MODIFIED RISK TOBACCO
PRODUCT APPLICATIONS

Swedish Match
General Snus Products

MR0000020-MR0000029

Presenters: Jim Solyst, Lars-Erik Rutqvist and Joe Rodricks
Swedish Match (Company) appreciates this opportunity to present its Modified Risk Tobacco Product Applications (MRTPAs) to TPSAC.

Who we are, what we are proposing, and provide an overview of the areas of evidence that will be presented this morning.

The Swedish Match MRTPA is a significant step in the two decade-long discussion on tobacco harm reduction, and we seek to contribute to and share in the mission of reducing the harm cause by cigarettes.

We share this mission with many other stakeholders, including:
- Congress, which chose to include the Section 911 modified-risk provisions in the Family Smoking Prevention and Tobacco Control Act;
- FDA’s Center for Tobacco Products, which acknowledges the concept of continuum of risk and emphasized the need for comprehensive federal policy on nicotine-delivery products; and
- Public health and tobacco control communities, who bring important perspectives to the strategic dialogue on harm reduction.
Like many others, Swedish Match believes that the following components are essential to tobacco harm reduction:

- that scientific evidence should be the basis of regulatory decision-making;
- that the public, and smokers in particular, should be provided accurate and appropriate information about the risks of nicotine-delivery products;
- that transparency is an essential component to regulation and product stewardship;
- that there is a need for the type of governance elements recommended by the Institute of Medicine’s (IOM’s) MRTP Committee (IRB, Advisory Panel);
- that industry can benefit from outside advice, guidance and direction from independent tobacco control and other experts; and
- that manufacturing and product standards (such as GOTHIATEK®, the Company’s proprietary quality standard) are important tools for improving the quality and health risk profiles of tobacco products.
We understand the sensitivities surrounding the Applications and the concept of harm reduction generally, and we appreciate the implications of a product being designated as the first MRTP. So it is only fair to ask:
- Is this the product that should be first?
- Is this the product with the best evidence?
- Is this the right company?

We believe, of course, that our Swedish snus products (including the ten General products we sell in the US) are the right products for, and are supported by the strongest evidence for, an MRTP order.
- The combination of extensive observational evidence from Scandinavia, along with clinical trials, a premarket consumer perception study, and a dynamic population modeling application provides compelling evidence of snus’s reduced risk profile.
- It is highly significant that the evidence presented in the MRTPAs is product-specific: specific to the Swedish Match products.
- It is also highly significant that the product-specific observational evidence from Sweden and Norway was collected through studies conducted by government and academic authorities, not industry.
We also believe that Swedish Match is the right company.
- We are not a big tobacco company.
- We do not manufacture cigarettes.
- We do not have a large staff.

Our corporate headquarters are in Stockholm, Sweden, and our North America headquarters are in Richmond, Virginia.

Snus is our signature product. The Company (and its predecessors) have been manufacturing snus since the early twentieth century.
- There was virtually no competition in Sweden until the 2000s. Since that time, the Company has maintained a market share of close to 90%.
- In Norway, market share was above 90% until 2005 and has ranged from 70-90% since that time.

Presenters
- Jim Solyst, Vice President of Federal Regulatory Affairs
- Lars-Erik Rutqvist, Senior Vice-President for Scientific Affairs
- Joe Rodricks, ENVIRON Arlington (consultant)

The Company has a track record of doing the right thing.
We have worked well with governmental authorities in Sweden, where snus is regulated as a food product.
- GOTHIATEK® was developed in coordination with the Swedish Food Agency.

We have also been active participants in FDA’s regulatory science process.
- We have submitted comments to FDA dockets, participated in CTP-sponsored events, and engaged in scientific discourse with TPSAC (e.g., Dr. Lars-Erik Rutqvist presented on the Swedish Experience at the January 2012 TPSAC meeting).

Three recent milestones in the Company’s history are illustrative:
- 1999: the Company stopped manufacturing cigarettes;
- 2000: the Company formally announced its voluntary, comprehensive quality standard GOTHIATEK®; and

This history has made it possible for us to be an industry leader in tobacco regulatory science and to be able to serve as “trailblazers.”
The MRTP Advisory Panel, which was formed in early 2013, is but one example of our trailblazing role.

Swedish Match initiated the advisory panel process by soliciting advice from leaders in the research, tobacco control, and public health communities.
- We approached two well-respected leaders in the field of tobacco research: Dr. Karl Fagerström, the President of Fagerström Consulting, and Dr. John Hughes, Professor of Psychology and Psychiatry at the University of Vermont.
- The two agreed to serve as founding members of an external advisory body on the condition that they would develop their own mission statement and operating principles which would be used to recruit prospective members and to “test the waters” with their colleagues in the research and tobacco control communities.

The Panel ultimately adopted the following mission statement:
- To present advice on matters relating to the FDA Modified Risk Tobacco Product Application and review process and to serve as a model for the interaction between FDA, the scientific community, and tobacco companies. The Advisory Panel’s deliberations will be guided by public health interests and will advance tobacco regulatory science.
The Panel’s significant contributions are best exemplified in the preparation of the Premarket Consumer Perception Study.

The Company had developed a draft protocol, which it shared and discussed with CTP during a meeting.

Shortly thereafter, in the Spring of 2013, the Panel met in person for the first time, and reviewed the study protocol during and after the meeting, resulting in a revised protocol, which was submitted to CTP along with a request for another meeting.

During this meeting (the 3rd devoted to the protocol) CTP could see the enhancements made by the Advisory Panel and asked that the Panel conduct one final review before the study was initiated.

Clearly, the Panel’s involvement enhanced the credibility and quality of the Study.
What is Swedish Snus

- It is a moist or semi-moist oral product which is traditionally produced and used in Sweden and manufactured using a heat treatment process.

- It differs from other types of smokeless tobacco, including some snus-like products recently introduced in the United States market which have distinctly different characteristics.

- Swedish snus contains only finely ground tobacco mixed with water, additives (e.g., table salt, sodium carbonate, etc.) and flavors.

- In Sweden, the product is classified as food, contains only food-approved ingredients, and is manufactured in premises that are hygienically suitable for food production.

- Swedish snus is typically placed between the upper lip and the gum and does not require expectoration during use.

- All 10 MRTPA products are made in the same manner.
The risk of a man dying from a tobacco-related disease is less in Sweden than in any other European country – despite the fact that total tobacco consumption is comparable to that of other countries in Europe.

This is often referred to as “the Swedish Experience,” a phenomenon which is most likely explained by the unique form of tobacco use among Swedish men, which largely takes the form of Swedish snus.

- Swedish men smoke substantially less than their counterparts in other countries with comparable rates of tobacco consumption, and the use of snus among Swedish men is more common than smoking.
- Although snus use has increased as smoking has declined, the overall rate of tobacco consumption in Sweden has also steadily declined.

The positive effect of this is a very low frequency of tobacco-related illnesses (e.g., lung and oral cancers) among Swedish men and low smoking-related mortality rates.
Most of the American public, and smokers in particular, have little to no understanding of the compelling Swedish Experience evidence, or the harm reduction potential of Swedish snus more generally.

This is attributable, in part, to the fact that the currently mandated label warnings for smokeless tobacco products include a number of statements that are not consistent with the scientific evidence for Swedish snus.

We believe the individual and public health in the US are best served by making available accurate scientific information regarding the significantly lower risk presented by Swedish snus as compared to cigarettes.

To that end, the Company has submitted MRTPAs for the ten (10) Swedish snus products that it markets in the United States, seeking FDA authorization to amend the warning labels for these products to conform to the science.
The MRTPAs are themselves another example of our trailblazing role.
- Setting a standard for others to follow.
- Demonstrating how a company interacts with and responds to CTP.
- Obligation to share experiences.

The remainder of today’s presentation will review the scientific evidence demonstrating that Swedish Match’s *General* snus products meet the two-part statutory standard for modified risk tobacco products.
- (1) The Tobacco Control Act states that it must be determined that a proposed MRTP: “as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users….”
  • Our Applications present evidence to demonstrate that by switching from cigarettes to Swedish Match snus, a smoker reduces his or her individual risk of tobacco-related harm and disease.
- (2) The Act further states that an MRTP order should “benefit the health of the population as a whole” taking into account both users and non-users of tobacco products.
  • Our Applications present evidence to demonstrate that providing more accurate information about the relative risks of cigarettes and Swedish snus will benefit the health of the US population as a whole.
The evidence is presented through the prism of the MRTP Applications’ proposed warning labels for the snus products, namely:

- removal of the current mouth cancer, and gum disease and tooth loss labels, which are associated with the statute’s individual risk reduction standard;
- replacement of the current “not a safe alternative to cigarettes” label with a “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes” label, which is associated with the public health benefit standard; and
- retention of the current addiction warning.

The MRTPAs request label changes only.

The proposed labels are in keeping with our shared mission and beliefs about the essential components of harm reduction—notably that (i) scientific evidence must be the basis of decision-making and (ii) the public, and smokers in particular, should be provided accurate and appropriate information about the relative risks of nicotine-delivery products.
The MRTP Applications contain five key categories of evidence:
- Swedish human health evidence, referred to as the Swedish Experience
- Norwegian behavior evidence, based on studies conducted by the Norwegian Ministry of Health Care Services
- Swedish Match-funded clinical trials on smoking cessation potential and on nicotine pharmacokinetics and pharmacodynamics
- Premarket consumer perception study designed to assess the effects of the proposed “substantially lower risks” warning label
- Dynamic Population Modeler, or DPM, to assess the public health impact of introducing a MRTP

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<th>FDCA Statutory Standard for MRTP Order</th>
<th>Proposed MRTPA Warning Labels</th>
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                         |   -Public Health Benefit |  -deletion of mouth cancer warning
                         |                          |   -deletion of gum disease and tooth loss warning |
| Norwegian Behavior Evidence | -Public Health Benefit |                              |
| Swedish Match-funded Clinical Trials on Smoking Cessation Potential and Nicotine PK and PD | -Individual Risk Reduction
                         |   -Public Health Benefit |  |
| Premarket Consumer Perception Study | -Public Health Benefit |  -inclusion of “substantially lower risks to health” warning |
| Dynamic Population Modeler | -Public Health Benefit |  |
GOTHIATEK

- Representative of the Company’s longstanding commitment to product stewardship and indicative of why and how Swedish Match snus is low in nitrosamines and other harmful and potentially harmful constituents (HPHCs).

- Combines analytical methods, chemical quality control programs, brands testing programs, and agrochemical management programs to manufacture snus according to the Company’s high quality standard for snus products.

- GOTHIATEK® is described in the Briefing document and there are staff here who can answer all questions, but the principal components of the standard are:
  - Constituent standards
  - Manufacturing standards
  - Consumer information

- GOTHIATEK® contributes to the reduced risk claim and benefits the public health by providing a model that contribute to the development of a FDA product standard.
Founding Principal of ENVIRON, and an internationally recognized expert in toxicology and risk analysis.

Consulted for hundreds of manufacturers, government agencies and for the World Health Organization in the evaluation of health risks associated with human exposure to chemical substances of all types.

15-year career as a scientist at the US Food and Drug Administration (FDA). In his last four years at the FDA, he served as Associate Commissioner for Health Affairs.

Experience ranges from pharmaceuticals, medical devices, consumer products and foods, to occupational chemicals and environmental contaminants.

Served on the National Research Council’s Board on Environmental Studies and Toxicology, and on 30 boards and committees of the National Academy of Sciences and the Institute of Medicine, including the committees that produced the seminal works Risk Assessment in the Federal Government: Managing the Process (1983), and Science and Decisions–Advancing Risk Assessment (2009).

He has nearly 150 scientific publications and has received honorary awards from three professional societies for his contributions to toxicology and risk analysis.
Assessing the Scientific Literature on Swedish Snus - Presentation to TPSAC
On Behalf of Swedish Match

Joseph V. Rodrigks, PhD, DABT
Carol Ward, DrPH
Greg Mariano, MPH
History of ENVIRON and Role with Swedish Match

- Consultancy in health and environmental science since 1982
- 1,200 scientists and engineers worldwide
- Approached by Swedish Match in late 2007 to provide product stewardship support
  - Maintain a data base of scientific literature in areas of product chemistry, exposure biomarkers, nonclinical toxicology, and human health
  - Provide periodic reviews and reach independent conclusions
- Following Tobacco Control Act
  - Expanded areas of interest: social and behavioral, comparison to smoking
  - Submission of reports to FDA as part of MRTPA
Tobacco sales in Sweden 1916-2008

- Cigarettes
- Cigars
- Pipe & RYO
- Snus
- Other ST

Year

Metric tonnes
Patterns of tobacco use among males in the VIP cohort, Sweden

Norberg et al. 2011 (4: 5613 - DOI: 10.3402/gha.v4i0.5613
The Swedish Experience:

opportunity for product-specific, large-scale observational study

- Widespread use of a single manufacturer’s product, snus
- National databases of health outcomes
- Major cohorts with exposure assessment on tobacco use
- Studies conducted independent of manufacturer: by government, academic institutions, independent research
ENVIRON Reports cited in the MRTPA submitted to the FDA as appendices

- Snus Monograph: a review of the health effects studies
- Harmful and Potentially Harmful Constituent (HPHC) Comparison
- Tobacco-related Knowledge, Attitudes, and Beliefs (KABs) in Scandinavia
- Tobacco Use Behaviors in Scandinavia and the US
- Dynamic Population Model
Review of Scientific Literature on Snus – content of the report

• Studies reviewed: all published or publicly available studies on Swedish snus in the areas of:
  – Chemical properties and composition
  – Biomarkers of exposure
  – Non-clinical toxicology studies
  – Health effects –
    • Strength of this literature base – over 100 primary epidemiology studies of human health effects
    • Approximately 100 studies of chemical composition, human exposure, and toxicity
    • Includes cohorts from the early 1970s, several followed prospectively through the 2000s
    • Over 50 health endpoints and categories, with replication for most major endpoints
    • Conducted by highly regarded institutions including the Karolinska Institute and major universities.
Review of Scientific Literature on Snus – content of the report (continued)

• The report contains:
  – Tabular summaries of individual studies: study information, outcome and exposure measurement, confounders, results, conclusions, comments (assessment of biases, study limitations)
  – Narrative summaries: discussion of individual study results and limitations, commentaries, meta-analyses, and conclusions
Review of Scientific Literature on Snus – drawing conclusions

- Closely resemble the IOM classifications for describing associations used for numerous evaluations
- Based on judgments of the weight, strength and consistency of the evidence for observing an association likely to be free of chance variation, bias and confounding – considered the Bradford Hill guidelines
Conclusion Categories

• **Clear evidence of no association:** sufficient high quality evidence of no association

• **Clear evidence of an association:** sufficient high quality evidence of an association
Conclusion Categories (continued)

Where evidence was not definitive:

- **No association but limitations:** Available studies show no association but not definitive due to limitations (e.g., only a single study, small sample, lack of control for confounders)

- **Evidence overall suggests no association but limitations:** Generally consistent in showing no association, with the exception of at least one study showing an association

- **Possible association/uncertainty:** At least one study showing an association; supporting evidence is plausible for an association or there is uncertainty as to adequacy of the overall data
Conclusion Categories (continued)

- **No evidence, but association unlikely:** Diseases almost certainly related to inhalation of tobacco smoke are unlikely to be caused by snus
Human health effects – conclusions

<table>
<thead>
<tr>
<th>Clear evidence of an association</th>
<th>Clear evidence of no association</th>
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<tr>
<td>Acute blood pressure and heart rate increases</td>
<td>Oral cancer</td>
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<td>Reversible snus-induced lesions</td>
<td>Lung cancer</td>
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<tr>
<td>Some adverse pregnancy outcomes</td>
<td>CVD/MI/Stroke</td>
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</table>
Human health effects – conclusions (continued)

<table>
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<tr>
<th>No association – but limitations</th>
<th>Evidence overall suggests no association – but limitations</th>
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<tr>
<td>All cancers combined</td>
<td>All-cause mortality</td>
<td>Body weight/gain</td>
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<td>Atherosclerosis</td>
<td>Dental caries</td>
<td>Diabetes/MetSy</td>
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<td>Periodontal disease</td>
<td>Esophageal cancer</td>
<td>Post-CVD survival</td>
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<td>Dental plaque</td>
<td>Gingivitis</td>
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<td>Kidney cancer</td>
<td>Pancreatic cancer</td>
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<td>Bladder cancer</td>
<td>Stomach cancer</td>
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<td>Laryngeal cancer</td>
<td>Respiratory mortality</td>
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<td>Leukemia</td>
<td>Tooth loss and wear</td>
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<td>Some pregnancy outcomes</td>
<td>Pre-eclampsia</td>
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<td>Waist-to-hip ratio</td>
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</table>
Human health effects – conclusions (continued)

No evidence but association unlikely

COPD, emphysema, other respiratory morbidity outcomes
Comparing Risks of Cigarette Smoking to Use of Swedish Snus

• Appendix to the Snus Monograph: considered the subset of studies (n=31) that presented risks for snus and smoking, in the same populations, using the same methodologies, for the diseases leading to the highest proportion of smoking-related deaths (lung cancer, COPD and other respiratory causes of death, and CVD)

• Provided detailed and graphical summaries of these studies

• Also presented summary relative risks from the snus meta-analyses and smoking literature
As laid out in the detailed summaries,

• given our conclusion of no association between use of snus and the major smoking-related diseases – lung cancer, COPD and other respiratory causes of death, and CVD, which account for 80+ percent of smoking-related illness –

• then the use of snus presents significantly lower risks of smoking-related diseases that result in the greatest number of deaths among smokers.
Scientific Agreement that Risk Among Snus Users is Lower Compared to Smokers

– Allowing for the small number of scientific studies of its health effects, it seems clear that while snus is not harmless it poses considerably less risk than smoking. *(Swedish National Board of Health and Welfare, 2012)*

– Smokeless tobacco products are associated with oral cavity cancers...however, the overall risk is lower than for cigarette smoking, and some products such as Swedish snus may have no increased risk. *(IOM 2001)*
– The development of oral cancer ...has not been proven for Swedish moist snuff (snus)...Overall, in relation to the risks of the major smoking-related diseases, ...STP[s] are **clearly less hazardous**, and in relation to respiratory and cardiovascular diseases **substantially less hazardous**, than smoking. *(SCENIHR 2008)*

– On toxicological and epidemiological grounds, some of the Swedish smokeless (snus) products appear to be associated with the lowest potential for harm to health *(Royal College of Physicians 2007)*
Final Words

• There is clear evidence of significantly reduced risk of major smoking related diseases − thus meeting the standard in Section 911 − the product will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users.

• While evidence for some diseases is less clear or are not well studied, there is no evidence that risks for these outcomes are any higher than those of smoking.

• The science base for decision-making is compelling.
Norwegian Behavior Evidence

Jim Solyst
The Norwegian evidence was collected after the movement from cigarettes to snus had occurred in Norway. The studies were designed to determine why the shift occurred and what the impacts to individuals and the public health.

In effect, the Norwegian studies evidence are postmarket surveillance of snus users, examining:
- whether the switch resulted in smoking cessation;
- the extent of dual use that occurred
- whether adolescents initiated tobacco use via snus; and
- whether the switch delayed cessation from all tobacco products.

A 2013 article, “Tobacco harm reduction in the real world: has the availability of snus in Norway increased smoking cessation?, summarizes all of the previous Norwegian Ministry of Health funded snus studies.

The article includes the line: “Norway and Sweden, with its long tradition of snus use, constitutes a natural laboratory in which we can study how snus competes for market share with cigarettes.”
In Norway, as in Sweden, snus is reported by ever-smokers to be the most preferred method for quitting, and former smokers make up the largest segment of snus users.

The quit rate for smoking is consistently observed to be higher for snus users than for smokers who have no experience of use of snus.

Snus users are more likely to have quit smoking completely or considerably reduced their cigarette smoking, than users of medicinal smoking cessation products.

The combination of usage and efficacy suggests a higher level of efficiency of snus than medicinal nicotine as a smoking cessation aid.
Norwegian Evidence: Dual Use

- The increase in snus use among men in Norway has not been paralleled by an increase in dual use of snus and cigarettes.

- The typical pattern of dual use is daily use of one product paired with occasional use of the other.

- Cigarette consumption among dual users is 40 percent lower compared to exclusive smokers. There is no evidence that dual use decreases plans to quit smoking.

- Smoking cessation is a widespread motive for additional snus use, supporting a hypothesis that dual use might be regarded as a transient phenomenon – a stepping stone either to exclusive use of snus or preferably freedom from tobacco altogether.
## Relationship to MRTP Order

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|                                                             | - Public Health Benefit                                    |                                                            |
| Premarket Consumer Perception Study                         | - Public Health Benefit                                     | - inclusion of “substantially lower risks to health” warning|
| Dynamic Population Modeler                                  | - Public Health Benefit                                     |                                                            |
Lars-Erik Rutqvist, MD, PhD

- Senior Vice President, Scientific Affairs since 2006

- Previously with the Karolinska Institute, where he had been Professor & Head, Department of Oncology, and Chairman of the Research Ethics Committee.

- Broad experience in the fields of oncology, epidemiology, and public health.

- Extensive experience of both designing, conducting, and analyzing randomized clinical trials as well as meta analyses of such trials.

- Served in an advisory capacity to governmental or other state agencies as well as NGOs on issues related to public health policies, risk modification, harm reduction, and research ethics.

- Worked with pharmaceutical and biotechnological companies providing advice on drug development.
Clinical Trials & Meta-Analysis of Snus as an Aid in Complete Smoking Cessation

Lars-Erik Rutqvist, MD, PhD
Background

• Discussions within the academic and tobacco control communities in Sweden in the early 2000s about the determinants of the “Swedish Experience”, particularly the role of snus

• Critics supporting the use of NRTs pointed out the lack of experimental data on snus as an aid to smoking cessation

• Discussions on European level about the transferability of the “Swedish Experience” to other countries
Background, cont’d

• Discussions between academic researchers and Swedish Match in 2006-2007 led to initiation of two independent randomized clinical trials (in the U.S. and in Serbia) where the company acted as the formal sponsor.

• The trials were initiated before passage of the US Tobacco Control Act in 2009.

• Snus has never been marketed as a smoking cessation aid and the MRTPAs do not include a smoking cessation health claim.

• Sponsorship reflection of Swedish Match’s stewardship role for the snus category.
Trial governance

• Protocols developed in collaboration between the individual research teams and the sponsor according to internationally accepted guidelines
• Study performed in accordance with local national laws (as applicable), the guidelines of the International Conference on Harmonization (ICH), and the guidelines of the Declaration of Helsinki
• Study approved by an appropriately constituted institutional review board (IRB) or independent research ethics committee (IEC)
• Trial conducted according to ICH-GCP (“Good Clinical Practice”)
• Management of all clinical and other study-related information, including monitoring, conducted by Contract Research Organizations (CRO:s) with extensive experience of controlled clinical trials of pharmaceutical products (i3 Research, Covance)
• All data handling and statistical analyses conducted by external contractors according to a pre-specified statistical analysis plans
• Prospective registration in public databases such as www.clinicaltrials.gov
• Commitment by the sponsor to publish results irrespective of trial outcome
• Publication in peer-reviewed scientific journals according to the CONSORT guidelines
• Commitment to make raw study data available for systematic reviews and/or meta-analyses conducted according to internationally accepted guidelines (e.g PRISMA)
SM 08-01: Randomized, Placebo-Controlled, Double-Blind Clinical Trial of a Smokefree Tobacco Product (Snus) to Increase the Quit Rate Among Cigarette Smokers Who Wish to Stop Smoking (N=250)

Centres
- Evansville, KY
- Portland, OR
- Daytona Beach, FL
- Austin, TX
- Dallas, TX

Screening
Include:
- 25-65 yrs
- >9 cigs/day during >1 yr
- Motivated to quit smoking

Exclude:
- Current ST use (< 6 months)
- NRT (< 3 months)
- Alcohol or drug abuse
- Significant medical condition

Baseline
Snus product (1.0 or 0.5 g pouches ad lib.) N=125
Placebo snus product (1.0 or 0.5 g pouches ad lib.) (N=125)

Interventions
Week: 1-4 Study product testing 5-16 Smoking cessation after TQD (target quit date) 17-28 Clinical follow-up
Behavioral counseling at all visits
Study product usage week 1-16

Study week | -2 ; 0 | 0 | 1 | 6 | 10 | 16 | 28
--- | --- | --- | --- | --- | --- | --- | ---
Visit 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓
CO in exhaled air | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓
Biomarkers 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓
Participant diary (incl. smoking status & study product usage) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓

1: Clinical visit or telephone call  2: WBC, CRP, cholesterol, HDL, LDL, fibrinogen, cotinine
SM 07-01: Serbian Smoking Reduction/Cessation Trial, 2SRT (N=319)

Screening

**Include:**
- 20-65 yrs
- >10 cigs/day during >1 yr
- Motivated to reduce/quit smoking
- Good general health

**Exclude:**
- NRT (< 3 months)
- Current alcohol or drug abuse
- Significant medical condition

Baseline

**Include:**
- Snus (1.0 or 0.5 g pouches, two flavors ad lib.) N=158

**Exclude:**
- Placebo snus (1.0 or 0.5 g pouches, two flavors ad lib.) N=161

Interventions

**Week: 1-24**

End point: smoking reduction

- Participants who achieved "smoking reduction" at wk 24 (>50% reduction in self-reported smoking and reduction of CO in exhaled air <1 ppm compared to baseline)

**Week: 25- 48**

End point: complete smoking cessation

**Behavioural counseling at all visits**

**Study product usage week 1- 48**

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<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

**Participant diary (incl. smoking status & study product usage)**

- To be filled in weekly during week 1 through 48

1: Clinical visit or telephone call  2: Blood tests: WBC, CRP, cholesterol, HDL, LDL, fibrinogen, cotinine
## Selected participant characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>US (n=250) %</th>
<th>Serbia (n=319) %</th>
<th>Combined(^2) (n=569) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>39</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>61</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>45.0</td>
<td>43.6</td>
<td>44.3</td>
</tr>
<tr>
<td>No. of cigarettes smoked per day in the year before baseline(^1)</td>
<td>Mean</td>
<td>20.4</td>
<td>26.7</td>
<td>23.9</td>
</tr>
<tr>
<td>Age of starting to smoke (years) (^1)</td>
<td>Mean</td>
<td>18.4</td>
<td>19.0</td>
<td>18.7</td>
</tr>
<tr>
<td>Fagerström score(^1)</td>
<td>Mean</td>
<td>5.6</td>
<td>6.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Previous quit attempt(^1)</td>
<td>Yes</td>
<td>88</td>
<td>36</td>
<td>59</td>
</tr>
<tr>
<td>Previous exposure to NRT(^1)</td>
<td>Yes</td>
<td>50</td>
<td>1</td>
<td>23</td>
</tr>
</tbody>
</table>

1: Difference between studies statistically significant (p<0.001)  
2: Distribution of baseline characteristics similar in the snus and placebo groups in both studies as well as overall (p always >0.1)
Rationale for meta-analysis

• Combining the evidence from the two trials allows more powerful tests of whether snus affects the rate of quitting

• A formal meta-analysis improves statistical precision and allows better insight into the main hypothesis of interest
Meta-analysis methodology

• Availability of primary subject data allowed comparable definition of outcomes and potential confounding variables, identical statistical analyses of the two studies, and calculation of exact rather than approximate probabilities
Primary outcome
(Continued cessation during 23-24 wks)

Secondary outcome 1
(1-week point prevalence cessation)

Secondary outcome 2
(1-week point prevalence cessation)

Secondary outcome 3
(1-week point prevalence cessation)

Secondary outcome 4
(Continued cessation during 4 weeks)

Secondary outcome 5
(Continued cessation during 12 weeks)

Study week:
25-48 (Serbia)
6-28 (US)

Test of CO in exhaled air
Meta-analysis of primary outcome

Biochemically verified, continued smoking cessation during 23-24 weeks

Primary outcome was defined as biologically verified cessation during weeks 6-28 (US), or weeks 24-48 (Serbia)

- **US**
  - Snus: 4.0% (n=125)
  - Placebo: 1.6% (n=125)
  - OR 2.50 (0.49-12.7) p = 0.45

- **Serbia**
  - Snus: 5.7% (n=158)
  - Placebo: 1.9% (n=161)
  - OR 3.06 (0.84-11.1) p = 0.13

- **Total (adjusted for study)**
  - Snus: 4.9% (n=283)
  - Placebo: 1.7% (n=286)
  - OR 2.83 (1.03-7.75) p = 0.06
  - (chi-squared p = 0.03)
Meta-analysis of secondary outcome 5
Biochemically verified, continued smoking cessation during weeks 17-28 (US), weeks 37-48 (Serbia)

<table>
<thead>
<tr>
<th></th>
<th>Snus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>9.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Serbia</td>
<td>9.5%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Total (adjusted for study)</td>
<td>9.5%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

OR 2.00 (0.77-5.16)  
*p = 0.22*  

OR 2.55 (0.1-6.40)  
*p = 0.06*  

OR 2.27 (1.17-4.39)  
*chi-squared p = 0.01*
Efficacy of snus vs baseline characteristics

• No statistically significant evidence that the relative success rate with snus differed according to:
  – Gender
  – Age at entry
  – Age at starting to smoke
  – Fagerström score
  – Previous quit attempt
  – Previous exposure to NRT
Conclusions

• Biologically verified, continuous, complete cessation during 23-24 weeks was 2.5-3 times higher in the group allocated to snus (in both Serbia and the U.S.) with a meta-analysis relative success rate of 2.83 (1.03-7.73; exact p=0.06, chi-squared p=0.03)

• For all biologically verified secondary outcomes in the meta-analysis (continued abstinence during shorter time periods and 1-week point prevalence abstinence) success rate was about twice as high in the group allocated to snus (p<0.05)

• Results thus equal to or better than with NRTs, possibly related to the nicotine pharmacokinetics of snus
Conclusions, cont’d

• No evidence that success rate was modified by baseline characteristics including previous quit attempts with NRTs
• Snus was safe and generally well tolerated
• The trial results support and enhance findings from observational Scandinavian studies on the role of snus for complete smoking cessation
• Smoking cessation with the aid of snus was achieved in geographical settings without history of use of any form of smokeless tobacco (Serbia), or without history of snus use (U.S.)
### Relationship to MRTP Order

<table>
<thead>
<tr>
<th>MRTPA Areas of Evidence</th>
<th>FDCA Statutory Standard for MRTP Order</th>
<th>Proposed MRTPA Warning Labels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Human Health Evidence</td>
<td>-Individual Risk Reduction</td>
<td>-deletion of mouth cancer warning</td>
</tr>
<tr>
<td></td>
<td>-Public Health Benefit</td>
<td>-deletion of gum disease and tooth loss warning</td>
</tr>
<tr>
<td>Norwegian Behavior Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swedish Match-funded Clinical Trials on Smoking Cessation Potential and Nicotine PK and PD</td>
<td>-Individual Risk Reduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Public Health Benefit</td>
<td></td>
</tr>
<tr>
<td>Premarket Consumer Perception Study</td>
<td>-Public Health Benefit</td>
<td>-inclusion of “substantially lower risks to health” warning</td>
</tr>
<tr>
<td>Dynamic Population Modeler</td>
<td>-Public Health Benefit</td>
<td></td>
</tr>
</tbody>
</table>
Premarket Consumer Perception Study

Lars-Erik Rutqvist, MD, PhD
Statutory language on labeling of tobacco products

• “A tobacco product shall be deemed to be misbranded if its labeling is false or misleading in any particular....” (FDCA § 903(a)(1))

• Currently mandated four warning statements:
  – 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

The scientific evidence included in the MRTPAs indicate that the current label statements cause the snus products to be misbranded!
Consumer Perception Study

• Quantitative, randomized, controlled study of 13,200 subjects aged 18-64 years (6,600 current users of tobacco products, 6,600 non-users)
• Protocol with defined study hypotheses, end-points, and statistical methods
• Done by research contractor with extensive experience of consumer research and online data acquisition
• Subjects sourced from consumer panels and via advertising
• Online questionnaire
• Methods build on those routinely used for industry-sponsored consumer research but procedures enhanced to comply with FDA guidance
• IRB review
• Input from SM’s Advisory Panel and from CTP
FDA Guidance Document: general principles for scientific studies

- Well-designed study that allow for critical analysis and replication by other investigators
- Clear objectives, hypotheses
- Protocol with standardized, validated methods for analysis
- Adequate sample size
- Appropriate control groups
- Procedures to minimize bias and permit generalization to the U.S. population
- Analyses that adequately address the effects of study measures
- Appropriate methods for assigning subjects
- Oversight by an IRB
Study objectives

• Assess consumer understanding, tobacco use behavior, and perceptions of health risks among subjects exposed to one out of the four existing warning statements, and two test statements.

• Overall, according to current tobacco use, and in demographic subgroups:
  – 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

-----
  – No tobacco product is safe but this product presents a lower risk to health than cigarettes
  – No tobacco product is safe but this product presents a substantially lower risk to health than cigarettes
Linguistics of tested statements

- 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
- No tobacco product is safe but this product presents a lower risk to health than cigarettes
- No tobacco product is safe but this product presents a substantially lower risk to health than cigarettes
Study design: random allocation

<table>
<thead>
<tr>
<th>Randomly allocated statement</th>
<th>Tobacco users (N=6,600)</th>
<th>Non-users (N=6,600)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Oral cancer&quot;</td>
<td>1,100</td>
<td>1,100</td>
</tr>
<tr>
<td>&quot;Gum disease&quot;</td>
<td>1,100</td>
<td>1,100</td>
</tr>
<tr>
<td>&quot;Not safe alternative&quot;</td>
<td>1,100</td>
<td>1,100</td>
</tr>
<tr>
<td>&quot;Addictive&quot;</td>
<td>1,100</td>
<td>1,100</td>
</tr>
<tr>
<td>&quot;Lower risk&quot;</td>
<td>1,100</td>
<td>1,100</td>
</tr>
<tr>
<td>&quot;Substantially lower risk&quot;</td>
<td>1,100</td>
<td>1,100</td>
</tr>
</tbody>
</table>
Example of research stimuli:
Color photographs shown to participants allocated to “No tobacco product is safe but this product presents lower risk to health than cigarettes”
Sample demographics

<table>
<thead>
<tr>
<th></th>
<th>Current users (%)</th>
<th>Non-users (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>25-44</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>45+</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Midwest</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>South</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>West</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minorities</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Non-Minorities</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td><strong>Annual income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 K</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>45K+</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

Sample balanced for gender, age, geography, income according to CDC’s Morbidity and Mortality Weekly Report 60: 35
Results

• Ease of understanding
  – Q51. “Having seen the warning label on the snus package, using the scale below, please indicate how easy or difficult is it to understand the meaning of the warning label on the package you just viewed”

• Believability
  – Q59. “How believable is the warning label on this package of snus?”

• Risk perception of snus vs cigarettes
  – Q61. “How does the information you saw on the warning label directly influence your perception of the personal health risks associated with using snus compared to the personal health risks posed by cigarettes?”

• Motivation to buy snus
  – Q58. “How does the information you saw on the warning label directly impact how motivated you are to buy snus?”

• Likelihood to use snus
  – Q53. “After viewing the information in the warning label, how does the information you saw on the warning label directly influence your likelihood to use snus?”
Ease of Understanding Warning Claim

While two-thirds of those who evaluated the test warning labels found the claims to be easy to understand, this is a significantly lower proportion than those who evaluated any of the current label claims. The claims easiest to understand specifically mention gum disease/tooth loss and mouth cancer.

Q51. Having seen the warning label on the snus package, using the scale below, please indicate how easy or difficult is it to understand the meaning of the warning label on the package you just viewed.

Base: Concept 1: n=2201; Concept 2: n=2211; Concept 3: n=2202; Concept 4: n=2201; Concept 5: n=2202; Concept 6: n=2186
Believability of Warning Claim

Respondents overall were significantly less likely to find the two test claims to be believable compared to all current claims.

<table>
<thead>
<tr>
<th>Concept 1: Gum disease/Tooth loss</th>
<th>Top 2 NET</th>
<th>Bottom 2 NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Not at all believable</td>
<td>11%</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>9%</td>
<td>2,4,5,6</td>
</tr>
<tr>
<td>3</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>4- Neither believable nor unbelievable</td>
<td>59%</td>
<td>71%</td>
</tr>
<tr>
<td>5</td>
<td>4%</td>
<td>5,6</td>
</tr>
<tr>
<td>6</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>7- Extremely believable</td>
<td>8%</td>
<td>77%</td>
</tr>
<tr>
<td>8</td>
<td>2%</td>
<td>2,4,5,6</td>
</tr>
<tr>
<td>9</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 2: Is addictive</th>
<th>Top 2 NET</th>
<th>Bottom 2 NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Not at all believable</td>
<td>3%</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>13%</td>
<td>5,6</td>
</tr>
<tr>
<td>3</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>4- Neither believable nor unbelievable</td>
<td>58%</td>
<td>13%</td>
</tr>
<tr>
<td>5</td>
<td>13%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>6</td>
<td>6%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>7- Extremely believable</td>
<td>77%</td>
<td>3%</td>
</tr>
<tr>
<td>8</td>
<td>2%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>9</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 3: Mouth cancer</th>
<th>Top 2 NET</th>
<th>Bottom 2 NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Not at all believable</td>
<td>10%</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>8%</td>
<td>5,6</td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>4- Neither believable nor unbelievable</td>
<td>62%</td>
<td>13%</td>
</tr>
<tr>
<td>5</td>
<td>2%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>6</td>
<td>6%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>7- Extremely believable</td>
<td>77%</td>
<td>3%</td>
</tr>
<tr>
<td>8</td>
<td>2%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>9</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 4: Not a safe alternative</th>
<th>Top 2 NET</th>
<th>Bottom 2 NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Not at all believable</td>
<td>17%</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>1,3</td>
<td>5,6</td>
</tr>
<tr>
<td>3</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>4- Neither believable nor unbelievable</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>5</td>
<td>15%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>6</td>
<td>5%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>7- Extremely believable</td>
<td>68%</td>
<td>3%</td>
</tr>
<tr>
<td>8</td>
<td>3%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>9</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 5: Substantially lower risks</th>
<th>Top 2 NET</th>
<th>Bottom 2 NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Not at all believable</td>
<td>9%</td>
<td>39%</td>
</tr>
<tr>
<td>2</td>
<td>1,3,4</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>4</td>
<td>8%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>5</td>
<td>23%</td>
<td>17%</td>
</tr>
<tr>
<td>6</td>
<td>1,2,3,4</td>
<td>14%</td>
</tr>
<tr>
<td>7- Extremely believable</td>
<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>8</td>
<td>17%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>9</td>
<td>14%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>10</td>
<td>4%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>11</td>
<td>8%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>12</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>13</td>
<td>1,2,3,4</td>
<td>14%</td>
</tr>
<tr>
<td>14</td>
<td>16%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>15</td>
<td>14%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>16</td>
<td>6%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>17</td>
<td>26%</td>
<td>1,2,3,4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 6: Lower risks</th>
<th>Top 2 NET</th>
<th>Bottom 2 NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Not at all believable</td>
<td>9%</td>
<td>40%</td>
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<tr>
<td>2</td>
<td>1,3,4</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>4</td>
<td>8%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>5</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>6</td>
<td>1,2,3,4</td>
<td>14%</td>
</tr>
<tr>
<td>7- Extremely believable</td>
<td>26%</td>
<td>13%</td>
</tr>
<tr>
<td>8</td>
<td>17%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>9</td>
<td>14%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>10</td>
<td>4%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>11</td>
<td>8%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>12</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>13</td>
<td>1,2,3,4</td>
<td>14%</td>
</tr>
<tr>
<td>14</td>
<td>16%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>15</td>
<td>14%</td>
<td>1,2,3,4</td>
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<tr>
<td>16</td>
<td>6%</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>17</td>
<td>26%</td>
<td>1,2,3,4</td>
</tr>
</tbody>
</table>

Q59. How believable is the warning label on this package of snus?
Base: Concept 1: n=2201; Concept 2: n=2211; Concept 3: n=2202; Concept 4: n=2201; Concept 5: n=2202; Concept 6: n=2186
Respondents largely internalized the message of the test warning claims. Half exposed to either test claim felt snus would be ‘somewhat less harmful’ than cigarettes, which is significantly higher than any of the current claims.

<table>
<thead>
<tr>
<th>Concept 1: Gum disease/Tooth loss</th>
<th>No risk</th>
<th>Somewhat less harmful</th>
<th>Equal</th>
<th>Somewhat more harmful</th>
<th>Much more harmful</th>
<th>Label had no impact</th>
<th>Harmful NET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20%</td>
<td>49%</td>
<td>9%</td>
<td>14%</td>
<td>2%</td>
<td>7%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>5,4</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>2,4,5,6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 2: Is addictive</th>
<th>3%</th>
<th>21%</th>
<th>46%</th>
<th>7%</th>
<th>11%</th>
<th>12%</th>
<th>18%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5,4</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 3: Mouth cancer</th>
<th>14%</th>
<th>55%</th>
<th>10%</th>
<th>13%</th>
<th>2%</th>
<th>6%</th>
<th>23%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,2</td>
<td>5,6</td>
<td>2,4,5,6</td>
<td>13%</td>
<td>5,6</td>
<td>5,6</td>
<td>2,4,5,6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 4: Not a safe alternative</th>
<th>14%</th>
<th>57%</th>
<th>8%</th>
<th>11%</th>
<th>8%</th>
<th>3%</th>
<th>19%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,2</td>
<td>5,6</td>
<td>1,2</td>
<td>5,6</td>
<td>1,2,5,6</td>
<td>5,6</td>
<td>5,6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test Claims</th>
<th>No risk</th>
<th>Somewhat less harmful</th>
<th>Equal</th>
<th>Somewhat more harmful</th>
<th>Much more harmful</th>
<th>Label had no impact</th>
<th>Harmful NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concept 5: Substantially lower risks</td>
<td>3%</td>
<td>51%</td>
<td>23%</td>
<td>6%</td>
<td>7%</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>1,2</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>1,2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept 6: Lower risks</th>
<th>3%</th>
<th>50%</th>
<th>25%</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
<th>12%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,2</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>5,6</td>
<td>1,2</td>
</tr>
</tbody>
</table>

Q61. How does the information you saw on the warning label directly influence your perception of the personal health risks associated with using snus compared to the personal health risks posed by the tobacco products below?

Base: Concept 1: n=1833; Concept 2: n=1888; Concept 3: n=1883; Concept 4: n=1858; Concept 5: n=1866; Concept 6: n=1832
Motivation to Buy Snus Based on Warning Claim

Though small proportions (11% and 10% respectively), both test claims would be significantly more likely to motivate overall respondents to buy snus compared to all current labels.

<table>
<thead>
<tr>
<th>Concept</th>
<th>Motivation to Buy Snus Based on Warning Claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concept 1: Gum disease/Tooth loss</td>
<td>50% 2.4, 5.6 5% 6% 29% 3% 3% 4% 7% 55% 2.4,5.6</td>
</tr>
<tr>
<td>Concept 2: Is addictive</td>
<td>37% 5.6 5% 6% 41% 1.3 4% 3% 5% 8% 42% 5.6</td>
</tr>
<tr>
<td>Concept 3: Mouth cancer</td>
<td>53% 2.4, 5.6 5% 6% 27% 3% 4% 6% 58% 2.4,5.6</td>
</tr>
<tr>
<td>Concept 4: Not a safe alternative</td>
<td>40% 5.6 5% 6% 39% 1.3 4% 5% 7% 45% 5.6</td>
</tr>
<tr>
<td>Concept 5: Substantially lower risks</td>
<td>24% 4% 5% 47% 1.2, 3.4 9% 5% 6% 11% 1.2,3,4 28%</td>
</tr>
<tr>
<td>Concept 6: Lower risks</td>
<td>28% 4% 5% 47% 1.2, 3.4 7% 4% 6% 10% 1.2,3,4 32%</td>
</tr>
</tbody>
</table>

Q58. How does the information you saw on the warning label directly impact how motivated you are to buy snus? Base: Concept 1: n=2201; Concept 2: n=2211; Concept 3: n=2202; Concept 4: n=2201; Concept 5: n=2202; Concept 6: n=2186
Likelihood To Use Snus Based On Warning Claim

While it is a small proportion (14%), the test claim of ‘a substantially lower risk than cigarettes’ is significantly more likely to influence snus usage among overall respondents than claims about being addictive, causing mouth cancer or not being a safe alternative to cigarettes.

However, the claim simply stating ‘a lower risk than cigarettes’ performs on par with current claims.

Q53. After viewing the information in the warning label, how does the information you saw on the warning label directly influence your likelihood to use snus?

Base: Concept 1: n=2201; Concept 2: n=2211; Concept 3: n=2202; Concept 4: n=2201; Concept 5: n=2202; Concept 6: n=2186
Likelihood To Use Snus Based On Warning Claim

No claims stand out as one that would influence non-users to use snus.

<table>
<thead>
<tr>
<th>Concept</th>
<th>Top 2 NET</th>
<th>Bottom 2 NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum disease/ Tooth loss</td>
<td>1- Not at all 67% 5,6</td>
<td>3% 3% 14% 4% 3% 6%</td>
</tr>
<tr>
<td>Is addictive</td>
<td>1- Not at all 63% 5</td>
<td>4% 3% 19% 13% 4% 5%</td>
</tr>
<tr>
<td>Mouth cancer</td>
<td>1- Not at all 71% 2,4, 5,6</td>
<td>3% 3% 12% 3% 5%</td>
</tr>
<tr>
<td>Not a safe alternative</td>
<td>1- Not at all 63% 5</td>
<td>4% 3% 19% 13% 4% 4%</td>
</tr>
<tr>
<td>Substantially lower risks</td>
<td>1- Not at all 57%</td>
<td>4% 3% 23% 1,3 5% 3% 5%</td>
</tr>
<tr>
<td>Lower risks</td>
<td>1- Not at all 61%</td>
<td>4% 4% 21% 1,3 5% 4%</td>
</tr>
</tbody>
</table>

Q53. After viewing the information in the warning label, how does the information you saw on the warning label directly influence your likelihood to use snus?

Test Claims

- Concept 1: n=1101
- Concept 2: n=1110
- Concept 3: n=1100
- Concept 4: n=1101
- Concept 5: n=1104
- Concept 6: n=1094
None of the claims tested are likely to influence former users to use snus, with a significant proportion of those exposed to the test claims citing the claims ‘had no impact’ on their likelihood to use snus.

Q53. After viewing the information in the warning label, how does the information you saw on the warning label directly influence your likelihood to use snus?

Base: Concept 1: n=108; Concept 2: n=135; Concept 3: n=126; Concept 4: n=115; Concept 5: n=116; Concept 6: n=99
Conclusions

• The two tested new statements resulted in respondents being better informed about the relative risk of snus versus cigarettes

• Impact on motivation to buy and likelihood to use snus restricted to current users of tobacco products

• No adverse impact on current non-users of tobacco product from the tested new statements
Conclusions, cont’d

• Findings among young adults (18-24 years), minorities, and respondents from low income households
  – Results were similar to those for the total populations of current users and non-users of tobacco products
  – Study findings thus do not raise unique issues or concerns for these demographic subsets

• Premarket data indicate that the tested two new statements are unlikely to produce unintended consequences
Independent analysis

• Advisory Panel much involved in the development of the protocol for the premarket study
• Two panel members together with others have conducted their own, independent analysis
• Publication of results is underway
• Findings do not contradict the analyses and conclusions included in the MRTPAs
• Raw data from the study made available
Premarket data and behavioral intentions

• There will always be an element of uncertainty in premarket studies
• In real life humans may not act the way we say we will in a research setting, we may be influenced by unexpected situational or subconscious stimuli
• Postmarket data concern actual behaviors
  – Final protocol not required until after an MRTP order has been issued
## Relationship to MRTP Order

<table>
<thead>
<tr>
<th>MRTPA Areas of Evidence</th>
<th>FDCA Statutory Standard for MRTP Order</th>
<th>Proposed MRTPA Warning Labels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Human Health Evidence</td>
<td>-Individual Risk Reduction</td>
<td>-deletion of mouth cancer warning</td>
</tr>
<tr>
<td></td>
<td>-Public Health Benefit</td>
<td>-deletion of gum disease and tooth loss warning</td>
</tr>
<tr>
<td>Norwegian Behavior Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swedish Match-funded Clinical Trials on Smoking Cessation</td>
<td>-Individual Risk Reduction</td>
<td></td>
</tr>
<tr>
<td>Potential and Nicotine PK and PD</td>
<td>-Public Health Benefit</td>
<td></td>
</tr>
<tr>
<td>Premarket Consumer Perception Study</td>
<td>-Public Health Benefit</td>
<td>-inclusion of “substantially lower risks to health” warning</td>
</tr>
<tr>
<td>Dynamic Population Modeler</td>
<td>-Public Health Benefit</td>
<td></td>
</tr>
</tbody>
</table>
Dynamic Population Modeler

Lars-Erik Rutqvist, MD, PhD
Key concept in the public health standard for an MRTP

• “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.”
“Benefit the health of the population...”

• Smoking affects:
  – Incidence & mortality (cancer, CV disease, COPD)
  – Morbidity (e.g., COPD, diabetes)
  – Quality of life

• In our applications we have defined “benefit” as a decrease in population overall mortality
  – Overall mortality is an accepted basic outcome measure in evaluations of public health effects
  – Data are readily available & unequivocal
  – No data gaps or conceptual ambiguities
Public health standard for an MRTP

• Population monitoring of effects of the marketing of an MRTP will inevitably generate a multitude of early metrics, such as:
  – Total prevalence of MRTP use
  – MRTP use in population subsets by age, gender, socioeconomic status, ethnicity
  – Effects on smoking prevalence overall & in subsets
  – Measures of dual smoking and MRTP use
  – Quit rates: assisted and unassisted

• A biostatistical model could potentially synthesize relevant metrics to a global measure about likely population effects, and might be used to model potential population scenarios including use of an MRTP
Dynamic Population Modeler (DPM)

• Swedish Match and RAI funded and supported ENVIRON’s early development and validation of the DPM in its original version that focuses on overall mortality.

• All DPM results presented in the Applications are based on the original version of the model.

• DPM was used to compare benefit of switching from cigarettes to snus, to the potential risks of dual use, tobacco initiation via snus, and use of snus instead of complete tobacco cessation.
Dynamic Population Modeler

- The DPM estimates all cause-mortality for a hypothetical population who at the beginning have never used tobacco and who, as they age, may transition into and out of different tobacco exposure states including current and former smoking, or MRTP use.
- The DPM compares number of survivors in a base case scenario comprised of current, former, and never smokers followed as they age, with the number of survivors in an alternative exposure scenario that also includes current, former, and never users of the MRTP.
DPM validation

• Validation exercises based on observed population data for the US and Sweden demonstrate that the DPM can accurately predict life tables in a population with little or no MRTP use (US), and a population with extensive MRTP use (Sweden)
Selected model specifications

• Hypothetical cohort of 1,000,000 never tobacco users initially 12 years old followed until age 72
• Age-specific mortality for 5-year age intervals for never, current, and former smokers based on Kaiser-Permanente Cohort Study data and the 2000 US census
• Base case transition probabilities (initiation, cessation of smoking) derived from US data for 2005-2008
• Excess relative risk (0.11) for current users of a low nitrosamine STP product such as snus versus current smokers based on published consensus data (Levy et al, 2004)
• Excess relative risk for dual users was set at 1.0, that is, same risk as for current smokers
Scenarios suggested in the FDA Guidance

- **Adverse population outcomes**
  - Some who remain never tobacco users in the base case instead initiate MRTP use
  - Some who remain never tobacco users in the base case initiate MRTP use and then switch to smoking (gateway)
  - Some who quit tobacco in the base case instead switch to the MRTP

- **Beneficial population outcomes**
  - Some who initiate smoking in the base case instead initiate the MRTP
  - Some current smokers who continue to smoke in the base case instead switch completely to the MRTP

- **Mix of adverse and beneficial outcomes**
  - “Tipping points”
“Naturalistic” worst case scenario

• What would happen if a “Swedish scenario” in terms of transitioning to snus plays out at least to some extent in the US (with returning to smoking as well as a possible “gateway effect” doubled compared to observed Swedish transition rates)?

  – A substantial and statistically significant overall survival benefit even if US transition rates to snus are only 50%, 25% or 10% of those observed in Sweden

(See Table 6-68 in the MRTPAs)
Conclusions

• DPM modeling confirms that introduction of snus would result in a net population benefit even if its adopted by a small proportion of smokers

• Profound effect on overall mortality from current smokers quitting (irrespective of whether they quit tobacco completely or switch to an MRTP)

• Substantial and statistically significant population benefit even if a “Swedish scenario” only plays out to a small extent in a US setting
## Relationship to MRTP Order

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<td>- inclusion of “substantially lower risks to health” warning</td>
</tr>
<tr>
<td>Dynamic Population Modeler</td>
<td>- Public Health Benefit</td>
<td></td>
</tr>
</tbody>
</table>
We have described the areas of evidence presented in the MRTPA and how they support the two statutory standards and the proposed warning label changes.

**The individual risk standard is supported by:**
- Swedish human health evidence; and
- Swedish Match-funded clinical trials.

**The public health benefit standard is supported by:**
- Swedish human health evidence;
- Norwegian evidence;
- Clinical trials;
- Dynamic Population Model; and
- Premarket consumer perception study.

**The proposed mouth cancer, gum disease and tooth loss warning label deletions are supported by:**
- Swedish human health evidence.

**The proposed “substantially lower risks to health” proposed warning label is supported by:**
- Premarket consumer perception study.
THANK YOU FOR YOUR ATTENTION.

Clarifying Questions?