reduction</td>
<td>Significant cytotoxicity</td>
</tr>
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<td><strong>in vitro genotoxicity</strong></td>
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1. Historical data; literature review
## Camel Snus Does Not Manifest Systemic or Organ-Specific Toxicity or Carcinogenicity in Rodent Studies

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<thead>
<tr>
<th>Rodent Studies</th>
<th>Camel Snus</th>
<th>Cigarette Smoke</th>
</tr>
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<tbody>
<tr>
<td>Subchronic (90-day)</td>
<td><strong>No significant</strong> organ or system toxicity</td>
<td><strong>Significant</strong> histopathologic and inflammatory respiratory changes¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>1 year <strong>No significant</strong> toxicity</td>
<td><strong>Significant</strong> malignant epidermal tumors¹</td>
</tr>
<tr>
<td></td>
<td>2 year <strong>No significant</strong> tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>occurrences due to snus</td>
<td></td>
</tr>
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1. Historical data; literature review
Camel Snus Extracts Are Less Cytotoxic than Cigarette Smoke

Mammalian Cell Assay for Cytotoxicity: Neutral Red Assay

Reduction in cytotoxicity observed for Camel Snus relative to commercial cigarette comparators, normalized per mg of nicotine

RJRT Study Data
Camel Snus Extracts are Less Mutagenic than Cigarette Smoke

Bacterial Cell Assays for DNA Damage at the Gene Level: Ames Assay (Mutagenicity)

- Camel Snus (all 6 variants)
- Cigarettes (2 brands, 2 smoking regimens)

![Graph showing the comparison between Camel Snus and Cigarettes in terms of mutagenicity. The x-axis represents Nicotine (mg)/Plate, while the y-axis represents Mean Revertants/Plate. The graph indicates that Camel Snus extracts are less mutagenic than cigarette smoke.](image-url)
All Preclinical Study Results Support Proposed MRTP Advertising

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<tr>
<td>2 year</td>
<td>No tumors</td>
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<tr>
<td><em>in vitro</em> cytotoxicity</td>
<td>Substantial reduction</td>
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<tr>
<td><em>in vitro</em> genotoxicity</td>
<td>Substantial reduction</td>
<td>Significant genotoxicity</td>
</tr>
</tbody>
</table>

1. Historical data; literature review
Clinical and Preclinical Results are Consistent with the Epidemiology

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II

<table>
<thead>
<tr>
<th>Disease</th>
<th>Smokers 1</th>
<th>Switchers 2</th>
<th>Smokeless Tobacco Users 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>Hazard Ratio</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td>Oral Cancer</td>
<td>10.9</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>3.2</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>2.8</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

Smokers who switch completely from cigarettes to Camel Snus can greatly reduce their risks for lung cancer, oral cancer, respiratory disease, and heart disease.

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005
NR = Not Reported
Dashed line represents hazard ratio = 1.0

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco
Risk Perceptions, Comprehension, and Likelihood of Use

Saul Shiffman, PhD
Senior Scientific Advisor, Pinney Associates, Inc.
Professor of Psychology, Psychiatry, Pharmaceutical Sciences & Clinical Translational Science, University of Pittsburgh
Disclosure

Through Pinney Associates, Dr. Shiffman consults on tobacco cessation and harm reduction products to RAI Services Company and other subsidiaries of Reynolds American, Inc. and British American Tobacco
Behavioral Research

- Risk perceptions
- Message comprehension
- Likelihood of use
WARNING: This product can cause mouth cancer.
Three Executions: Variations in Key Modified Risk Text

Execution 1

Smokers who switch completely from cigarettes to Camel SNUS can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.

Execution 2

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer, oral cancer, respiratory disease and heart disease.

Execution 3

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease.
Research Questions for Population Testing

- Do people viewing the advertising understand that switching to Camel Snus carries less risk than smoking, but still has risk?
Do you think that some smokeless tobacco products, such as chewing tobacco, snus, and snuff are less harmful to a person’s health than cigarettes?

- **Yes**: 10.9%
- **No**: 66.8%
- **Don’t know**: 22.2%
Study to Assess Risk Perceptions and Comprehension of Balancing Information

• **Sample:** 4,924 adults from online research panels
  – 3 equal strata: current, former, never tobacco users
  – Diverse sample, balanced and weighted to U.S. population

• **Viewed Camel Snus modified risk advertisement**
  – 4 statutory smokeless tobacco warnings rotated randomly

• **Assessment**
  – Online quantitative assessment
  – Absolute and relative risk perceptions; Camel Snus vs. cigarettes
  – Comprehension of balancing information regarding Camel Snus
Indirect and Direct Comparisons¹ of Risk: Snus vs. Cigarette Smoking

• **Indirect comparison: Camel Snus and cigarette smoking each rated independently**
  – Assessed for each disease in modified risk advertisement
    • Absolute risk on 1-7 scale (‘no risk’ to ‘substantial risk’)
    • Compare numerically

• **Direct comparison: Camel Snus relative to cigarette smoking**
  – Assessed for each disease in modified risk advertisement

<table>
<thead>
<tr>
<th>No Risk</th>
<th>Substantial Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>●</td>
</tr>
<tr>
<td>2</td>
<td>●</td>
</tr>
<tr>
<td>3</td>
<td>●</td>
</tr>
<tr>
<td>4</td>
<td>●</td>
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<tr>
<td>5</td>
<td>●</td>
</tr>
<tr>
<td>6</td>
<td>●</td>
</tr>
<tr>
<td>7</td>
<td>●</td>
</tr>
</tbody>
</table>

---

Camel SNUS has...

<table>
<thead>
<tr>
<th>Same level of health risk as continuing to smoke</th>
<th>Less health risk than continuing to smoke, but has some risk</th>
<th>No health risk at all</th>
<th>I don’t know/not sure</th>
</tr>
</thead>
<tbody>
<tr>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

¹. e.g., Persoskie A, Nguyen AB, Kaufman AR, Tworek C. *Addict Behav* 2017;67:100-105.
People Understand that Cigarette Smoking Carries Substantial Risk

- Risk of oral cancer
- Risk of heart disease
- Risk of respiratory disease
- Risk of lung cancer

Absolute Risk Ratings for Cigarettes (±S.E.M.)

No Risk

Substantial Risk
Absolute Risk Ratings for Cigarettes and Camel Snus (±S.E.M.)

- Risk of oral cancer
- Risk of heart disease
- Risk of respiratory disease
- Risk of lung cancer

Indirect Comparison: People Understand Camel Snus has Less Risk, but Still Some Risk
Camel Snus has Less Risk, but Still Some Risk, Understood in All Three Executions

Absolute Risk Ratings by Product (±S.E.M.)

Execution 1
- Oral cancer
- Heart disease
- Respiratory disease
- Lung cancer

Execution 2
- Oral cancer
- Heart disease
- Respiratory disease
- Lung cancer

Execution 3
- Oral cancer
- Heart disease
- Respiratory disease
- Lung cancer

Cigarettes
Camel Snus

No Risk
Substantial Risk
Snus Presents Lower Risk of *Generally Poorer Health* Understood in All Executions

**Execution 1 (N=8,404)**
- Cigarettes: No Risk
- Camel Snus: No Risk

**Execution 2 (N=4,924)**
- Cigarettes: No Risk
- Camel Snus: No Risk

**Execution 3 (N=4,906)**
- Cigarettes: Substantial Risk
- Camel Snus: Substantial Risk

Absolute Risk Ratings by Product (±S.E.M.)
Direct Comparison: Large Majorities Understand Camel Snus Presents Some Risk; Few Believe it has No Risk at All

Risk of Disease for Camel Snus Relative to Cigarettes

- Same risk as smoking
- Less risk than smoking
- No risk at all
- Don’t know/not sure

- Oral cancer
- Heart disease
- Respiratory disease
- Lung cancer

% (±S.E.M.)
Camel Snus Presents Some Risk; Few Believe No Risk at All, in All Three Executions

Risk of Disease for Camel Snus Relative to Cigarettes
- Same risk as smoking
- Less risk than smoking
- No risk at all
- Don't know/not sure

Execution 1
- Oral cancer
- Heart disease
- Respiratory disease
- Lung cancer

Execution 2
- Oral cancer
- Heart disease
- Respiratory disease
- Lung cancer

Execution 3
- Oral cancer
- Heart disease
- Respiratory disease
- Lung cancer

% (±S.E.M.)
Large Majority Comprehends Need to Switch Completely to Capture Reduction in Risk

“According to the ad, what do smokers need to do in order to receive a health benefit from using Camel Snus?”

- Stop smoking, use instead: 80% (±S.E.M.)
- No change in smoking, use in addition: 10% (±S.E.M.)
- Don't know: 10% (±S.E.M.)
Majority Comprehends Need to Switch Completely, in All Three Executions

“According to the ad, what do smokers need to do in order to receive a health benefit from using Camel Snus?”

- Stop smoking, use instead
- Use in addition
- Don’t know

Execution 1

Execution 2

Execution 3

*Bar combines "reduce smoking by half, use in addition" (hatched area) and "no change in smoking, use in addition.”
Research Findings from Population Testing

- People understand that Camel Snus carries less risk, but still has risk
  - Strong majority understands need to switch completely to benefit
Research Questions for Population Testing

• People understand that Camel Snus carries less risk, but still has risk
  – Strong majority understands need to switch completely to benefit

• Do people seeing the advertising understand that:
  – Camel Snus is addictive
  – Non-users of tobacco should not use Camel Snus
  – The best choice for health-concerned smokers is to quit
Large Majorities Understand Balancing Information

- Camel Snus is addictive
- Tobacco non-users should not use
- Best choice for smokers is to quit

Correct
Incorrect
Don't know/not sure

% (±S.E.M.)
Large Majorities Understand Balancing Information, in All Three Executions

Execution 1
- Camel Snus is addictive
- Tobacco non-users should not use
- Best choice for smokers is to quit

Execution 2
- Camel Snus is addictive
- Tobacco non-users should not use
- Best choice for smokers is to quit

Execution 3
- Camel Snus is addictive
- Tobacco non-users should not use
- Best choice for smokers is to quit

Correct | Incorrect | Don’t know/not sure
Research Findings from Population Testing

- People understand that switching to Camel Snus carries less risk than smoking, but still has some risk
- **People understand the balancing statements convey that:**
  - Camel Snus is addictive
  - Non-users of tobacco should not use Camel Snus
  - The best choice for health-concerned smokers is to quit
Camel Snus Impact on Population Health Depends on Who Uses Camel Snus

- Adoption by continuing smokers benefits population health
- Adoption by non-users of tobacco conveys harm
  - Current non-users (never and former users)
  - *Expected* non-users (smokers likely to quit otherwise)
- “Likelihood of Use” study projected use by relevant populations
Research Questions for Population Testing

• People understand that switching to Camel Snus carries less risk than smoking, but still has some risk
• People understand the balancing statements convey that:
  – The best choice for smokers is to quit
  – Non-tobacco users should not use Camel Snus
  – Camel Snus is addictive
• Who is likely to use Camel Snus?
Likelihood of Use Study

- **Sample**: 11,302 adults from online research panels
  - Tobacco user status (current, former, never tobacco user) per population proportions
  - Balanced and weighted to U.S. population
- **Viewed a Camel Snus advertisement, randomized to either**:
  - Advertisement with modified risk information and balancing statements
  - Control advertisement with neither
- **Assessment**
  - Online quantitative assessment
  - Rated likelihood to purchase/use (1-10 rating)
Estimating Likelihood of Use

- Respondents rated likelihood to purchase/use (1-10 rating)
- Ratings used to project probability of purchase/use, using empirically derived logistic regression algorithm
  - Derived from prior longitudinal study connecting ratings to actual tobacco product purchase/use 9 months later
  - Algorithm includes moderators of rating→likelihood relationship
Projected Use Substantially Highest Among Current Smokers, Who are Also Differentially Attracted by Modified Risk Information

Probability of Use by Tobacco Status

- Modified risk advertisement
- 'Control' advertisement

Current smoker
- Projected % Use of Camel Snus (±S.E.M.)

Former tobacco user

Never tobacco user

Projected % Use of Camel Snus (±S.E.M.)
Projected Use Highest Among Current Smokers, Who are Also Differentially Attracted by Modified Risk Information

- Need to differentiate those NOT likely to quit
- Based on expected abstinence in 9 months
Among Current Smokers, Projected Use Highest Among Those Not Likely to Quit

Probability of Use Among Current Smokers by Quitting Status

- **Modified risk advertisement**
- **'Control' advertisement**

Not likely to quit:

- **Projected % Use of Camel Snus (±S.E.M.)**

Likely to quit:

- **Projected % Use of Camel Snus (±S.E.M.)**

'Likely to quit' = expect to be tobacco-free in 9 months
Projected Use Highest in Current Smokers Not Likely to Quit, in All Three Executions

Probability of Use Among Current Smokers by Quitting Status

- Modified risk advertisement
- 'Control' advertisement

Execution 1
- Not likely to quit
- Likely to quit

Execution 2
- Not likely to quit
- Likely to quit

Execution 3
- Not likely to quit
- Likely to quit

Projected % Use of Camel Snus (±S.E.M.)
Very Low Projected Use Among Never Tobacco Users Across All Ages

Probability of Use Among Never Tobacco Users

- Modified risk advertisement
- 'Control' advertisement

ALL never tobacco users

Projected % Use of Camel Snus (±S.E.M.)

• Consider susceptibility to smoking
  - Pierce et al.\(^1\) measure, predicts subsequent smoking initiation

Very Low Projected Use Among Young Adult (18-22) Never Tobacco Users, Especially Those Not Susceptible to Smoking

Susceptible to smoke = potentially would smoke in next year or if offered by friend (Pierce et al., 1996)
Very Low Projected Use Among Young Adult (18-22) Never Tobacco Users Not Susceptible to Smoking, All Three Executions

Probability of Use Among Never Tobacco Users

Ages 18-22

- **Modified risk advertisement**
- **'Control' advertisement**

**Execution 1**
- Susceptible to smoke
- NOT susceptible to smoke

**Execution 2**
- Susceptible to smoke
- NOT susceptible to smoke

**Execution 3**
- Susceptible to smoke
- NOT susceptible to smoke

Projected % Use of Camel Snus (±S.E.M.)

0% 1% 2% 3% 4% 5% 6% 7% 8% 9% 10%
Projected Use Highest Among Continuing Smokers, Lowest Among Non-Susceptible Never Users, All Executions

Probability of Use by Tobacco Status

- **Modified risk advertisement**
- **'Control' advertisement**

<table>
<thead>
<tr>
<th>Execution</th>
<th>Smokers not likely to quit</th>
<th>Non-susceptible never users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Execution 1</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>Execution 2</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>Execution 3</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
</tbody>
</table>

Projected % Use of Camel Snus (±S.E.M.)
Projected Use: Continuing Smokers vs. Non-Susceptible Never Users; Women and Men

Probability of Use by Tobacco Status

- **Modified risk advertisement**
- **'Control' advertisement**

**Female**
- Smokers not likely to quit
- Non-susceptible never users

**Male**
- Smokers not likely to quit
- Non-susceptible never users

Projected % Use of Camel Snus (±S.E.M.)
Projected Use: Continuing Smokers vs. Non-Susceptible Never Users; Caucasian, African-American, Hispanic Individuals

Probability of Use by Tobacco Status

- **Caucasian**
  - Smokers not likely to quit
  - Non-susceptible never users

- **African-American**
  - Smokers not likely to quit
  - Non-susceptible never users

- **Hispanic**
  - Smokers not likely to quit
  - Non-susceptible never users

Projected % Use of Camel Snus (±S.E.M.)
Research Findings from Population Testing

- People understand that switching to Camel Snus carries less risk than smoking, but still has some risk.

- People understand the balancing statements convey that:
  - The best choice for smokers is to quit.
  - Non-tobacco users should not use Camel Snus.
  - Camel Snus is addictive.

- Camel Snus most likely to be used by smokers not likely to quit, who would benefit from switching:
  - Lower projected use among smokers likely to quit.
  - Much lower projected use among former tobacco users.
  - Almost no projected use among never tobacco users.
Proposed Camel Snus
Modified Risk Advertisements

- Relative risk information is understood
  - Reduced risk, but not *no* risk
Proposed Camel Snus
Modified Risk Advertisements

• Relative risk information is understood
• Balancing information is understood
  – Snus contains nicotine and is addictive
  – Non-users of tobacco should not use snus
  – The best option for smokers is to quit
Proposed Camel Snus
Modified Risk Advertisements

- Relative risk information is understood
- Balancing information is understood
- Appeal to those who can benefit from switching to Camel Snus
  - Smokers who would continue to smoke, more than smokers likely to quit
  - Very low appeal to those not using tobacco
Proposed Camel Snus
Modified Risk Advertisements

- Relative risk information is understood
- Balancing information is understood
- Appeal to those who can benefit from switching to Camel Snus
- Statistical modeling integrates rates of projected use by relevant populations
Proposed Camel Snus
Modified Risk Advertisements

• Relative risk information is understood
• Balancing information is understood
• Appeal to those who can benefit from switching to Camel Snus
• Statistical modeling integrates rates of projected use by relevant populations
• Camel Snus with modified risk information is likely to benefit population health
Population Health Benefit Projected for Camel Snus with Modified Risk Advertising

Results from Statistical Modeling

Geoffrey Curtin, PhD
Senior Director, Scientific & Regulatory Affairs
RAI Services Company
Modeling Camel Snus as Modified Risk Product

- Modeling estimates overall health effect for full population by following multiple cohorts over time
  - Accounts for both beneficial and harmful changes in use patterns by tobacco users and non-users
  - Integrates evidence on changes in use and health consequences of those changes to estimate effect on population mortality
Camel Snus Modeling Projects Overall Benefit

- Projects ~350,000 to ~450,000 additional survivors for population as a whole
- Direction and magnitude of population effect provides high confidence in benefit
High Confidence in Population Health Benefit

- Modeling projects population health benefit for Camel Snus with modified risk advertising
  - Uses validated model
  - Accounts for all unintended, harmful changes in tobacco use
  - Relies on empirically derived model inputs
  - Includes sensitivity testing
Modeling Based on Cohort Framework

- **Dynamic Population Modeler** uses cohort framework to compare projected number of survivors for two scenarios
  - ‘What currently is’ (simplified base case; cigarette use only)
  - ‘What could be’ (counterfactual; cigarette and/or Camel Snus use)
- **Mortality tracked across 5-year age intervals through age 102, then contrasted through age 72 to project differences**
  - Changes in tobacco use may occur for scenarios at each 5-year age interval
Full Accounting of Behaviors for Never Users

- **Never tobacco user**
- **Headed to smoking?**
  - YES
  - NO
Full Accounting of Behaviors for Never Users

- **Never tobacco user**
- **Headed to smoking?**
  - **NO**
  - **Adopt snus?**
    - **NO**
    - **Never tobacco user**
  - **YES**
Full Accounting of Behaviors for Never Users

Never tobacco user

Headed to smoking?

NO

YES

Adopt snus?

NO

YES

Additional initiation

Never tobacco user
Full Accounting of Behaviors for Never Users

- **Never tobacco user**
- **Headed to smoking?**
  - **NO**
  - **YES**
    - **Adopt snus?**
      - **NO**
      - **YES**
        - **Additional initiation**
          - **NO**
          - **YES**
            - **Leads to smoking?**
              - **NO**
              - **YES**

- **Snus user**
Full Accounting of Behaviors for Never Users
Full Accounting of Behaviors for Never Users

- Never tobacco user
  - Adopt snus?
    - YES
      - Headed to smoking?
        - YES
          - Adopt snus?
            - YES
              - Additional initiation
            - NO
              - NO
            - YES
              - Leads to smoking?
                - NO
                  - NO
                - YES
                  - Gateway effect
  - NO
    - NO
      - NO
        - NO
          - Never tobacco user
        - YES
          - Adopt snus?
            - NO
              - Headed to smoking?
            - YES
              - NO
                - NO
                  - Never tobacco user
Full Accounting of Behaviors for Never Users
Full Accounting of Behaviors for Never Users

- **Never tobacco user**
  - Adopt snus?
    - YES: Alternative initiation
    - NO: Headed to smoking?
      - YES: Adopt snus?
        - YES: Additional initiation
        - NO: Never tobacco user
      - NO: Leads to smoking?
        - YES: Delayed smoking
        - NO: Smoker
  - NO: Adopt snus?
    - YES: Additional initiation
    - NO: Never tobacco user
Full Accounting of Behaviors for Smokers

- **Never tobacco user**
  - Adopt snus?
    - YES
      - Alternative initiation
      - Leads to smoking?
        - YES
          - Delayed smoking
        - NO
          - Headed to quitting?
  - NO
    - Headed to smoking?
      - YES
        - Adopt snus?
          - YES
            - Additional initiation
            - Leads to smoking?
              - NO
              - Gateway effect
              - Smoker
              - Headed to quitting?
                - YES
              - NO
            - YES
          - NO
    - NO
      - Headed to smoking?
Full Accounting of Behaviors for Smokers

- **Never tobacco user**
  - Adopt snus? (NO)
    - Headed to smoking? (NO)
      - Never tobacco user
    - Adopt snus? (YES)
      - Additional initiation
      - Leads to smoking? (NO)
        - Headed to smoking? (NO)
          - Never tobacco user
        - Leads to smoking? (YES)
          - Snus user
      - Leads to smoking? (YES)
        - Smoker
        - Leads to smoking? (NO)
          - Headed to quitting? (NO)
          - Abstinent from tobacco (NO)
        - Leads to smoking? (YES)
          - Smoker
          - Leads to smoking? (NO)
            - Headed to quitting? (NO)
            - Abstinent from tobacco (NO)
          - Smoker
          - Leads to smoking? (YES)
            - Smoker
            - Leads to smoking? (NO)
              - Headed to quitting? (NO)
              - Abstinent from tobacco (NO)
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            - Smoker
            - Leads to smoking? (NO)
              - Headed to quitting? (NO)
              - Abstinent from tobacco (NO)
          - Smoker
          - Leads to smoking? (YES)
            - Smoker
            - Leads to smoking? (NO)
              - Headed to quitting? (NO)
              - Abstinent from tobacco (NO)
          - Smoker
          - Leads to smoking? (YES)
            - Smoker
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              - Headed to quitting? (NO)
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          - Leads to smoking? (YES)
            - Smoker
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          - Smoker
          - Leads to smoking? (YES)
            - Smoker
            - Leads to smoking? (NO)
              - Headed to quitting? (NO)
              - Abstinent from tobacco (NO)
Full Accounting of Behaviors for Smokers

- **Never tobacco user**
  - Adopt snus? NO
  - Headed to smoking? NO
  - Adopt snus? NO
  - Never tobacco user

- **Headed to smoking? NO**
  - Adopt snus? NO
  - Headed to quitting? NO
  - Abstinent from tobacco

- **Headed to smoking? YES**
  - Adopt snus? YES
  - Leads to smoking? NO
  - Snus user
  - Adopt snus? NO
  - Additional initiation
  - Adopt snus? NO
  - Headed to smoking? NO
  - Never tobacco user

- **Adopt snus? YES**
  - Alternative initiation
  - Leads to smoking? NO
  - Delayed smoking
  - Smoker
  - Gateway effect
  - Headed to quitting? NO
  - Diversion from quitting

- **Adopt snus? NO**
  - Headed to quitting? YES
  - Abstinent from tobacco

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Full Accounting of Behaviors for Smokers

- Adopt snus?
- Alternative initiation

- Leads to smoking?
- Delayed smoking

- Snus user
- Gateway effect

- Smoker
- Headed to quitting?

- Abstinent from tobacco

- Adopt snus?
- Diversion from quitting

- Return to smoking?
- Snus user
Full Accounting of Behaviors for Smokers

- Adopt Snus?
  - Headed to smoking?
    - Adopt Snus?
      - Additional initiation
        - Leads to smoking?
          - NO
            - Abstinent from tobacco
          - YES
            - Diversion from quitting
  - Headed to quitting?
    - Adopt Snus?
      - Additional initiation
        - Leads to smoking?
          - NO
            - Relapse
          - YES
            - Smoker
    - NO
      - Return to smoking?
        - YES
          - Smoker
        - NO
          - Snus user
  - NO
    - Never tobacco user
Full Accounting of Behaviors for Smokers

- **Never tobacco user**
  - Adopt snus? NO
  - Headed to smoking? NO
  - Adopt snus? NO

- **Smoker**
  - Adopt snus?
    - Leads to smoking? NO
    - Headed to quitting? NO
  - Snus user
    - Adopt snus?
      - Leads to smoking? NO
      - Headed to quitting? NO
  - Smoker
    - Adopt snus?
      - Leads to smoking? NO
      - Headed to quitting? NO
Full Accounting of Behaviors for Smokers

[Diagram showing decision paths for smokers, never tobacco users, and snus users.]

- Never tobacco user
  - Headed to smoking?
    - Adopt snus?
      - YES: Additional initiation
      - NO: Never tobacco user
    - NO: Snus user
      - Leads to smoking?
        - YES: Smoker
        - NO: Delayed smoking
          - Gateway effect
            - NO: Adopt snus?
              - YES: Alternative initiation
              - NO: NO
            - YES: Smoker
          - YES: Smoker
            -_headed to quitting?
              - NO: Adopt snus?
                - YES: Diversion from quitting
                - NO: NO
              - YES: Smoker
            - YES: Smoker
              - Return to smoking?
                - NO: NO
                - YES: Resumed smoking
      - NO: NO
    - NO: Headed to smoking?
      - Adopt snus?
        - YES: Additional initiation
        - NO: NO
      - NO: NO
  - NO: Headed to smoking?
    - Adopt snus?
      - YES: Alternative initiation
      - NO: NO
    - NO: Should stay abstinent from tobacco
      - YES: Diversion from quitting
        - NO: NO
        - YES: Smoker
      - NO: NO

Full Accounting of All Harmful Behaviors

Diagram:
- **Never tobacco user**
  - Adopt snus?
    - YES: Heads to smoking?
    - NO: Never tobacco user
- Adopted snus?
  - Additional initiation
  - Leads to smoking?
    - YES: Switching
    - NO: Delayed smoking
  - Snus user
    - Leads to smoking?
      - YES: Additional gateway effect
      - NO: NO
    - Smoker
      - Leads to smoking?
        - YES: Resumed smoking
        - NO: Return to smoking?
          - YES: Relapse
          - NO: Abstinent from tobacco
Key Driver of Population Effect is Switching

‘Switching’ has largest effect on population survival

Unintended changes have relatively low potential for harm
# Empirically Derived Model Inputs

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<th>Mortality rates</th>
<th>Model Inputs</th>
<th>Supporting Source Data</th>
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Sensitivity Testing of Primary Inputs

- Projected benefit of ~350,000 to ~450,000 additional survivors sensitive to model inputs
  - Reducing empirical projections for use of Camel Snus by 75% still provides benefit of ~95,000 to ~120,000 additional survivors
Sensitivity Testing of Primary Inputs

- Projected benefit of ~350,000 to ~450,000 additional survivors sensitive to model inputs
  - Reducing empirical projections for use of Camel Snus by 75% still provides benefit of ~95,000 to ~120,000 additional survivors
  - Risk reduction for snus of ≥53% compared to smoking still provides benefit
Overall Population Health Benefit for Camel Snus

- High confidence in modeling that projects overall population health benefit
  - Uses validated model
  - Accounts for unintended, harmful changes in tobacco use
  - Relies heavily on empirically derived model inputs
  - Includes sensitivity testing
Overall Population Health Benefit for Camel Snus

- Multiple cohort modeling based on empirical probabilities of use projects ~350,000 to ~450,000 additional survivors
- Projected benefit makes it highly likely that Camel Snus with modified risk advertising will benefit public health
Conclusions

Michael Ogden, PhD
Senior Vice President, Scientific & Regulatory Affairs
RAI Services Company
Benefits of Advertising Camel Snus as an MRTP

• Smokers who switch completely can greatly reduce their risk for four smoking-related diseases:
  – Lung cancer
  – Oral cancer
  – Respiratory disease
  – Heart disease

• Authorization of the proposed advertising is highly likely to yield a significant net public health benefit
Risk Perception and Likelihood of Use

• ‘Balancing information’ in the ads effective, with majority of subjects understanding that:
  – No tobacco product is safe
  – Camel Snus still presents some risk
  – Camel Snus is addictive
  – The best option for smokers is to quit completely

• Ads appealed most to smokers who are not likely to quit
  – Comparatively low likelihood of use among former smokers and never smokers
Postmarket Surveillance

• We will work with FDA to develop and implement a robust postmarket surveillance program
• We will immediately share information of concern with the Agency and will file mandated annual reports
• There are strong safeguards built into the MRTP process
  – FDA has authority to rescind authorization if warranted
  – MRTP order must be renewed after FDA-designated time frame
Camel Snus Meets MRTP Requirements

- Significantly reduces individual risk of:
  - Lung cancer
  - Respiratory disease
  - Oral cancer
  - Heart disease

- Overall population benefit
Overall Conclusion

Authorizing the modified risk messaging for Camel Snus is a scientifically sound step toward significantly reducing the harm caused by cigarettes for individuals and the population as a whole.
## Additional Experts

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliation</th>
<th>Specialization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Michael Borgerding, PhD</strong></td>
<td>Vice President, Scientific &amp; Regulatory Affairs, RAI Services Company</td>
<td><em>Camel Snus</em></td>
</tr>
<tr>
<td><strong>Rachael Claxton</strong></td>
<td>Vice President, Consumer Marketing Reynolds Brands Inc.</td>
<td><em>Marketing</em></td>
</tr>
<tr>
<td><strong>Dan Heck, PhD, DABT, ATS</strong></td>
<td>Principal Scientist, Scientific &amp; Regulatory Affairs, RAI Services Company</td>
<td><em>Clinical and pre-clinical research</em></td>
</tr>
</tbody>
</table>
| **Jack Henningfield, PhD**        | - Vice President, Research, Health Policy, and Abuse Liability, Pinney Associates  
   - Professor (Adjunct), Behavioral Biology, The Johns Hopkins University School of Medicine | *Abuse liability*                        |
| **Michael Polster, PhD**          | Senior Vice President, Health & Life Sciences Naxion Research Consulting | *Consumer research*                      |
| **Sandra Sulsky, MPH, PhD**       | Principal Ramboll US                                  | *Population modeling*                    |
| **Aaron Williams, PhD**           | Senior Vice President, Research & Development RJ Reynolds Tobacco Company | *Camel Snus product development*         |
Sponsor slides shown during Q&A: September 13, 2018
Oral Cancer:
Smokeless Tobacco vs. Cigarette Smoking

Smokeless tobacco values control for alcohol consumption
*adjusted for smoking, n=10
**never smokers, n=9
Tipping Point Analyses for Additional Initiation
**Oral Cancer:**
Dual Use vs. Exclusive Smoking

- **Schildt et al. 1998**
  - Dual User: Risk Estimate
  - Exclusive Smoker: Risk Estimate

- **Wyss et al. 2016**
  - Dual User: Risk Estimate
  - Exclusive Smoker: Risk Estimate

---

*Head and neck cancer; includes poly use - smoking includes cigarettes, cigars, pipes; smokeless includes chewing tobacco and/or snuff*
Myocardial Infarction (MI): Dual Use vs. Exclusive Smoking

Risk Estimates, Compared to Non-/Never Tobacco Users

- Huhtasaari et al. 1999
  Any
- Hergens et al. 2005
  Any
- Hergens et al. 2005
  Non-fatal
- Wennberg et al. 2007
  Any

FATAL MI

- Hergens et al. 2005
- Wennberg et al. 2007
Dual Use (Smokeless Tobacco & Smoking) as a Transitional State

- Most switching from smoking to smokeless is through dual use
  - Zhu et al. (2009): 16 x (compared to rate from exclusive smoking)
  - Wetter et al. (2002): 12 x
  - Tomar (2003): 42 x (adolescents)

- Dual users more likely to make quit attempts
  - Zhu et al. (2013): snus ~ 62% vs. 33%
  - Richardson et al. (2014): SLT 50% vs 38% (snus OR 2.92)
  - Jones et al. (2018): SLT 63% vs. 47%

Tomar SL. Nicotine Tob Res 2003;5:561-569.
CSD0905 – Mean Product Acceptability Ratings

<table>
<thead>
<tr>
<th>Smoking Goal</th>
<th>100%</th>
<th>75%</th>
<th>50%</th>
<th>25%</th>
</tr>
</thead>
</table>

![Graph showing Mean (±S.E.M.) over visits for Cigarettes and Camel Snus.](CL-150)
Snus Use Patterns in Current Snus Users

- Snus Only: 6%
- Complete Switchers*: 40%
- Dual Users: 53%

* Former smokers, now exclusive snus
Zhu et al. (2013); N=80
TCA Mandated Warnings

• WARNING: This product can cause mouth cancer.
• WARNING: This product can cause gum disease and tooth loss.
• WARNING: This product is not a safe alternative to cigarettes.
• WARNING: Smokeless tobacco is addictive.
## Product Use Rates by Smokers and Dual Users of Camel Snus and Cigarettes (CSD0904 – Natural Adopters Study)

<table>
<thead>
<tr>
<th>User Group</th>
<th>Pouches/Day (Mean ± SD)</th>
<th>Cigarettes/Day (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusive Cigarettes</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18 ± 7 cigarettes</td>
</tr>
<tr>
<td>Dual Use Camel Snus + Cigarettes</td>
<td>2 ± 2 pouches</td>
<td>15 ± 8 cigarettes</td>
</tr>
</tbody>
</table>

<sup>a</sup>. Not Applicable
Snus and Cigarette Use Patterns: Exclusive Snus Users, Exclusive Smokers, and Dual Users

<table>
<thead>
<tr>
<th></th>
<th>Current Exclusive Snus Users n=373</th>
<th>Current Exclusive Smokers n=41,179</th>
<th>Current Dual Users n=4,127</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean uses/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snus</td>
<td>3.6</td>
<td>—</td>
<td>1.3</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>—</td>
<td>12.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Mean days/month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snus</td>
<td>15.9</td>
<td>—</td>
<td>7.9</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>—</td>
<td>25.0</td>
<td>15.9</td>
</tr>
<tr>
<td>Mean uses/day on days used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snus</td>
<td>4.8</td>
<td>—</td>
<td>3.6</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>—</td>
<td>13.4</td>
<td>9.4</td>
</tr>
</tbody>
</table>
Oral Cancer: Risks of Smokers, Switchers, and Quitters

Schildt et al. 1998

Odds Ratio, Compared to Never Tobacco Users

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco
Increases in Product Content Do Not Translate Into Increased Exposure – Nicotine

*Values cited from FDA Briefing Document
Increases In Product Content Do Not Translate Into Increased Exposure – NNN

*Values cited from FDA Briefing Document

CH-92
Arsenic Exposure

• Evaluation of biomonitoring data, NHANES, 2003-2008¹

<table>
<thead>
<tr>
<th>Arsenic</th>
<th>Cigarette Smokers</th>
<th>Smokeless Tobacco Users</th>
<th>Non-users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine (µg/g Creatinine)</td>
<td>7.98 (7.08, 9.00)</td>
<td>6.14 (4.86, 7.74)</td>
<td>9.56 (8.92, 10.27)</td>
</tr>
</tbody>
</table>

Values are geometric means adjusted for age, gender, race/ethnicity, body mass index, survey year, arsenobetaine, tobacco consumption category

• Regression of serum cotinine and urine arsenic
  – No significant associations among cigarette smokers, smokeless tobacco users, or nonusers²

¹. Marano et al. 2012b
². Naufal et al. 2011
HPHCs in Camel Snus vs. Moist Snuff, Loose Leaf, and Dry Snuff – Arsenic

Minimum/Maximum (ng/g)

Arsenic

Camel Snus
Moist Snuff
Loose Leaf
Dry Snuff

Minimum/Maximum (ng/g)
Unlike Adults, Adolescents’ Likelihood of Use is Not Increased by Modified-Risk Claims

Adults: Switching from Smoking to Smokeless Tobacco Occurs Primarily Through Dual Use

- **Smoking**: 0.3% in 1 year and 1.4% in 4 years
- **SLT & Smoking**: 4.9% in 1 year and 17.4% in 4 years

Notes:
1. Zhu et al. (2009); Tobacco Use Supplement to the Current Population Survey
2. Wetter et al. (2002); Working Well Trial

*a. Males only*
Modified-Risk Statement Regarding Oral Cancer Informs Risk Perceptions

Execution 2: Oral Cancer Modified-risk Statement (N=4,924)
Execution 3: NO Oral Cancer Modified-risk Statement (N=4,906)
Modified-Risk Statement on Oral Cancer Interacts with Warnings to Affect Relative Risk Perceptions

- Saw Mouth Cancer Warning
- Saw Warnings Unrelated to Oral Disease

Execution 2: Oral Cancer Modified-risk Statement
Execution 3: NO Oral Cancer Modified-risk Statement