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List of Abbreviations

ALS	Amyotrophic lateral sclerosis
AUCinf	Area under the plasma concentration-time curve from time zero to infinity
B(a)P	Benzo(a)pyrene
BMI	Body mass index
BROMS	Children's Smoking and Environment in Stockholm County
Cmax	Maximum serum concentration
COPD	Chronic Obstructive Pulmonary Disease
CTP	FDA Center for Tobacco Products
CVD	Cardiovascular disease
DPM	Dynamic Population Modeler
ENVIRON	ENVIRON International
ESTOC	European Smokeless Tobacco Council
EU	European Union
FDA	U.S. Food and Drug Administration
FDCA	Federal Food, Drug and Cosmetic Act
g	Gram
HACCP	Hazard Analysis Critical Control Point
HPHC	Harmful or Potentially Harmful Constituent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOM	Institute of Medicine
IRB	Institutional Review Board
ISO	International Organization for Standardization
KI	Karolinska Institutet

mg	Milligram
MI	Myocardial infarction
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MRTTP	Modified Risk Tobacco Product
MRTPA	Modified Risk Tobacco Product Application
ng	Nanogram
NRT	Nicotine Replacement Therapy
PD	Pharmacodynamics
PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAI	RAI Services Company
SALLS	Swedish Annual Level-of-Living survey
SALT	Screening Across Lifespan Twin study
SCC	Squamous Cell Carcinomas
SCENIHR	Scientific Committee on Emerging and Newly-Identified Health Risks
SES	Socioeconomic status
SIRUS	Norwegian Institute for Alcohol and Drug Research
SMNA	Swedish Match North America, Inc.
SRNT	Society for Research on Nicotine and Tobacco
STAB	Svenska Tobaksaktiebolaget
STAGE	Study of Twin Adults: Genes and Environment
STM	Svenska Tobaksmonopolet
STP	Smokeless tobacco product
TSNA	Tobacco-specific Nitrosamine

µg	Microgram
ULF	Swedish Level of Living Survey
ULSAM	Uppsala Longitudinal Study of Adult Men
US	United States of America
VIP	Västerbotten Intervention Program
WHO	World Health Organization

EXECUTIVE SUMMARY

Swedish Match North America, Inc. (SMNA) has submitted Modified Risk Tobacco Product Applications (MRTPAs or the Applications) to the U.S. Food and Drug Administration (FDA or the Agency) pursuant to Section 911 of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act), as amended by the Family Smoking Prevention and Tobacco Control Act (the Tobacco Control Act) seeking FDA approval to make modified-risk claims for ten Swedish snus smokeless tobacco products that are currently marketed in the United States (Snus Products or the Products). The MRTPAs contain 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. The data also show that providing more accurate information about the relative risks of cigarettes and Swedish snus would benefit the health of the population as a whole.

The MRTPAs do not propose new claims describing the health benefits of Swedish snus. Rather, they seek to modify the warning labels that are otherwise required for smokeless tobacco products so that they are no longer inconsistent with the extensive, product-specific evidence related to the health effects of snus. In particular, consistent with the available data, the Applications propose that warning labels concerning mouth cancer, and gum disease and tooth loss be removed and that the current “Not a safe alternative to cigarettes” warning be revised to “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” The MRTPAs propose to retain the current addiction warning.

The most applicable evidence submitted in support of the proposed modified risk claims is the result of research conducted using Swedish Match snus products. Typically, such product-specific evidence is generated only by the application sponsor. However, Swedish Match is fortunate to be able to submit an abundance of product-specific evidence derived from third-party studies undertaken by, and with the support of, Swedish academic institutions and governmental authorities. This Swedish-based epidemiology evidence, also referred to as the “Swedish Experience,” is set forth in hundreds of published articles derived from approximately a dozen key Scandinavian cohorts. This evidence demonstrates a significant reduction in smoking and smoking-related illness in Swedish males and has been widely cited by public health agencies and scientific institutions around the world.

The human health evidence from Sweden is supplemented by use behavior studies undertaken by the Norwegian Institute for Alcohol and Drug Research (SIRUS), an independent administrative government body under the Norwegian Ministry of Health Care Services. The SIRUS studies focus on tobacco harm reduction and, specifically, the role of snus in the dramatic decrease in smoking among Norwegian men. In a 2013 article, SIRUS Research Director Dr. Karl Erik Lund noted that, “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.”

To supplement the studies undertaken by academic institutions and governmental authorities, Swedish Match sponsored a series of clinical trials which address many of the key areas of investigation suggested in FDA’s *Draft Guidance for Industry: Modified Risk Tobacco Product Applications*¹ (MRTP Guidance). The clinical trials were initiated prior to the passage of the

¹ FDA, Draft Guidance for Industry: Modified Risk Tobacco Product Applications (Mar. 2012), available at <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf>.

Tobacco Control Act and reflect Swedish Match's longstanding commitment to product stewardship and consumer protection. Five trials were conducted: two focused on the smoking cessation potential of Swedish snus, and three addressed nicotine pharmacokinetics and pharmacodynamics.

Swedish Match also conducted premarket consumer perception research designed to assess the effects of the proposed modified risk warning labels on Swedish snus packaging on both current users and non-users of tobacco products, and how exposure to the test and control warning labels impacts consumer behavior, understanding, and perception of the health risks associated with the product.

Additional product-specific evidence was derived from the results of secondary data analysis and modeling using the Dynamic Population Modeler (DPM) developed by ENVIRON International, and funded by Swedish Match and RAI Services Company (RAI), to assess the public health impact of introducing a modified risk tobacco product to the population under different use scenarios and assumptions. The DPM forecasts the public health impact of the proposed MRTPs by estimating changes in all-cause mortality for a hypothetical population of persons who 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.

Taken together, these data provide compelling evidence that Swedish Match's Snus Products are modified risk tobacco products. They are less harmful than cigarettes and provide significant individual and public health benefits. Much of this benefit is attributable to GOTHIA TEK®, the Swedish Match Group's (Swedish Match's or the Company's) proprietary quality standard which subjects all Swedish Match products to rigorous controls in order to maintain the highest quality throughout all stages of the manufacturing process from tobacco plant to consumer. Pursuant to GOTHIA TEK®, the Snus Products that are the subject of the MRTPAs contain extremely low levels of TSNAs and meet the World Health Organization (WHO) Tobacco Regulatory Study Group recommendations for tobacco and thus also for smokeless tobacco products.

Swedish Match undertook the efforts to prepare and submit the MRTPAs based on its belief that individual and public health are served by making available accurate scientific information regarding the significantly lower risk presented by Swedish snus. This effort is consistent with the Company's longstanding commitment to governance and the public dissemination of information, which were exemplified throughout the MRTPA process. The Company is proud of its history, which is marked by three milestones: in 1999, the Company stopped manufacturing cigarettes; in 2000, the Company formally announced its voluntary, comprehensive quality standard GOTHIA TEK®; and in 2014, the Company unveiled its vision statement: "A World Without Cigarettes." The MRTPA process brought about additional milestones, including the establishment of a MRTP Advisory Panel and a proactive and inclusive outreach campaign to various tobacco stakeholders.

Swedish Match believes strongly that voluminous, product-specific scientific evidence clearly demonstrates the individual and public health benefits of the Company's Snus Products described in the MRTPAs. Consistent with that data, Swedish Match urges the Tobacco Products Scientific Advisory Committee (TPSAC) to recommend that FDA designate these Products as MRTPs.

1. INTRODUCTION

Swedish Match North America, Inc. (SMNA) has submitted Modified Risk Tobacco Product Applications (MRTPAs or the Applications) to the U.S. Food and Drug Administration (FDA or the Agency) pursuant to Section 911 of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act), as amended by the Family Smoking Prevention and Tobacco Control Act (the Tobacco Control Act) seeking FDA approval to make modified-risk claims for ten Swedish snus smokeless tobacco products that are currently marketed in the United States. The MRTPAs contain 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. The data also show that providing more accurate information about the relative risks of cigarettes and Swedish snus would benefit the health of the population as a whole.

The MRTPAs do not propose new claims describing the health benefits of Swedish snus. Rather, they seek to modify the warning labels that are otherwise required for smokeless tobacco products so that they are no longer inconsistent with the extensive, product-specific evidence related to the health effects of snus. In particular, consistent with the available data, the Applications propose that warning labels concerning mouth cancer, and gum disease and tooth loss be removed and that the current “Not a safe alternative to cigarettes” warning be revised to “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” The MRTPAs propose to retain the current addiction warning.

As shown in Appendix I, the MRTPAs were prepared in accordance with the requirements of Section 911 of the FDCA. They are also consistent with the MRTP Guidance, following FDA’s recommended organizational framework and addressing every suggested area of evidence. Preparation of the Applications was also influenced by the consensus report *Scientific Standards for Studies on Modified Risk Tobacco Products* (IOM Report) prepared by the Institute of Medicine’s (IOM’s) Committee on Scientific Standards for Studies on Modified Risk Tobacco Products. The Briefing Document is organized as follows:

- Section 2 of the Briefing Document describes the snus products that are the subject of the MRTPAs.
- Section 3 provides an introduction to the Company.
- Section 4 provides an overview of the statutory and regulatory framework governing modified risk tobacco product applications.
- Section 5 summarizes the scientific evidence submitted in the MRTPAs, including the observational epidemiology studies comprising the Swedish Experience (5.1), the clinical trials supporting the Applications (5.2), and the Consumer Perception Study (5.3), and the Dynamic Population Modeler (5.4) that Swedish Match sponsored to support the MRTPAs.
- Section 6 describes the Swedish Match’s proprietary, quality standard GOTHIA TEK®.
- Section 7 describes the information demonstrating the individual risk reduction benefit of switching from cigarettes to Swedish snus, including the lower risk of lung cancer and cardiovascular disease among others. It also discusses the evidence supporting the

proposed changes to the warning labels to remove the warnings related to oral cancer and non-cancer oral effects including tooth loss and gum disease.

- Section 8 describes the information demonstrating the Snus Products' benefit to the population as a whole, with particular focus on the dual use of snus and cigarettes, smoking cessation impacts, and the potential for initiation of tobacco use by youth and adolescents. Section 8 also discusses the public health benefit of providing accurate relative risk information.
- Section 9 of the Briefing Document describes Swedish Match's commitment to governance and outreach, including the role of the Swedish Match MRTP Advisory Panel.
- Section 10 describes the Postmarket Surveillance efforts that the Company will undertake following receipt of the requested MRTP orders from FDA.

2. DESCRIPTION OF THE SNUS PRODUCTS

The ten (10) products which are the subject of the MRTP Applications are a form of Swedish snus, a world-unique smokeless tobacco product which originated in the Nordic region of Europe nearly 200 years ago. According to the European Smokeless Tobacco Council (ESTOC), "snus" is defined as a smokeless tobacco product for oral use which is traditionally produced and used in Sweden and manufactured using a heat treatment process. This definition distinguishes Swedish snus from all other types of smokeless tobacco, including some snus-like products recently introduced in the United States market which have distinctly different characteristics.

Swedish snus is made from selected, mainly air-dried tobacco varieties, various salts, flavoring, and moisture-preserving substances. Put another way, Swedish snus contains only finely ground tobacco mixed with water, additives (e.g., table salt, sodium carbonate, etc.) and flavors. In Sweden, snus is equated with food, contains only food-approved ingredients, and is manufactured in premises that are hygienically suitable for food production. All Swedish Match snus is manufactured in compliance with Swedish laws governing food products and in compliance with the quality standards of ISO 9001: 2000, the environmental standard 1401:1996, and the Company's proprietary quality control system, GOTHIA TEK®.

Swedish snus is a moist (45-60% moisture) to semi-moist (25-45% moisture) oral smokeless product which is placed between the upper lip and the gum and does not require expectoration during use. This distinguishes Swedish snus from all other American smokeless tobacco products, including dry nasal snuff, which is inhaled through the nasal cavity, or moist snuff that is placed under the lower lip and requires expectoration during use.

All of the Snus Products are part of Swedish Match's *General* line of snus products. All ten products are manufactured in Sweden according to Swedish Match's proprietary product quality standard, GOTHIA TEK®, and have the same health and risk profiles. The Products contain extremely low levels of TSNAs and meet WHO Tobacco Regulatory Study Group recommendations for tobacco and, thus, for smokeless products.

As is more fully described in the MRTPAs, one of the Snus Products is loose snus, and the other nine (9) products are portion (or pouched) snus. Loose snus was the traditional variant used in Sweden for centuries, but portion snus has been used since the early 1970s. Upon usage, the pouched snus or a pinch of loose snus is placed between the gum and the upper lip. A recent population-based study regarding the patterns and behaviors of snus use in Sweden found that on average, a user consumed approximately 11-12 g/day of pouched snus, while users of loose snus consumed 29-32 g/day (Digard et al., 2009).

3. THE COMPANY

Swedish Match's mission is to responsibly develop, manufacture, market, and sell market-leading brands in a number of product areas, including snus, other tobacco products, and lights (i.e., matches and lighters). Swedish Match and its predecessor companies, Svenska Tobaksmonopolet (STM) and Svenska Tobaksaktiebolaget (STAB), have been selling snus in Scandinavia since the early twentieth century.

Currently, Swedish Match consists of five operating divisions, including among them SMNA and the Scandinavia Division. SMNA is headquartered in Richmond, Virginia, and is responsible for sales and marketing of snus, snuff, and chewing tobacco in the US. The Scandinavia Division's head office is located in Sweden and is responsible for the manufacture and supply chain management for the Company's smokeless tobacco products.

Swedish Match recently marked three important milestones: in 1999, the Company stopped manufacturing cigarettes; in 2000, the Company formally announced its voluntary, comprehensive quality standard GOTHIA TEK®; and in 2014, the Company unveiled its vision statement, "A World Without Cigarettes." Throughout this history, the Company has remained committed to policies of openness, transparency, product stewardship, and product improvement. It is in this spirit that, upon passage of the Tobacco Control Act in 2009, Swedish Match initiated plans to prepare and submit MRTP Applications for its Snus Products. Swedish Match believes that the Applications are an important step toward ensuring that US consumers have accurate, science-based information about the relative risks of tobacco products. To this end, the MRTPAs propose certain modifications to the current smokeless tobacco warnings that, as applied to the Snus Products, are consistent with the extensive scientific evidence available regarding the products.

Swedish Match has engaged FDA's Center for Tobacco Products (CTP) throughout the preparation process for the MRTPAs. The first MRTPA-related meeting between the Company and CTP occurred in late 2011, followed by a series of meetings and conference calls leading up to the submission of the MRTPA in June 2014. The MRTPAs were largely prepared by Company staff, with contributions from (b) (4), and external consultants, ENVIRON International Corporation (ENVIRON) and GlobalSubmit.

4. MODIFIED RISK TOBACCO PRODUCTS

4.1. The Concept of “Modified-Risk”

The Tobacco Control Act was enacted to establish a regulatory framework to address the public health and societal problems attributable to tobacco. One of the statute’s declared purposes is “to ensure that there is effective oversight of the tobacco industry’s efforts to develop, introduce, and promote less harmful tobacco products.” This means, as the IOM Report notes, that the prospect of a less hazardous tobacco product is “not in and of itself problematic” but rather the “fundamental issue is that if a product is going to be marketed as being ‘safer’, then the claim must be true.” Accordingly, the Tobacco Control Act provides a regulatory framework for FDA’s oversight of the development and marketing of products making such modified risk claims.

The FDCA defines a modified risk tobacco product (MRTP) as a tobacco product that is sold or distributed for use to reduce harm and the risk of tobacco-related disease associated with commercially marketed tobacco products. This definition includes, among other things, a tobacco product that represents in its label, labeling, or advertising, either implicitly or explicitly, that it presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products.

Swedish Match submits that Swedish snus, as manufactured by Swedish Match, is significantly less harmful than cigarettes, and that Congress has provided a mechanism under the Tobacco Control Act to inform adult consumers of snus’s harm reduction potential.² Thus, the Company’s MRTP Applications seek product-specific modifications to the statutorily-mandated health warnings for smokeless products in order to better communicate to consumers the risks of Swedish snus as compared to other commercially marketed tobacco products. The Company’s proposed modified risk claims will be communicated to consumers through the product label, but Swedish Match does not plan to otherwise communicate, highlight, or promote the proposed modified risk claims to consumers using other labeling or advertising.

4.2. Statutory Standard for Approval of the MRTP Application

Before an MRTP can be introduced or delivered for introduction into interstate commerce, FDA must issue an MRTP order for the product. Section 911(g)(1) of the FDCA provides that FDA shall issue an MRTP order based on an MRTP applicant’s demonstration that a product, as actually used by consumers, will “(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.” In making this determination, FDA must take into account the following: (i) the relative health risks to individuals of the proposed MRTP; (ii) the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the proposed MRTP; (iii) the increased or decreased likelihood that non-users of tobacco products will start using the proposed MRTP; (iv) the risks and benefits to persons from

² Some commenters to FDA’s public docket for the MRTP Applications have challenged the legal basis for using the modified risk provisions of the Tobacco Control Act to amend the currently-mandated smokeless tobacco warning label statements for the Snus Products. These objections are untimely and without merit, and should have no bearing on FDA’s review of the filed Applications.

the use of the proposed MRTP as compared to the use of smoking cessation products approved to treat nicotine dependence; and (v) comments, data, and information submitted by interested persons.

The potential for individual risk reduction by switching from cigarettes to a smokeless tobacco product has been widely accepted within the regulatory science community. In particular, the Swedish human health evidence convincingly demonstrates the reduction in individual risk associated with the use of Swedish snus compared to smoking cigarettes. Swedish Match believes that these studies, and by extension the MRTPAs, provide the evidence necessary to demonstrate that use of the Snus Products will significantly reduce individual risk.

Due to the inherent difficulties in assessing, on a premarket basis, the effect of an MRTP's introduction on the public health, FDA has encouraged the development and application of innovative analytical methods to estimate the potential health effects expected to result from changes in the distribution and use of different tobacco products in a given population. To this end, Swedish Match and RAI funded ENVIRON's development of a Dynamic Population Modeler (DPM), an innovative analytical tool that enhances tobacco regulatory science and is a vital part of the MRTPAs. Swedish Match used the DPM to compare the benefit of switching from cigarettes to Swedish snus, to the potential risks of dual use, tobacco initiation via snus, and use of snus in lieu of complete tobacco cessation. Application of the DPM to the data on Swedish snus demonstrated a clear public health benefit, taking into account both users and non-users of tobacco products.

The DPM's quantitative estimates of the population-level effects of Swedish snus are corroborated by the compelling epidemiological evidence presented in the Applications. Both the Swedish and Norwegian experiences demonstrate that a transition from smoking to Swedish snus can occur with limited negative impacts and a clear public health benefit. Swedish men have the lowest prevalence of smoking in the European Union (EU), but they also have a high rate of snus use, 12% and 19% respectively. The rate of smoking among Swedish women is comparable with that of other EU member states, and the prevalence of snus use is low, 16% and 4% respectively. The experience in Norway is similar. Swedish Match believes that these data are highly relevant to CTP's consideration of the MRTPAs, as both countries provide a "natural laboratory" (Lund 2013) for the study of how snus typically competes with cigarettes and contributes to smokers' recognition of the harm reduction potential of snus.

In sum, the MRTPAs clearly demonstrate that switching to Swedish snus presents a lower risk to individual health than smoking cigarettes, and a benefit to the health of the population as a whole. But maximizing the public health benefit of the proposed MRTPs requires that consumers—and particularly, current smokers—receive accurate information about the relative health risks of different types of nicotine-containing products. Accordingly, Swedish Match proposes to remove the warnings stating that the products cause mouth cancer, and gum disease and tooth loss, so as to conform the warning labels for the Snus Products to the scientific data. These same data support the Company's proposal to replace the current required warning stating that snus is *"not a safe alternative to cigarettes"* with the more accurate, science-based statement, *"No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."* Swedish Match's premarket consumer perception study has assessed the impact of this proposed new language and demonstrated that the change will result in improved understanding of the relative risk of the Snus Products.

The remainder of this Briefing Document summarizes the key evidence presented in the MRTPAs. Sections 5 and 6 summarize the scientific evidence and the GOTHIA TEK® standards supporting the modified-risk determinations for the Snus Products, respectively. They are followed by sections applying the FDCA's statutory standards to the evidence to demonstrate the reduced individual risk of the Snus Products (Section 7) and the benefit of the MRTPAs to the population as a whole (Section 8)

5. OVERVIEW OF SCIENTIFIC EVIDENCE

The IOM Report addresses the types of evidence and studies necessary to support modified-risk claims for existing, commercially-available tobacco products. With respect to the evidence and studies relating to the health effects of tobacco products, IOM stated that “[o]bservational epidemiologic studies play a critical and central role in the evaluation of MRTPs.” According to IOM, “these methods form the basis for most evaluation studies of regulated products in the community. Long, intensive, and robust observational studies of actual health outcomes may be required to fully evaluate the net effects of MRTPs relative to conventional tobacco products.” IOM further indicated that such studies should be supplemented by experimental designs, and in particular, randomized controlled trials.

IOM's findings are reflected in the scientific evidence presented in the MRTPAs. Consistent with IOM's recommendations, Application evidence is derived largely from observational, product-specific epidemiologic studies and enhanced by clinical trials. The Swedish epidemiological evidence provides the foundation for the MRTPAs and is applicable to the assessment of individual risk and public health benefit. The Swedish evidence is complemented by Norwegian behavior evidence, clinical trials funded by the Company, a premarket consumer perception study assessing the impact of the proposed label changes, and Dynamic Population Modeler estimates of changes in all-cause mortality.

The most applicable evidence submitted in support of the proposed modified risk claims is the result of research conducted using Swedish Match snus. Typically, such product-specific evidence is generated only by the application sponsor. However, Swedish Match is fortunate to be able to submit an abundance of product-specific evidence derived from third-party studies undertaken by, and with the support of, Swedish academic institutions and governmental authorities. This Swedish-based epidemiology evidence, also referred to as the “Swedish Experience”, demonstrates a significant reduction in smoking and smoking-related illness in Swedish males and has been widely cited by public health agencies and scientific institutions around the world. Importantly, during the time period in which these epidemiological studies were being conducted, Swedish Match dominated the Scandinavian snus market. There were no snus manufacturers other than Swedish Match in Sweden until the 1990s, and since that time, Swedish Match has historically maintained a market share of more than 80-90%. **(Figure 5.1)** As a result, the data generated in these studies is highly specific to Swedish Match snus, and the Swedish Experience is the foundation for the modified risk claims presented in the Applications.

Compelling human health evidence from Sweden is supplemented by use behavior studies undertaken by the Norwegian Institute for Alcohol and Drug Research (SIRUS). The SIRUS studies focused on tobacco harm reduction and, specifically, the role of snus in the dramatic decrease in smoking among Norwegian men. During the time period of the SIRUS studies the

Swedish Match volume market share in Norway was greater than 90% (until 2005), and ranged from 70-90% from 2006-2011. (Figure 5.2)

Figure 5.1 Swedish Match Product Volume Share in Sweden

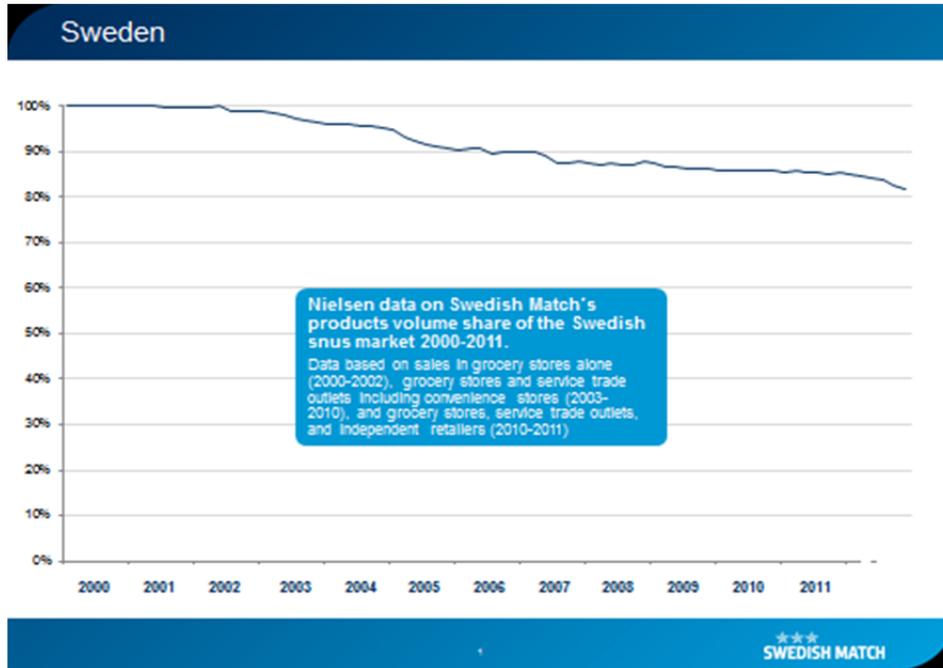
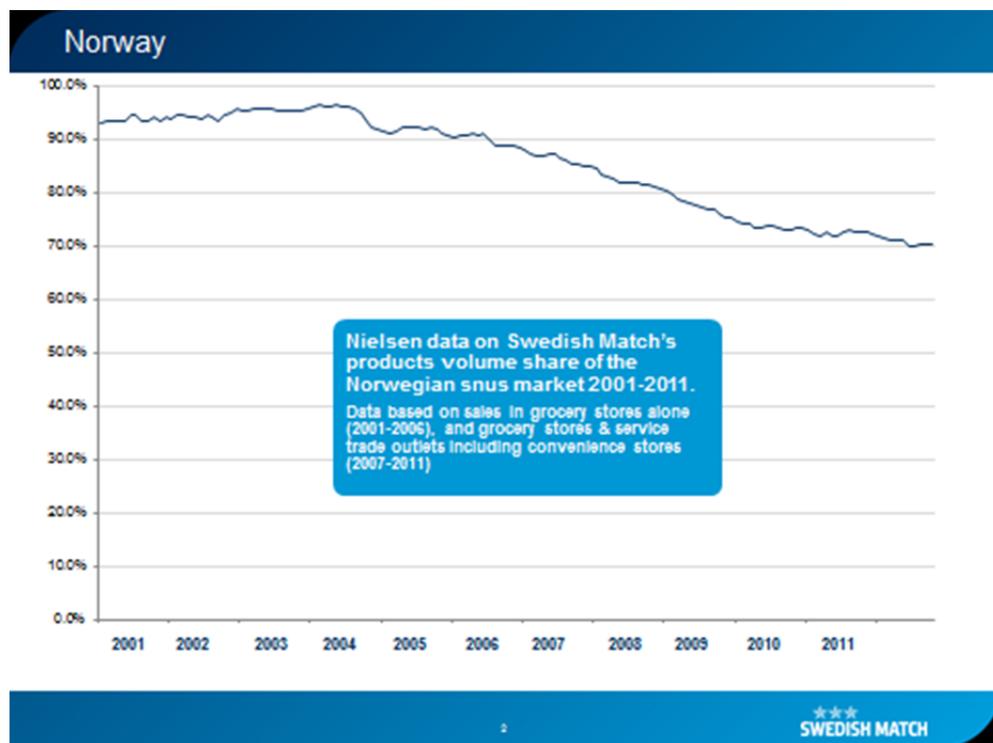


Figure 5.2 Swedish Match Product Volume Share in Norway



To supplement the studies undertaken by academic institutions and governmental authorities, Swedish Match sponsored a series of clinical trials which address many of the key areas of investigation suggested in the MRTP Guidance. The clinical trials were initiated prior to the passage of the Tobacco Control Act and reflect Swedish Match’s longstanding commitment to product stewardship and consumer protection. Five trials were conducted; two focused on the smoking cessation potential of Swedish snus, and three addressed nicotine pharmacokinetics (PK) and pharmacodynamics (PD).

The two placebo-controlled, double-blind, randomized smoking cessation clinical trials were conducted at two sites in Serbia and five sites in the United States during 2008-2010 and are particularly relevant to the MRTPAs. Both studies demonstrated that adult smokers motivated to quit or substantially reduce their smoking were two to three times more likely to quit smoking completely when allocated snus compared to placebo. (Fagerstrom et al. 2012; Joksic et al. 2011; Rutqvist et al. 2013). These studies were complemented by three additional Swedish Match studies comparing the nicotine PK and PD of various snus products compared to select nicotine replacement therapies (NRTs). These nicotine uptake trials showed that the PK and PD of snus are comparable to commercially available NRT products, although absorption of nicotine is somewhat faster with snus, which may explain the higher smoking cessation rate among Swedish snus users compared to those using other NRTs. Although faster absorption suggests that the abuse liability of snus may be somewhat higher than with NRTs, it remains clearly significantly lower than for cigarettes.

Swedish Match also conducted premarket consumer perception research designed to assess the effects of the proposed modified risk warning labels on Swedish snus packaging on both current users and non-users of tobacco products, and how exposure to the test and control warning labels impacts consumer behavior, understanding, and perception of the health risks associated with the product. The overall results of the study demonstrate that the proposed warning labels for the Snus Products are unlikely to produce significant unintended negative consequences for the population as a whole, or among key demographic subgroups.

Additional product-specific evidence derives from the results of secondary data analysis and modeling using the Dynamic Population Modeler developed by ENVIRON (and funded by Swedish Match and RAI) to assess the public health impact of introducing a modified risk tobacco product to the population under different use scenarios and assumptions. The DPM forecasts the public health impact of the proposed MRTPs by estimating changes in all-cause mortality for a hypothetical population of persons who 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.

Different questions can be addressed using the DPM by specifying different rates of initiation, cessation of use, and return to use of cigarettes and the MRTP. For example, it may be of interest to determine if survival is higher, and by how much, if some smokers switch to the MRTP instead of continuing to smoke. Conversely, survival may be lower if some smokers switch to the MRTP instead of quitting smoking. The DPM provides quantitative estimates of the effect on survival if either pattern occurs. It also can be used to estimate the proportion of the population that must make a harmful behavior change (e.g., switching to the MRTP instead of quitting smoking) to overcome a beneficial change (e.g., switching to the MRTP instead of continuing to smoke), or vice versa. Analyses that provide estimates of the proportion needed to change their exposure in a specified way in order to overcome a harm or benefit from a different exposure pattern are called “tipping point” analyses. Such tipping point analyses conducted for the MRTPA demonstrate that the potential that a few non-smokers will initiate snus use is counter-balanced by the benefit of some smokers who would have continued to smoke instead initiating snus use. Thus, at a population level, it takes a very small percentage of smokers switching to snus instead of smoking to result in a significant public health benefit.

5.1. Observational Epidemiology Studies

5.1.1. The Swedish Experience

The observational epidemiology studies submitted in support of the modified risk claims are the result of research conducted in Sweden using Swedish Match snus products. The product-specific evidence is derived from third-party studies undertaken by, and with the support of, Swedish academic institutions and governmental authorities. This Swedish-based epidemiology evidence, also referred to as the “Swedish Experience”, has been widely cited by public health agencies and scientific institutions around the world, and it is fundamental to the analysis of the modified risk claims presented in the Applications.

These studies are highly product specific. During the time period the Swedish experience studies were being conducted Swedish Match dominated the Scandinavian snus market. There were no snus manufacturers other than Swedish Match in Sweden until the 1990s. Since then,

Swedish Match has historically maintained a market share of more than 80-90%. In Norway, the Swedish Match volume market share was above 90% until 2005, and ranged from 70-90% from 2006-2011. Thus, all of the Scandinavian epidemiological studies that have assessed the effects of smokeless tobacco—irrespective of whether the word “snus” or “snuff” was used to describe the studied product—almost certainly concerned Swedish snus as manufactured by Swedish Match and its predecessors. (For purposes of clarity and consistency, the term “snus” is used throughout this Briefing Document to describe these products.) Moreover, all of the Swedish epidemiological studies have studied Swedish snus as manufactured by Swedish Match, regardless of whether this fact was specified in the published reports.

The scientific conclusions supported by the Swedish Experience are set forth in hundreds of published research articles, most of which derive from approximately 10-15 key Scandinavian cohorts. These studies provide an analysis of risk factors, including snus use, and consider the life histories of segments of populations and the individuals who constitute these segments. The studies all examine specific cohorts that share a common characteristic or experience within a defined period. Like all cohort studies, Swedish Experience studies have their strengths and weaknesses, including varying cohort size, participation rates, regional characteristics, and consideration of confounding factors. Nevertheless, these studies are considered to be the most useful and authoritative sources of information globally for the study of Swedish snus, and have been cited widely by public health authorities and scientific and academic researchers around the world.

Numerous scientific articles have been published based on the Scandinavian cohorts. For example, for several years, researchers in the Department of Medical Epidemiology and Biostatistics at the Karolinska Institutet (KI), Sweden’s premier medical research institution, published numerous studies of the health risks related to snus use. These KI studies have profoundly influenced regulatory actions all over the world. Perhaps the best known are those based on the Swedish Construction Worker cohort of up to 340,000 subjects which served as the basis for epidemiologic follow-up studies investigating associations between many risk factors and diseases.

One of the most convincing outcomes of the various Swedish Experience cohort studies is the replicability of findings across different data sets, strongly suggesting convergent validity. The credibility of these studies is further enhanced by a number of important factors, including Sweden’s (i) widespread use of a unique personal identification number that permits computerized record linkages; (ii) population registers with high coverage that permit a highly reliable verification of vital status, immigration and emigration dates, and other information; (iii) national cancer registration since 1958 with a high coverage of detected cancer cases; (iv) national cause-of-death registration; and (v) availability of population-based registers for several disease outcomes such as cardiovascular diseases. That these studies were conducted by governmental or non-profit organizations, and not by industry, further contributes to their relevance and credibility.

The cohorts comprising the Swedish Experience are identified in **Table 5.1** below. Significant cohorts include the following:

- One of the most significant cohorts applicable to Swedish snus is the Swedish Construction Industry’s Organization for Working Environment, Safety and Health Cohort. This initiative started as a health service offered to construction workers; it was not originally intended to form the basis for epidemiological research. However, after a

few years, the collected data were computerized and the information was made available to researchers at Swedish universities, including the KI. The epidemiology studies based on this cohort collected data on snus use over the 24-year period from 1969-1993. The primary strengths of the study were the large sample size (i.e., up to more than 340,000 men depending on exclusion criteria), the high prevalence of snus use (i.e., 28%), and the large number of never-smoking snus users (i.e., 28%) (e.g., Luo et al. 2007). The primary limitation of these studies is the ambiguity in the coding of smoking status, most notably in the early years of data collection, and the lack of data on potential confounding factors, such as alcohol intake.

- Another fundamental cohort study is the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project that collected data over a 13-year period on, among other things, daily use of Swedish snus and other forms of smokeless tobacco among adults in the two most northern counties of Sweden. The strengths of the study include the accurate and consistent definitions of tobacco use, standardized data collection methods, and a high percentage of participants receiving a follow-up examination. A limitation of the study (and of most cohort studies generally) is that a change in tobacco status could have occurred at any time during the study and follow-up period.
- The Swedish Twin Registry cohort is the largest population-based twin registry in the world and has been the basis of several significant research studies on Swedish snus, including a study by Hansson et al. (2009). The study cohort is representative of the general Swedish population, and controls for many important potential confounders of cardiovascular disease (e.g., age, smoking status, diabetes, high blood pressure, and high cholesterol).
- The Children's Smoking and Environment in Stockholm County, or BROMS cohort is an important element of the Swedish Experience that assesses tobacco use behaviors in youths. The BROMS study surveyed more than 3,000 fifth graders during the 1997-1998 school year and conducted annual follow-up surveys until 2005. The children were asked a series of questions relating to the use of Swedish snus (called "snuff" in the study), including: whether they had ever tried oral snus, age at initiation, symptoms at first use, progression to regular use, quit attempts, circumstances of tobacco use, and preferred brands. These data formed the basis of several significant publications, including those by Galanti et al. (2001b; 2001a) and (2008), Rosendahl et al. (2003), and Post et al. (2005).
- Other key studies include the Malmö Diet and Cancer Cohort, two Uppsala County Cohorts, Swedish Annual Level-of-Living Survey and Swedish Survey of Living Conditions, Swedish Birth Registry, and the Northern Swedish Cohort.

The Scandinavian epidemiological evidence provides the scientific foundation for the MRTPAs. The evidence is also critical to the assessment of all tobacco products and NRTs. In fact, it is arguably the best human health data available on nicotine delivery products to date.

TABLE 5.1 - SUMMARY OF SCANDINAVIAN COHORTS AND PUBLICATIONS BASED ON EACH COHORT

COHORT	DESCRIPTION	SNUS USE ASSESSMENT AND CONSUMPTION DATA	COMMENTS	REFERENCES
Malmö Diet and Cancer Cohort	Years: 1991-1996 Baseline n=28,449 adults 45-73 years in Malmö, Sweden	Self-administered questionnaire regarding use of snus and chewing tobacco Blood sampling, anthropometric measurements. Among snus users: Men: 1-2 packages/week: 54.5% 3-5 packages/week: 32.2% >6 packages/week: 9.0% Women: 1-2 packages/week: 58.7% 3-5 packages/week: 14.7% >6 packages/week: 0.1%	Adjusted for age, BMI, smoking habits, diabetes, hypertension, physical activity, marital status and occupation. Does not control for some other classic risk factors such as cholesterol level.	Janzon and Hedblad 2009 (CVD, MI and Stroke); Lee (2011)
Northern Sweden Monitoring of Trends and Determinants in Cardio-vascular Disease (MONICA) Project	Years 1986, 1990, 1994, 1999 Baseline n=3,429 adults 25-64 years in 1986 and 1990 and 25-74 years in 1994 and 1999 in Norrbotten and Vasterbotten, the two most northern counties of Sweden	Daily use of smokeless tobacco: Never, former, current use In the 1990 cohort, plasma nicotine and cotinine were measured in a random sample of 321 participants to validate self-reported tobacco habits.		Eliasson et al. 2004 (Diabetes); Rodu et al. 2004 (Body weight)
Swedish Twin Registry (2 substudies: Study of Twin Adults: Genes and Environment (STAGE) and Screening across lifespan twin study (SALT))	Swedish twins born between 1986 and 2000 N=160,000 twins STAGE: began in 2005 Baseline n= 20,117 twins born between 1959-1985 SALT: conducted from 1998-2002, twins born in or before 1958 Final analysis: N=16,642 male twins	STAGE: Frequency of snus use, age at initiation SALT: Current, former, never snus use, frequency of snus use (regularly, now and then) and age at initiation The participants also reported leisure time physical activity, alcohol consumption, level of education, whether they had been diagnosed with diabetes mellitus, if they had had their blood pressure and cholesterol levels measured by a health professional within the last five years and if so, whether these levels were abnormal.	Largest population-based twin registry in the world.	Hansson et al. 2009 (CVD)

TABLE 5.1 - SUMMARY OF SCANDINAVIAN COHORTS AND PUBLICATIONS BASED ON EACH COHORT

COHORT	DESCRIPTION	SNUS USE ASSESSMENT AND CONSUMPTION DATA	COMMENTS	REFERENCES
Vasterbotten Intervention Programme (VIP)	Years: Enrollment 1985, Follow-up at ages 30, 40, 50, and 60 years. N=16,492 adults in Västerbotten (Northern Sweden)	Never, former, current use Amount (cans per week): <2, 2-4, 5-6, ≥7	Self-report of alcohol consumption in one study, while other study (Nafziger) did not control or comment on alcohol consumption.	Norberg et al. 2006 (Metabolic syndrome, Body weight); Nafziger et al. 2007 (Body weight)
Norway General Population Sample and Relatives of Norwegian Migrants to the US	Years: Enrollment 1964 and 1967; followed until 2001 N=10,136 from systematic sample of the general population of Norway identified from the 1960 census, and relatives of Norwegian migrants to the United States.	Regular current use, regular former users or never or occasional users. Tobacco smoking classified as never/current/former smoking of cigarettes/cigars/pipe.	Collected information on dietary habits, tobacco smoking, alcohol drinking, and anthropometric parameters. Lack of information on amount and duration of snus use and tobacco smoking after enrollment.	Boffetta et al. 2005 (Cancer)
Uppsala County, Central Sweden Cohort	Years: Baseline 1973-1974; followed until 2002. N=9,976 male residents of the municipalities of Enköping or Habo aged 15 years or older during the year of examination..	Never or ever daily use. Tobacco and alcohol information collected.	Exposure information collected up to 29 years prior to the occurrence of studied outcomes. In an analysis of 252 reexamined in 1993-95, among the 22 who were never users of tobacco in 1973-74 none had taken up smoking, but one had taken up daily snus use. Among 56 exclusively ever daily smokers in 1973-74 seven had become daily users of snus exclusively and 28 had stopped using tobacco. None of 60 exclusively snus users in 1973-74 had changed to smoking.	Roosaar et al. 2008 (Cancer, CVD and Respiratory death)
Uppsala Longitudinal Study of Adult Men (ULSAM)	Years: Baseline 1970-1973, followed through 2002 N=2,322 all 50-year-old men residing in Uppsala County in	'Do you use snus?' and 'How many tins of snus do you consume per week?'	Seventy three percent (73%) of the surviving men participated in a re-investigation from 1991-1995 (n=1221). Smoking was	Arefalk et al. 2011(CVD)

TABLE 5.1 - SUMMARY OF SCANDINAVIAN COHORTS AND PUBLICATIONS BASED ON EACH COHORT

COHORT	DESCRIPTION	SNUS USE ASSESSMENT AND CONSUMPTION DATA	COMMENTS	REFERENCES
	Central Sweden		adjusted for by using a current smoking dose and pack-year variables.	
Swedish Annual Level-of-Living survey (SALLS) / Swedish Survey of Living Conditions (ULF)	<p>SALLS</p> <p>Years: 1988 and 1989 Statistics Sweden national surveys; followed through 2000.</p> <p>N=3120 included all men aged 30-74 who were surveyed</p> <p>ULF</p> <p>Years: 1988 and 1989 surveys, followed through 2003</p> <p>N=5,002 men surveyed aged 16-74 years</p>	<p>Participants interviewed face-to-face.</p> <p>SALLS: Never/former/daily smoker and daily snus user.</p> <p>ULF: no tobacco, daily smoke (but not daily snus), daily snus (but not daily smoke), daily smoke and snus, and snus and/or smoke occasionally.</p>	<p>Collected information on living conditions, including complete information on socio-economic status, lifestyle and health indicators.</p> <p>Prevalence of diabetes and hypertension was by self-report .</p> <p>Only recorded tobacco use at baseline.</p>	<p>Johansson et al. 2005 (CVD);</p> <p>Haglund et al. 2007(CVD)</p>
Swedish Birth Registry	<p>England et al. 2003:</p> <p>Sweden-born women who were delivered of singleton infants during 1999-2000</p> <p>N=789 snus users, 11,240 smokers and 11,495 nonuser).</p> <p>Wikstrom et al. 2010a,b,c:</p> <p>Sweden-born women who were delivered of singleton infants during 1999-2006.</p> <p>N=more than 600,000 eligible women, with more than 7,500 snus users.</p> <p>Gunnerbeck et al. 2011:</p> <p>Sweden-born women who were</p>	<p>England et al. 2003:</p> <p>Nonuser, snus user, cigarette smoker, 1-9 cigarettes, ≥10 cigarettes.</p> <p>Wikstrom et al. 2010a,b,c:</p> <p>Nonuser, snus user, cigarette smoker, 1-9 cigarettes, ≥10 cigarettes, snus and cigarette user.</p>		<p>England et al. 2003 (Birth outcomes);</p> <p>Wikstrom et al. 2010a,b,c (Birth outcomes),</p> <p>Gunnerbeck et al. 2011 (Birth outcomes)</p>

TABLE 5.1 - SUMMARY OF SCANDINAVIAN COHORTS AND PUBLICATIONS BASED ON EACH COHORT

COHORT	DESCRIPTION	SNUS USE ASSESSMENT AND CONSUMPTION DATA	COMMENTS	REFERENCES
	delivered of singleton infants during 1999-2006. N=more than 600,000 eligible women, with more than 7,500 snus users.			
The Northern Swedish Cohort	Year: 1981, follow up in 1983 (age 18), 1985 (age 21), 1995 (age 30) and 2008 (age 43) N=1,083 (girls 506; boys 577) students who attended, or should have attended, the last year of compulsory school (age 16 years) in all schools in Lulea, Sweden.	Self-report of daily smoking (no/yes), daily snus use (no/yes)	Adjusted for SES, BMI, SBP, DBP, daily smoking, daily snus use, alcohol consumption, and physical inactivity.	Gustafsson et al. 2011 (Metabolic syndrome); Hammarstrom and Janlert 2012 (Background information)
Lund University Hospital Post-op complication cohort	Years: 2000- 2005 N=175 male patients (41 smokers, 21 oral snus users, and 113 non-smokers/non-snus users) undergoing knee operation and followed through recovery.	Non-smoker/non-snus user-, snus user		W-Dahl and Toksvig-Larsen 2007 (Post-op complications)
Multi-Center Post-op Impacts Cohort	Years: autumn 2006-spring 2008 N=355 patients over 18 years who were scheduled for one of three elective surgical procedures.	Smoker, snus user, smoker or snus user, non-nicotine user (yes/no).		Brattwall et al. 2010 (Post-op impacts)
Stockholm Public Health Cohort	Baseline year: 2002, follow-up 2007 N=9,954 adult men aged 18-84 years from a random sample of Stockholm County residents.	Self-report: No tobacco use; Snus/smoking (Stable current use, stable former use, quit during follow-up, began during follow-up).	Information on age, baseline weight, alcohol consumption, physical activity, education, consumption of fruit and berries, and frequency of having breakfast.	Hansson et al. 2011 (Body weight)

TABLE 5.1 - SUMMARY OF SCANDINAVIAN COHORTS AND PUBLICATIONS BASED ON EACH COHORT

COHORT	DESCRIPTION	SNUS USE ASSESSMENT AND CONSUMPTION DATA	COMMENTS	REFERENCES
Children's Smoking and Environment in the Stockholm County (BROMS)	Enrollment: 5th graders during 1997-1998 school year in Stockholm County Annual follow up until 2005 (6 follow-up surveys) n=3,019 at baseline	Ever tried oral snuff Age at initiation Symptoms at 1st use Progression to regular use Quit attempts Circumstances of tobacco use Preferred brands		Galanti 2001; Post 2005; Galanti 2008; Rosendahl 2003
Sweden Construction Industry's Organization for Working Environment Safety and Health cohort study (Bygghalsan)	Enrollment: 1969-1993 N=up to 340,000 (depending on exclusion criteria) male construction workers who attended outpatient health services through the Sweden Construction Industry's Organization for Working Environment Safety and Health, mean age 34.2 years	1969-1970 data not electronic 1971-1974: ever versus never snus use 1975-1978: no snus use assessment 1979-1993: grams per week of snus use, duration of snus use, time since cessation of snus use (years)	High prevalence of snus users (up to 28%). Control for ethnicity, education, most socioeconomic factors and possibly occupational exposure. Lack of specific information on alcohol consumption, hypertension, education, diet, physical activity, job type and diabetes. Limitations in coding smoking status 1971-1975 and no tobacco use information 1975-1977 .	Luo et al. 2007 (Cancer); Zendejdel et al. 2008 (Cancer); Bolinder et al. 1994 (Cancer; CVD, All-cause mortality); Fernberg et al. 2007 (Cancer); Fernberg et al. 2006 (Cancer); Odenbro et al. 2005 (Cancer); Odenbro et al. 2007 (Cancer); Nordenvall et al. 2011 (Cancer); Hergens et al. 2007; (CVD); Hergens et al. 2008a,b (CVD); Arefalk et al. 2011 (CVD); Fang et al. 2006 (ALS); Lindstrom et al. 2007 (post-op complications); Carlens et al. 2010 (Chronic inflammatory diseases)

5.1.2. Norwegian Experience

The Norwegian snus-related studies were conducted by SIRUS, an independent administrative government body under the Ministry of Health and Care Services of Norway. SIRUS conducts social- scientific research, compiles documentation, and provides information on substance use and abuse, including alcohol research, drug research, and tobacco research. In recent years, SIRUS funding has resulted in a number of scientific articles authored by SIRUS Research Director Dr. Karl Erik Lund which focus on the association between use of snus and quit rates for smoking.

The Swedish and Norwegian experiences with snus have many important parallels. For example, in both countries the shift away from smoking to snus use began with men, but in recent years the percentage of women snus users has increased. Further, in both countries, snus is reported by ever-smokers to be the most preferred method for quitting (Lund 2013), and in both countries Swedish Match snus products are widely used to do so.

Differences between the two countries' experiences relate to when, and over what period of time, the switch from cigarettes to snus occurred. In Sweden, the switch occurred over three decades and allowed for the collection of epidemiological information on health outcomes which resulted in the publication of numerous scientific articles demonstrating the reduction in individual risk. In Norway, the transition has been much more recent and rapid. Although this does not allow for epidemiological findings, research focusing on the smoking cessation potential of Swedish snus has flourished.

SIRUS's public health research builds on the Swedish evidence to evaluate public measures initiated in Norway from 2003-2008 to prevent the use of tobacco (Aaro et al. 2009). In 2009, SIRUS issued the report *A Tobacco-Free Society or Tobacco Harm Reduction? Which Objective Is Best for the Remaining Smokers in Scandinavia?* The report described the growing Norwegian experience with snus and examined the role of snus as a harm-reducing alternative to smoking.

Follow-up articles by Dr. Lund (funded by the Norwegian Directorate of Health and by the Norwegian Research Council) further address the public health benefit of the switch to snus and consider whether the Norwegian experience is transferable to other counties. A 2011 article (Lund et al. 2011) includes a section on "The Consequences for Public Health" and states that "[t]he extent and nature of the impact on public health will depend upon the relative risk hazard of snus and smoking, and the relative uptake and use by smokers and nonsmokers." The authors acknowledge that identifying the net effect of snus use from a public health perspective is a "complicated task" but note that "the conditions for carrying out this task are best in countries such as Norway and Sweden, using our observational data on the transition between cigarettes and snus."

In a 2012 article, *Association Between Willingness to Use Snus to Quit Smoking and Perception of Relative Risk Between Snus and Cigarettes*, Lund suggests that devising methods to inform smokers about the risk continuum of tobacco products could be an important research priority in countries where snus is allowed to compete with cigarettes for market share (Lund 2012). Lund's subsequent 2013 publication, *Tobacco harm reduction in the real world: has the availability of snus in Norway increased smoking cessation*, found that snus is reported by ever-smokers in Norway to be the most preferred method for quitting smoking, and that former smokers make up the largest segment of Norwegian snus users (Lund 2013).

5.1.3. ENVIRON Reports

Swedish Match recognized the importance and applicability of the Scandinavian human health evidence prior to the passage of the Tobacco Control Act, and contracted with ENVIRON to monitor the scientific literature and prepare a comprehensive compendium of the articles pertaining to snus. ENVIRON monitored all of the scientific literature related to snus, most of which was derived from key epidemiological studies of Scandinavian cohorts. ENVIRON then produced two reports that are particularly applicable to the MRTPA, namely *Review of the Scientific Literature on Snus (Swedish Moist Snuff)* and *Swedish Snus and US Smokeless Tobacco Use*.

The former report presents a comprehensive review of the scientific literature on the potential health risks associated with the use of Swedish snus. The latter report presents a review of the scientific literature on snus and smokeless tobacco use in the United States and Scandinavia as it relates to tobacco use behaviors, including dual use, gateway issues, and smokeless tobacco as a smoking cessation aid. Both reports were submitted in their entirety to FDA as part of the MRTPAs.

5.1.4. Transferability of the Swedish and Norwegian Experience to the United States

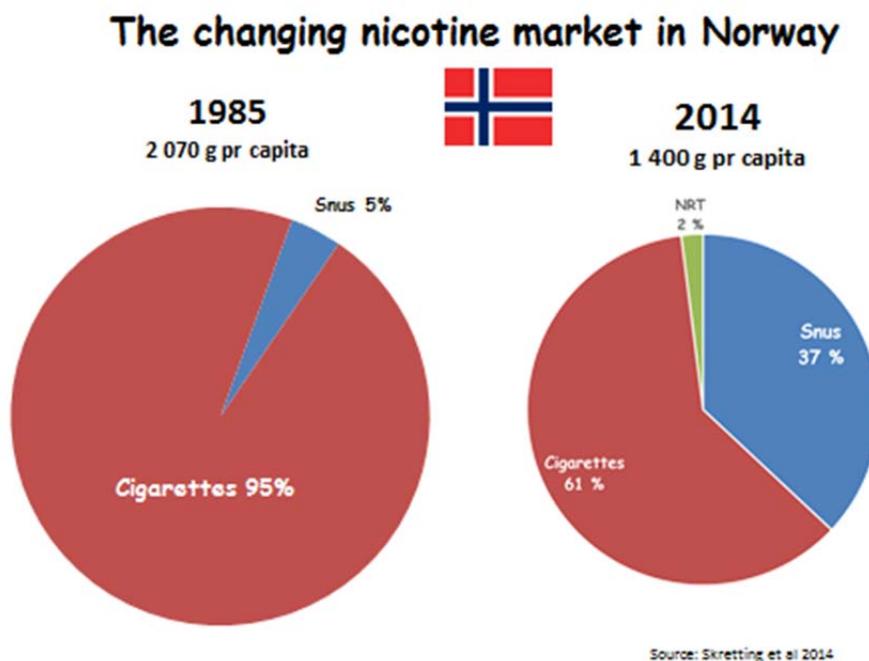
Assessing the transferability of the Swedish and Norwegian experiences with snus to the United States requires careful consideration of the conditions in the Scandinavian countries that account for the switch and an examination of the context in which the shift occurred. What occurred in Sweden and Norway is well documented—cigarette smokers wanting to quit smoking tried NRTs and various other alternatives, but many preferred Swedish snus and were able to use the product to successfully transition from cigarettes (Lund and McNeill 2013). The movement began as, and remains to this day, a grassroots phenomenon. The shift throughout Scandinavia from cigarettes to snus was not the result of nationally coordinated initiatives originating from the centers of political activity, but rather was a trend which started with common citizens at a local level. Indeed, both the Swedish and Norwegian experiences occurred in the complete absence of a national coordinated advertising campaign, and with very little support from the countries' public health and medical communities. Although there was limited snus advertising in Sweden in the 1970s, since then there has been no advertising in either country except at points of sale. Thus, Norwegian researcher Dr. Karl Erik Lund has noted that "the market shift has happened in a 'dark market' where any active promotion of snus has been banned for decades." (Lund 2013)

In Sweden, the movement from cigarettes to snus was likely in reaction to the mounting evidence of the negative health impacts of smoking. The switch from smoking to snus began to occur in the late 1960s to early 1970s. Thereafter, cigarette sales declined while snus sales rose and, by 1990, sales of the two products were equal. Since 1990, snus sales have continued to increase while cigarette sales have continued to significantly decline. During this same time period, smokers have increasingly acknowledged the negative health effects of smoking and begun considering alternatives. Most smokers were not aware of the full risk reduction offered by Swedish snus, rather they were seeking an alternative to cigarettes and tried snus, a traditional Swedish product (Lund and Scheffels 2012; Overland et al. 2008).

The Swedish grassroots movement eventually migrated to Norway, where snus is also a traditional product (though not to the same extent as in Sweden) and can be easily purchased.

(Norway is not a member of the EU which bans the sale of snus except in Sweden). The transition from cigarettes to snus (**Figure 5.3**) has occurred with a concomitant decrease in total consumption of tobacco. In Norway there has been a 15% reduction since 1985 (Lund and McNeill 2013).

Figure 5.3



5.1.4.1. Comparing Scandinavian Experiences to the US Experiences with Snus

The first condition that contributed to the Swedish and Norwegian Experiences—or any tobacco harm reduction transition—is the existence of a population of smokers that is willing to try alternative products in an attempt to quit. Historically, the percentage of current smokers attempting to quit—which is approximately 40-50%—has been similar in Sweden and Norway and the United States. (Lund 2013)

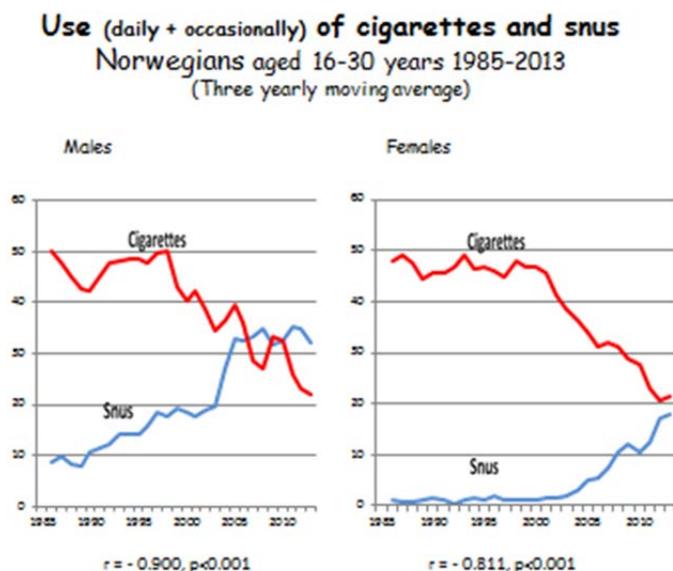
A second condition relates to smokers' knowledge of the various nicotine delivery products available. Smokers in all three countries are aware of NRTs and understand the risk reduction opportunities they offer. However, there are differences regarding smokers' knowledge and perception of Swedish snus. In Sweden and Norway, snus is the overwhelmingly dominant smokeless product. In the United States, the most popular form of smokeless tobacco are spit products, although snus is growing in popularity. (For example, in 2012, sales of Swedish Match snus products were expected to have doubled from the previous year). In all three countries, the majority of smokers overstate the health risk from snus compared to cigarettes (Lund and Scheffels 2013; Overland et al. 2008).

A third condition is that the alternative product must be able to satisfy smokers' needs. In his 2013 article, Lund identifies several reasons why snus is preferred over medicinal nicotine

products, including that (i) the snus nicotine dose is almost the same as for cigarettes and (ii) snus products, in contrast to nicotine chewing gum and nicotine patches, offer “functions that are identical to those offered by cigarettes” and, like cigarettes, “taste of tobacco and thus ha[ve] a sensory effect that medicinal nicotine products perhaps lack.” (Lund 2013).

A fourth condition necessary for a wholesale switch from cigarettes to snus is the existence of an initiative among smokers that results in a word-of-mouth movement toward a less risky product. Typically, such a movement grows exponentially once a critical mass has been reached. In Sweden that tipping point likely occurred around 1990 when the sales of cigarettes and snus were roughly equal. In Norway, by contrast, the tipping point seems to have occurred during the 2005-2008 timeframe during which SIRUS was conducting research. **(Figure 5.4)** A grassroots market for snus has yet to fully develop in the United States, but sales are steadily increasing and there is an ever-growing group of bloggers, journalists with tobacco periodicals, and other vocal snus users.

Figure 5.4



The significance of a word-of-mouth movement cannot be underestimated because governmental authorities are not aggressively communicating tobacco harm reduction and continuum of risk concepts to the public. None of the public health agencies in Sweden, Norway, or the United States provide science-based advice regarding the risk reduction potential of alternative tobacco products; rather the primary message in these three countries is to stop using tobacco products. Consequently, a smoker who turns to a public health agency website for advice is not going to receive any encouragement to try any alternative products to cigarettes other than NRTs. That said, there are subtle differences regarding how the public health and medical establishments refer to snus. For example, in Sweden, physicians and other public health professionals are more likely to acknowledge that snus use is preferable to smoking. They also are more likely to believe that it is acceptable to inform smokers—and

particularly smokers who have been unsuccessful in quitting—to try snus as a means to stop smoking. This willingness is due in part to the grassroots tipping point that has already occurred, and health professionals' difficulty in discounting the significance of the Swedish Experience.

Swedish medical professionals are also undoubtedly influenced by the message of some influential reports, including for example, the "Continued Decline for Smoking as Snus Consumption Increases" section of the 2005 Swedish Public Health Report. This report addresses whether snus is a smoking cessation aid or, alternatively, a gateway to smoking. It recognizes the general consensus that the health hazards of snus are minor as compared to those of smoking, and cites contemporary studies showing that snus does not increase the risk of myocardial infarction morbidity. Conversely, it also cites the scientific literature indicating snus may increase the risk of pancreatic cancer and cause injury to unborn and newborn babies, before concluding that, while the scientific source material is not always strong, the assumption should always be that snus is not harmless.

In Norway, the SIRUS Report and Lund articles provide similar support for health care professionals to acknowledge the harm reduction potential of snus.

5.1.4.2. Future Prospects for Snus in the United States

There will always be differences among the experiences with snus in Sweden, Norway, and the United States given these countries' differing tobacco regulatory environments. Tobacco regulation in Sweden is governed by an EU Directive which does not allow for modified risk claims. By contrast, Norway is not a member of the EU, and does not have a comprehensive tobacco control law, although current government-funded research focuses on the use of snus as a smoking cessation device. Finally, in the United States, the Tobacco Control Act establishes an MRTP review and approval process, but does not permit tobacco products to make smoking cessation claims. Notwithstanding these obvious differences, nearly all of the conditions that contributed to the Swedish and Norwegian experiences presently exist in the United States. Indeed, Swedish Match believes that the most fundamental difference between the US and Scandinavian experiences stems from snus's status as a traditional Scandinavian product. This heritage greatly contributed to the grassroots movement that led to an exponential increase in smokers switching to snus and prompted the public health community to conduct critical research and provide more nuanced information to smokers regarding the potential benefits of switching to snus.

Even though the Scandinavian tradition of snus use cannot be transferred to the United States, many other US developments can help to create conditions that will contribute to the beneficial impact of snus products as an alternative to smoking. Unlike Sweden and Norway, the United States has a comprehensive tobacco control law that includes a science-based process for determining whether a product can be marketed with modified risk claims. Implementation of the Tobacco Control Act has resulted in a significant increase in the attention paid to cigarette alternatives. MRTP orders for the Snus Products will likely increase public awareness and knowledge of this particular type of cigarette alternative, possibly leading to the type of grassroots movement that has occurred in Sweden and Norway. This grassroots phenomenon is particularly important given that the proposed modified risk claims for the Snus Products do not include a significant change in the advertising and marketing campaigns for the products

and the US market volume for the Snus Products will depend to a large extent on word-of-mouth sales and smokers' response to external influences.

Whether the Swedish and Norwegian experiences are, in whole or in part, transferable to the United States cannot be fully known until MRTP orders are granted for the Snus Products and postmarket surveillance is conducted. In the meantime, however, Sweden and Norway provide a "natural laboratory" (Lund 2013) for the study of how snus competes for market share with cigarettes and contributes to a growing recognition among smokers of the harm reduction potential of snus at both the individual and population levels.

5.2. Clinical Trials

Swedish Match sponsored a series of clinical trials which address many of the key areas of investigation suggested in the MRTP Guidance. The clinical trials were initiated prior to the passage of the Tobacco Control Act and reflect Swedish Match's longstanding commitment to product stewardship and consumer protection. Five trials were conducted: two focused on the smoking cessation potential of Swedish snus, and three addressed nicotine pharmacokinetics and pharmacodynamics.

5.2.1. Nicotine Uptake Studies

It is widely accepted that nicotine is the main dependence-producing constituent in tobacco and that rate of delivery from a tobacco product is closely related to its abuse potential. Yet the pharmacological effects of nicotine on the brain's "reward system" are also central to a smoker's liking of nicotine-delivering alternatives to cigarettes, and are likely an important determinant of a product's efficacy for smoking cessation purposes. Orally administered nicotine cannot produce the rapid, high peaks of nicotine in arterial blood to the brain that is typically associated with smoking. Even so, nicotine supplementation in the form of NRT is clearly associated with a modest increase of cessation rates among smokers motivated to quit.

It has been hypothesized that the relatively low level of efficacy observed for NRTs in controlled clinical trials and in population studies is related to the nicotine delivery profile of currently available NRT products, which may insufficiently reduce craving and urges to smoke. In Scandinavia, snus is the most commonly reported quitting aid among males, and appears to be associated with a higher success rate than NRT or counseling among both males and females.

Swedish Match has sponsored three clinical trials (SM WS 02, SM WS 06, and SM WS 12 studies) of the nicotine pharmacokinetics and subjective effects of different brands of Swedish snus (Lunell 2003; Lunell and Curvall 2011; Lunell and Lunell 2005) using nicotine gum (2 or 4 mg) or nicotine lozenges (6mg) as comparators. The main methodological strength of these studies was their use of randomized, cross-over designs, highly standardized administration of study products, and state-of-the-art methods for the chemical and pharmacokinetic analyses. Results of the first two studies have been published in international, peer-reviewed scientific journals, and publication of the third study is underway.

These nicotine uptake trials used pouched snus products with different characteristics relevant to nicotine uptake (e.g., pouch size, nicotine content, pH, and moisture) and covered the range of products currently marketed by Swedish Match in Scandinavia. The SM WS 12 study also

tested the simultaneous use of two pouches as this consumer behavior is not infrequent (Digard et al. 2009).

Swedish Match's proposed MRTP products are substantially similar to the products tested in the nicotine uptake trials. Although the tested snus products are not identical to the Snus Products, the tested products covered the range of relevant product characteristics (e.g., pouch size, humidity, pH, etc.) of all the Snus Products in the Application. Although the trials did not test any loose snus products, product form (i.e., pouch versus loose) has not been found to be a determinant of nicotine uptake from snus-like products (Digard et al. 2012).

Results from the three nicotine uptake trials illustrate that Swedish snus is generally associated with a somewhat faster absorption of nicotine than from pharmaceutical gum and lozenges, and a corresponding faster onset of subjective symptoms (e.g., head rush). In contrast, the estimated mean extracted amount of nicotine as well as AUC_{inf} was higher from a 4 mg gum compared to a 1.0 g snus pouch despite a lower C_{max}. There was high inter-individual variation in nicotine extraction and uptake from snus which was not linear with pouch size, suggesting that surface area, saliva penetration, and diffusion factors may be equally or even more important determinants of nicotine absorption from snus than pouch weight. Also, the more rapid nicotine delivery from snus compared to the selected NRT comparators may help to explain why many smokers have quit cigarettes completely by switching to snus, why snus is the most frequently reported cessation aid among male smokers in both Sweden and Norway, and why Scandinavian population surveys of the success rate with different quitting aids suggest that snus is superior to NRT.

These results show that the nicotine pharmacokinetics and pharmacodynamics of snus (and, relatedly, the Snus Products) are comparable to some commercially available NRT products, although time to C_{max} was consistently shorter with snus. This suggests that the abuse liability of snus may be somewhat higher than with NRTs, but clearly significantly lower than for cigarettes. Such a finding comports with a clinical study by (Fagerstrom et al. 2010) which showed a much higher tobacco cessation rate (33.5%) among placebo-allocated snus users included in a randomized trial of varenicline, than is typically seen in tobacco cessation trials among placebo-allocated cigarette smokers. Relatedly, the expression "continuum of dependence" was coined in a paper by Fagerström and Eissenberg (2012) in which they suggested that abuse potential was lowest among NRT users, intermediate among smokeless tobacco product users, and highest among smokers.

5.2.2. Smoking Cessation Studies

Between 2008 and 2010, Swedish Match sponsored two placebo-controlled, double-blind, randomized clinical trials to investigate the effectiveness of snus as an aid to smoking cessation (Fagerstrom et al. 2012; Joksic et al. 2011; Rutqvist et al. 2013). One of the studies was conducted at two sites in Serbia, and the other at five sites in the United States. Both studies tested whether ad lib provision of snus could affect subsequent smoking behavior among adult smokers motivated to quit (United States and Serbia) or substantially reduce their smoking (Serbia). The trials compared Swedish snus manufactured according to the GOTHIA TEK® standard with almost identical placebo products with no tobacco or nicotine. The trials included end-points related to biochemically-verified, complete smoking cessation. Measurements of abstinence, biochemical verification, and statistical analyses were conducted according to recommendations by the Society for Research on Nicotine and Tobacco (SRNT).

Since use of NRTs is quite prevalent among US smokers who want to quit, it was expected that a substantial proportion of the participants in the US study would have a history of previous unsuccessful quitting attempts with NRTs. The design of the US trial entailed a relatively short period (16 weeks) of active treatment during which participants were issued study products. Thereafter, subjects were instructed to refrain from nicotine-containing products, unless there was an imminent danger of smoking relapse among those who had managed to quit. This design mimics that typically used in many previous randomized trials of NRT products where the objective is not only to promote smoking cessation but also to treat the participants' dependence to nicotine (Silagy et al. 2007).

In the Serbian trial, it was expected that few participants would have tried NRT or other pharmaceutical cessation aids because the cost of such products typically is prohibitive for most Serbian smokers. Hence, it was hypothesized that recruitment to a smoking cessation program may be more successful if the proposed goal is to reduce smoking rather than total cessation. The primary outcome variable during the first six (6) months was smoking reduction. Among those participants who managed to substantially reduce their smoking at 6 months, the goal during the ensuing 6 study months was complete smoking cessation.

The minimal differences in the designs of the Serbian and US trials in part reflected differences between the two countries' social environments. In the United States, numerous smokeless tobacco products and prescription-free smoking cessation aids are readily available to most smokers at a cost comparable to cigarettes. By contrast, Serbian society tends to be much less supportive of smokers who are trying to quit. Smokers there have little access to cessation support programs, and pharmaceutical cessation aids are more expensive than cigarettes. The Serbian public is generally less informed than their American counterparts about the health hazards associated with smoking.

Swedish Match also sponsored a systematic review and meta-analysis of randomized trials of Swedish snus or snus-type products that include long-term smoking cessation as a clinical endpoint. The review and meta-analysis were conducted according to the internationally accepted Preferred Reporting Items for Systematic Reviews and Meta-Analyses ("PRISMA") guidelines, and the US and Serbian trials were the only studies meeting the defined criteria. Thus, the two clinical trials conducted by Swedish Match are the only randomized trials to date that have evaluated the role of Swedish snus or snus-type products for long-term smoking cessation.

Meta-analyses are frequently conducted for observational epidemiological studies in which there may be variation in study design (e.g., case-control or cohort), type of exposure, and extent of adjustment for potential confounding variables. Meta-analysis is also appropriate of relatively similar randomized controlled trials with the same active and placebo treatments. Thus, despite the differences between the two smoking cessation studies sponsored by Swedish Match, there are enough similarities to make it worthwhile to combine the evidence from the studies to allow a more powerful test of whether use of snus versus placebo affects the rate of quitting smoking. Both studies were relatively small (United States: 125 in each group; Serbia: 158 snus and 161 placebo), and a meta-analysis of appropriately defined endpoints allowed improved insight into the main hypotheses of interest, namely those related to biologically-verified, complete smoking cessation.

The first results of the individual trials were published in 2011 and 2012 (Fagerstrom et al. 2012; Joksic et al. 2011). The systematic review and meta-analysis were conducted in 2012, and a full report summarizing the main findings was published in 2013 (Rutqvist et al. 2013). The study

results are summarized below, and demonstrate that participants allocated to snus were 2-3 times more likely to quit smoking completely compared to those allocated to placebo:

- Based on the defined primary outcome in the meta-analysis (i.e., biologically-verified complete cessation during 23-24 weeks), the success rate was higher in the group allocated to snus in both Serbia (5.7% vs 1.9%), and the United States (4.0% vs 1.6%). The meta-analysis estimated the relative success rate at 2.83 (95% confidence interval: 1.03-7.75, exact p: 0.06, chi-squared p: 0.03).
- For all defined biologically-confirmed secondary outcomes in the meta-analysis (including continued abstinence rates during shorter time periods, and 1-week point prevalence abstinence rates), success rates were about twice as high in the group allocated to snus, and statistically significant ($p < 0.05$).
- For smoking cessation in the last four weeks of each study, the overall rates were 12.4% for snus and 6.6% for placebo (relative success rate 1.86, 95% confidence interval: 1.09-3.18), indicating that snus offers a real advantage to smokers who seek to quit smoking.
- There was no statistically significant evidence that the relative success rate with snus in terms of the defined primary outcome in the meta-analysis differed according to gender, age at entry, age at smoking initiation, Fagerström score, history of previous quit attempts, or history of previous exposure to NRT. However, the study's small sample size may have limited its power to detect statistically significant heterogeneity.
- An indirect comparison with results of a recent Cochrane overview (Silagy et al. 2007) in terms of relative success rate versus a placebo comparator suggests that the effect of snus is comparable to that achieved with NRT products. Indeed the hypothesis that snus may be even more efficacious is supported by population data from Sweden and Norway and is consistent with results from clinical studies on nicotine uptake from Swedish snus compared with nicotine chewing gum which show that the uptake from snus is comparable to but generally faster than from gum.
- The relatively low overall continuous quit rates observed in both studies may be attributable to a variety of factors, including (i) the fact that none of the participating centers has previous experience with smoking cessation interventions, (ii) the negative cultural connotations of using smokeless tobacco products in the United States, (iii) a social environment in Serbia which is not supportive of quit attempts among smokers, and (iv) the methods used for recruiting participants which differed from those typically used for trials of pharmaceutical smoking cessation interventions.
- Snus was safe and generally well tolerated in both the US and Serbian studies. Some treatment-related adverse events occurred more often in the snus groups, but they were generally classified as mild. These adverse events reflected the classical symptoms related to nicotine exposure, including nausea, salivation, vomiting, and hiccups. No serious adverse events associated with use of snus were reported.

In sum, the results from the US and Serbian trials were comparable to those from the Scandinavian studies. The experimental data on Swedish snus substantiate the observational population data from Scandinavia and support the conclusion that Swedish snus can increase

complete smoking cessation among smokers motivated to quit or substantially reduce their smoking.

Cessation studies including participants motivated to quit report 6-month continuous abstinence rates that typically are higher than those observed in the US and Serbian trials (Silagy et al. 2007). It is possible that the negative cultural connotations of smokeless tobacco in the US and the social environment in Serbia (i.e., a high smoking prevalence, few smoking restrictions, generally low public awareness of the dangers of smoking, and an environment not supportive of quit attempts among smokers who want to stop smoking) contributed to the trials' observed overall success rates. Higher cessation rates with snus are reported in real-life surveys of Swedish and Norwegian smokers (Lund et al. 2010; Lund et al. 2011; Ramström and Foulds 2006) which may be due to self-selection of subjects and perhaps due to phasing in snus use over a much longer period.

5.3. Consumer Perception

5.3.1. Consumer Understanding of Modified Risk Claims and Relative Risk Information

Swedish Match has identified a total of thirteen (13) published product-specific studies in which the knowledge, attitudes, and beliefs of adults and adolescents in Swedish and other Scandinavian populations were assessed (ENVIRON KAB Report 2014).

Only one study has specifically addressed consumers' ability to understand modified risk claims for Swedish snus. Borland and colleagues (2012) investigated the impact of providing factual information on the relative harms of snus and NRTs compared to smoked tobacco using a pre- and post-test comparison of knowledge about harms. The study was conducted in several locations worldwide (e.g., Australia, United Kingdom, and the United States), including among smokers in Sweden. After administration of the Fact Sheet, the authors observed that participant knowledge of the mechanisms of tobacco-related harms became more accurate among smokers in Sweden and the other countries investigated. Participants who read all or at least some of the Fact Sheet believed, post-survey, that snus was less harmful. Given the low levels of smokers' pre-test knowledge about the harmfulness of different nicotine delivery products, the authors concluded that the provision of information may be an effective means to educate smokers on alternative nicotine delivery products such as snus and NRTs. Increased knowledge levels on the relative harmfulness of snus and NRT compared to cigarettes increased participants' interests in using an NRT as a cessation aid and/or trying snus as a substitute for cigarette smoking.

Rolandsson and Hugoson (2000) conducted an intervention study among male ice-hockey players, aged 12-19 years (n=252). The intervention entailed administering tobacco-related information, namely over-head pictures on the harmful effects of tobacco in general and from the view of oral health. The questionnaires collected information on personal characteristics, socio-economics, behavior and knowledge of tobacco products. Questionnaires were administered three times on two separate occasions; the first two were provided at baseline, administered immediately before and after a 15-minute anti-tobacco information session conducted by two dental hygienists. The third questionnaire was provided three weeks later. Post-intervention, the authors noted that knowledge of tobacco and its harmful effects increased significantly; however, in spite of knowledge, tobacco use habits remained the same. Also, with

regards to differences between tobacco use groups, no significant difference could be observed among those snus users and non-users concerning their knowledge of the harmful effects of tobacco (there was only one smoker in this study).

Five cross-sectional studies investigated the perception of health risks related to snus use among adults (Bolinder et al. 2002; Borland et al. 2012; Lund and Scheffels 2012; Lund and Scheffels 2013; Lund 2012). These studies reported that Scandinavians had an exaggerated perception of the health risks associated with snus use. Lund and Scheffels (2013) investigated the differences in perceptions of the relative risk of some cancers from tobacco use, including lung cancer and cardiovascular diseases among Norwegian adults who were either current or former tobacco users. They reported that, for all diseases except lung cancer, a majority of smokers believed snus users had a higher or equal risk. Although none of the tobacco users believed the risk of lung cancer or CVD was far higher for snus, some participants perceived the risks to users of either tobacco type to be fairly similar. Lund (2012) reached similar conclusions, both former and current adult smokers inaccurately reported that the harm from snus and cigarettes was more or less equal or that snus was only somewhat less risky. However, smokers with a history of snus use were more likely to correctly predict that daily snus use was far less risky than daily cigarette smoking. Correct beliefs of differential risks between the two products were positively correlated with the willingness to use snus in future quit attempts or having used it for smoking cessation.

Two of the five studies observed that a significant percentage of the medical community hold beliefs that are in conflict with scientific consensus on the health risks of snus (Bolinder et al. 2002; Lund and Scheffels 2012). Bolinder and colleagues (2002) reported that half of the doctors surveyed believed that snus use probably increases the risk of oral cancer, hypertension, and some heart diseases. Lund and Scheffels (2012) observed that, among Norwegian general practitioners, snus was the least preferred smoking cessation aid. Some doctors reported that they never or seldom recommended snus as a cessation aid (Bolinder et al. 2002; Lund and Scheffels 2012).

In sum, the data showed that adults generally, and smokers in particular, had an exaggerated perception of the health risks related to snus use. Participants often overrated the harmfulness of snus compared to other tobacco types, and this same trend was also observed in the one available study on this topic in adolescents. Factors that were associated with exaggerated beliefs were male gender, young age, and a higher degree of dependency. Those with beliefs more closely aligned with facts related to the relative risks of snus and cigarettes were more likely to be snus users or to have tried the product.

The results of studies that provided tobacco health facts to participants suggest that participants were able to understand comparative tobacco risk information. However, no studies of sufficient duration or design were identified to determine whether imparting tobacco health facts resulted in changes in established tobacco habits.

5.3.2. Swedish Match's Premarket Consumer Perception Study

5.3.2.1. Study Overview

Swedish Match conducted a premarket consumer perception research study (Consumer Perception Study) to assess the effects on current tobacco users and non-users of the modifications to the Snus Products' warning labels proposed in the MRTPAs. The study assessed the effect of the proposed modifications on subjects' tobacco use behavior and their understanding and perception of the health risks associated with the Snus Products as a result of exposure to test and control warning labels.

In particular, the study evaluated the following label modifications:

- removal of the statement "WARNING: This product can cause mouth cancer."
- removal of the statement "WARNING: This product can cause gum disease and tooth loss."
- replacement of the statement "WARNING: This product is not a safe alternative to cigarettes" with the statement(s) "WARNING: No tobacco product is safe, this product presents substantially lower risks to health than cigarettes."
- retaining the statement "WARNING: Smokeless tobacco is addictive."

Further, and consistent with Section 911(g) of the Act and Section VI.A of the MRTP Guidance, the Consumer Perception Study also assessed the effect of marketing the Snus Products with a modified warning label on the following populations and behaviors:

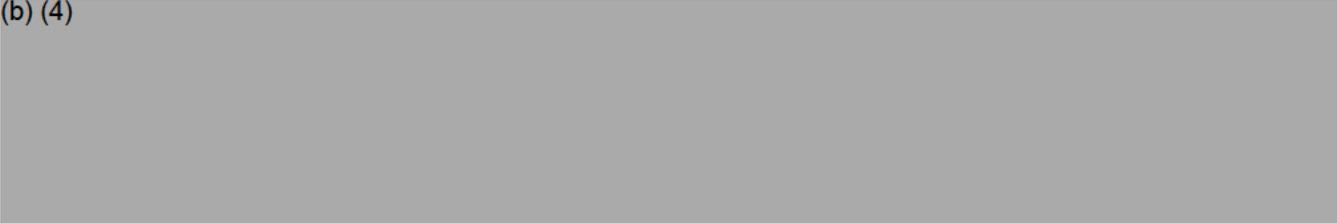
- tobacco use behavior among current tobacco users;
- tobacco use initiation behavior among non-users;
- consumer understanding and perceptions of the product;
- the population as a whole; and
- certain demographic groups.

Study results provided diagnostic learning about the intended use of the Snus Products among current tobacco users and non-users; assessed the potential for the proposed modified warning labels to produce unintended negative consequences to the population as a whole and to particular subgroups of interest; and assessed whether the proposed modified warning label is misleading.

The Consumer Perception Study was a quantitative, randomized, controlled study of 13,200 subjects comprised of 6,600 smokers and 6,600 non-tobacco users. Study subjects ranged in age from 18 to 64 years, with gender, age, income, ethnicity and geographic subgroups within

each group. The study was conducted by InsightExpress, a full service research provider specializing in online data acquisition, using an online questionnaire.

(b) (4)



Study subjects were split into six cells, each with a smoker and a non-tobacco user arm of 1,100 subjects each. Four control cells (comprised of four 1,100 subject smoker arms and four 1,100 subject non-tobacco user arms) were shown color images of a General Snus product container bearing one of the four warnings currently required for smokeless tobacco products. Two test cells (comprised of two 1,100 subject smoker and two 1,100 subject non-user arms) tested the proposed modified risk warning statements for the Snus Products. One of the test cells tested the statement "Warning: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes." The other tested the statement "Warning: No tobacco product is safe but this product presents lower risk to health than cigarettes."

(b) (4)



The Consumer Perception Study generated important and extensive data related to (i) the intended use of the Snus Products among current users of tobaccos and non-tobacco users; (ii) the proposed warning labels' potential to produce unintended negative consequences to the population as a whole, as well as to demographic subgroups of interest; and (iii) subjects' comprehension and understanding of the proposed warning labels to assess whether they are misleading.

Swedish Match's MRTP Advisory Panel (discussed in Section 9 below) reviewed and provided their input regarding the study protocol and results. The Panel acknowledges the long-term significance of the results, which expand the knowledge base regarding consumer tobacco use behaviors and perceptions and may provide the basis for several scientific publications. Swedish Match intends to facilitate use of the data by the scientific community in further investigations and publications.

5.3.2.2. Study Demographics

There were 13,203 total participants in the Consumer Perception Study. The population included 6,593 current users and 7,658 ever users of tobacco. Of the current tobacco users, 3,809 were male and 2,784 were female; 1,611 were between the ages of 18 and 24 years; 4,711 were minorities (defined to include African-American, Hispanic, Asian, Native American, Other, and Hawaiian or other Pacific Islander); and 6,570 had an income below \$45,000. The

current tobacco users included 1,556 daily smokers and 1,171 daily snus users. Thirty eight percent (38%) of the cigarette smokers and 42% of the snus users reported that they would definitely or most likely attempt to quit within the next month, and 42% of cigarette smokers and 46% of snus users reported that they would definitely or most likely attempt to reduce their consumption within the next month.

The study population also included 6,610 current non-users of tobacco. Of the current non-users, 3,736 were male, 2,874 were female, 2,026 were between the ages of 18 and 24, 1,997 were minorities, and 3,206 had an income below \$45,000. Seventeen percent (17%) of the current non users of tobacco reported that were they had used tobacco products in the past.

5.3.2.3. Summary of Results

The results from the Consumer Perception Study address four of the five key areas of investigation required to support an MRTP order, namely: the effect on tobacco use behaviors among current users; the effect on tobacco use initiation among non-users; the effect of marketing on consumer understanding and perceptions; and the effect on the population as a whole. The results of this research are specific to the Snus Products that are the subject of the MRTPAs, and support and supplement the Applications' extensive preclinical, toxicology and epidemiology data related to the effects and use of Swedish snus as compared to traditional cigarettes.

The presentation of the full study data prepared by InsightExpress is included at Appendix 6F of the MRTPAs. Highlights of the study results are as follows:

- *Effect of Modified Label on Tobacco Use Behavior of Current Tobacco Users:* The proposed modified risk claims resulted in a modest increase in the likelihood that current tobacco users would use or purchase snus, and a minimal increase in the likelihood that they would engage in dual use of both cigarettes and snus. The modified risk claims also increased the likelihood that imminent quitters and reducers would be more likely to use, more motivated to buy, and less likely to be discouraged from using snus. A quarter (25%) of the imminent quitters who were likely to use snus reported that they were likely to be dual users of snus and cigarettes, and most of those reported that they would use snus to reduce or quit cigarettes.
- *Effect of Modified Warnings on Tobacco Use Initiation among Tobacco Non-users:* The modified risk claims were no more likely than the current claims to encourage non-users of tobacco to use or buy snus. Although the current claims were more likely than the modified risk claims to deter snus use among non-users of tobacco, more of those exposed to the modified risk claims reported that the claims were not likely to impact their decision to buy snus. None of the claims were likely to influence former tobacco users to use or motivate them to purchase snus. As with the other non-users of tobacco, the modified risk claims were less likely to deter former users from using or purchasing snus, however significantly more reported that the claims would not impact their decision.
- *Effect of the Modified Warnings on Consumer Understanding and Perception:* While most of the total respondents, current users and current non-users of tobacco found the modified risk claims to be understandable and clear, these results were significantly

lower than those reported for the current warnings. This may be due to the greater concreteness of the current claims and consumers' greater familiarity with the currently mandated warning labels. Fewer than half of the total respondents, current users and current non-users considered the modified risk claims to be believable, while those rating the current claims as believable exceeded 60%.

Following exposure to the modified risk claims total respondents, tobacco users and non-users of tobacco were more likely to more accurately rate snus as posing a moderate risk and less likely to report that it was harmful or extremely harmful than they were prior to exposure to any of the claims. This contrasted with those exposed to the current claims, more of whom reported that snus was harmful or very harmful and fewer of whom reported that snus posed a moderate risk. A similar pattern was demonstrated in the results of the comparisons of snus to cigarettes. Significantly more of those exposed to the modified risk claim rated snus as somewhat less harmful than cigarettes compared to those exposed to the current claims, significantly more of whom reported that cigarettes and snus are equally harmful. These data suggest that the modified risk claims were somewhat successful in educating consumers about the actual and comparative risks of snus and cigarettes, and the results are more consistent with the message conveyed regarding the actual risk as reflected in the clinical and epidemiology studies of the Products.

- *Effect of the Modified Warnings on Youth (Ages 18-24 years):* The study did not raise concerns that the modified risk claims would have an adverse effect on youth ages 18 to 24 years. In general, this population found the claims to be clear and understandable. Their perception of the risk following exposure to the claims was similar to, but not as dramatic as, that reported by the total, user and non-user populations. Youth exposed to the modified risk claims were more likely to report that snus posed a moderate risk and a somewhat lower risk than cigarettes. The modified risk claims were also unlikely to cause or motivate non-users ages 18 to 24 to use or buy snus or initiate cigarette use. Overall, the study does not appear to raise unique issues or concerns for youth ages 18 to 24.
- *Effect of the Modified Warnings on the Population as a Whole:* The Consumer Perception Study assessed the effects of the modified risk warnings on the total population, total users of tobacco products, total non-users of tobacco products, and minority, low income and youth users and non-users of tobacco. It also assessed tobacco users who reported being imminent quitters or reducers; dual users of snus and other tobacco products and current non-users who reported being former users of tobacco. The study did not reveal an adverse impact of the modified risk warnings on the population as a whole or on any of the foregoing subpopulations.

The results of the Consumer Perception Study demonstrate that the proposed warning labels for the Snus Products are unlikely to produce significant unintended negative consequences for the population as a whole, or the former smoker, imminent quitter, minority, low income, or youth subgroups. Study results demonstrate subjects' comprehension and understanding of the proposed warning labels and support the conclusion that the modified risk claims are not misleading, but rather promote a better understanding of the actual health risks of snus as compared to cigarettes. While the modified warning label changed consumers' perception of the harmfulness of snus, the results suggest that additional measures may be needed to more

substantially alter consumer risk perception to make it more consistent with the scientific evidence.

These study results significantly contributed to Swedish Match's decision to include the term "substantially" in the proposed label change for the Snus Products, that is "No tobacco product is safe, but this product presents *substantially* lower risks to health than cigarettes." The survey results were consistent with the scientific literature on relative risk perception of snus (Lund and Scheffels 2013) and the term "substantially" is supported by the voluminous product-specific scientific evidence presented in the MRTPAs.

5.4. Dynamic Population Modeler

Swedish Match supported ENVIRON's development and application of a Dynamic Population Modeler designed to estimate changes in all-cause mortality due to modified risk tobacco products. The DPM estimates all-cause mortality for a hypothetical population of persons who 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 the number of survivors in a base case comprised of current, former, and never smokers followed as they age with the number of survivors in a counterfactual exposure scenario that includes current, former, and never users of the MRTP, as well as current and former users of cigarettes. Questions that can be addressed using the DPM include, among others, the following questions and combinations of these scenarios:

- How is population survival affected if, after introduction of the snus product as a MRTP, some who remain never tobacco users in the base case initiate the MRTP instead, thereby increasing risk?
- How is population survival affected if, after introduction of the snus product as a MRTP, some who remain never tobacco users in the base case initiate the MRTP instead, and then switch to smoking (i.e., gateway effect), thereby increasing risk?
- How is population survival affected if, after introduction of the snus product as a MRTP, some who quit smoking in the base case switch to the MRTP instead, thereby increasing risk?
- How is population survival affected if, after introduction of the snus product as a MRTP, some who initiate cigarette smoking in the base case initiate the MRTP instead, thereby decreasing risk?
- How is population survival affected if, after introduction of the snus product as a MRTP, some current smokers who continue to smoke in the base case switch to the product instead, thereby decreasing risk?

All commonly observed tobacco exposure histories can be accommodated including initiation, cessation, relapse, switching between products and use of both products.

The DPM follows a hypothetical population as it ages. All members of the population are assumed to be of the same age and never to have used either cigarettes or a MRTP at the

beginning of follow-up. Survival is compared between two scenarios: a base case where only cigarettes are available and a counterfactual scenario where a MRTP is available in addition to cigarettes. Changes in exposure (i.e., transitions) are allowed to occur throughout follow-up. Probabilities of transitioning from one exposure state to another can be derived from available data, or the transition probabilities can be specified to define a particular question of interest. Throughout follow-up, deaths are estimated by applying age-, smoking-, and/or MRTP-specific mortality rates and only survivors move to the next age interval, where they may remain in their current exposure category or transition to a different category. The DPM output includes the age-specific number of survivors under the base case and counterfactual scenario, their difference and estimates of the uncertainty of the results.

Using the DPM it is possible to determine which of the scenarios have the greatest potential to affect population survival and to estimate tipping points. If a proportion of the population experiences a beneficial change in tobacco use behavior that results in a survival benefit at the population level, the tipping point is the proportion of the population that must experience a harmful change in tobacco use behavior to eliminate this survival benefit. Tipping point analyses can also be constructed to estimate the proportion experiencing a benefit needed to eliminate a harm. Tipping point analyses can be relatively simple, addressing only one beneficial and one harmful exposure pattern. They can also be complex, addressing multiple interacting exposure patterns. DPM input values can be systematically changed to conduct sensitivity analyses.

Model validation exercises suggest that, given a sufficient induction period and reasonable input data, the DPM accurately predicts life tables in a population with no MRTP use and a population with widespread MRTP use. The results of the validation indicate that the DPM can provide meaningful data to compare the health effects of different hypothetical exposure distributions. If those distributions arise from alternative policies, then the DPM can be used to compare health consequences due to policy decisions.

The analyses prepared for the MRTPAs specifically evaluated effects due to use of the MRTP by those who, in the absence of the MRTP, would have remained tobacco-free (i.e., non-smokers) and those who would have quit smoking. The analyses in the Application also used the DPM to estimate the potential effects of the MRTP being more attractive than cigarettes to youth who are at risk of becoming tobacco users, the potential gateway effects of the MRTP to smoking, and the potential effects of an increased likelihood that former users (i.e., those who quit all tobacco and those who switched from cigarettes to MRTP) may relapse back to cigarettes. The results indicate that the introduction of Swedish snus, the proposed MRTP, can result in a net population-level benefit, particularly if the product is adopted by a sufficient number of smokers. A scenario in which introduction of Swedish Match snus results in more tobacco users compared to the base case (giving rise to a survival deficit) appears unlikely given the results of the premarket consumer perception research on the proposed label changes included in the Applications.

6. GOTHIA TEK

Although Swedish Match's current manufacturing methods for snus build on those that were introduced more than a century ago, the high quality of modern Swedish snus is largely due to improvements in production techniques and selection of raw materials in combination with several programs for quality assurance and quality control that were successively introduced by

Swedish Match since the early 1970s. In 2000 these developments formed the basis for a codified, voluntary quality standard named GOTHIA TEK®.

GOTHIA TEK® is a proprietary quality standard which subjects all Swedish Match snus products to rigorous controls in order to maintain the highest quality throughout all stages of the manufacturing process from tobacco plant to consumer. The standard is based on decades of research and development efforts dating back to the early 1970s. This voluntary standard and its focus on consumer protection and product safety is unique to Swedish Match, and draws upon the best available knowledge regarding selection of raw materials and manufacturing practices.

GOTHIA TEK® encompasses a standardized manufacturing process that controls every aspect of the production chain, from seed to finished can. Its requirements stipulate that the manufacturing process for Swedish snus must comply with Swedish law on food production and meet the requirements of quality standard ISO 9001:2000 and environmental standard 1401:1996. Swedish Match has also added its own additional objectives for quality and content beyond that which is required by law, including not limited to standards for raw material quality, manufacturing processes, consumer product information, and maximum permitted levels of undesirable substances in finished snus products.

GOTHIA TEK® 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. The principal components of the standard are:

- Constituent standards
- Manufacturing standards
- Consumer information

6.1. Constituent Standards

6.1.1. Constituent Limits

The GOTHIA TEK® standard includes limits for several constituents. **(Table 6.1)** The selected constituents reflect the toxicological science and production techniques of the 1990s. The constituents level achieved today in routine production are lower, or much lower, than the maximum levels defined by GOTHIA TEK®. Indeed, Swedish Match has introduced more stringent internal tolerance limits for the GOTHIA TEK® constituents and several additional constituents from the FDA's published HPHC List.³ Swedish Match has also developed procedures to control these additional constituents, to evaluate and revise existing internal tolerance limits, and to propose internal tolerance limits for the additional constituents.

³ FDA, Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List, 76 Fed. Reg. 20034 (Apr. 3, 2012).

Table 6.1. GOTHIA TEK® limits for constituents in snus products. 2014 limits are based on dry weight except for agrochemicals which is based on “as is”

Constituents	GOTHIA TEK® limits
(b) (4)	

In 2009 WHO published a proposal for smokeless tobacco product regulation which contained a recommended upper limit for the TSNAs, NNN plus NNK, and one polycyclic aromatic hydrocarbon, Benzo(a)pyrene (B(a)P). (WHO Technical Report Series No 955). A revision of the standard introduced in 2012 makes the GOTHIA TEK® standard compliant with the WHO recommendations.

The GOTHIA TEK® standard also includes guidance maximum levels for agrochemical residues in snus products. Accordingly, Swedish Match has established an Agrochemical Residue Management Program, which includes a formalized process for inclusion of agrochemicals to be tested, decisions about Guidance Residue Levels (GRLs), and procedures concerning the company’s stewardship in dealing with agrochemical residues in raw tobacco and snus products. The agrochemical residues limits in GOTHIA TEK® are lower than those mandated by any regulatory agency or published by any trade organization.

6.1.2. Chemical Testing

Chemical analyses on raw tobacco, tobacco blend, and finished product are included in several testing programs which are part of the GOTHIA TEK® standard. All analytical testing according to GOTHIA TEK® is performed by certified laboratories. Individual results are documented and stored, and results are reviewed continuously.

The test battery has changed over the years in order to ensure that internal requirements on product quality, conformity and safety, as well as, external requirements by all relevant national authorities are fulfilled. Currently, the Company's products are tested for GOTHIA TEK® constituents, as well as additional constituents on FDA's HPHC List.

Swedish Match also performs agrochemical residue testing of raw tobacco shipments prior to their release for snus manufacture. The sampling procedure is such that a representative sample is obtained of each individual tobacco grade for a given crop year. About 170 agrochemical residues, for which there are available and certified analytical methods, are included in the GOTHIA TEK® standard.

Agrochemical residue levels in all Swedish Match snus products are checked in an annual testing program. The testing is done on selected brands representing all different tobacco blends and processes.

6.1.3. Quality Control

To ensure that tobacco quality meets Swedish Match's standards for chemical constituents in the final product, thorough chemical quality control of the tobacco is performed at different stages of the tobacco procurement process, including:

- *Offer samples:* Before buying tobacco from areas where Swedish Match has not previously conducted business, offer samples are collected by suppliers and sent to Swedish Match for thorough investigation. The tobacco undergoes inspection for physical, chemical and sensory properties to determine its usability for snus production.
- *Early warning samples:* Swedish Match has implemented an "Early Warning System" to obtain an early indication of the chemistry and cleanliness of the tobacco for a given crop year. Representatives from Swedish Match visit tobacco growing areas on a regular basis and instruct the dealers on how to collect tobacco samples for chemical analysis directly after curing.
- *Packed tobacco samples:* Chemical quality control is performed throughout the entire tobacco packing process.

Laboratory tests for quality control are performed throughout the entire process, ensuring that the tobacco meets Swedish Match's criteria for approval before a final purchase decision is made. The tobacco is shipped to Sweden only after final approval of the chemical analysis results.

The tobacco blend recipes for each grinding batch are composed based on chemical results from samples of packed raw tobacco in order to comply with the GOTHIA TEK® standard for the finished products.

Standard limits and internal tolerance limits are verified on a regular basis in the Chemical Quality Control Program, in which all snus products are analyzed. Results show that the levels of the tested compounds for Swedish Match snus are below the GOTHIA TEK® limits and have been so for many years. Moreover, most of the snus products tested had levels below Swedish Match's internal limits.

6.1.4. Product Stability During Storage

The recommended shelf lives for snus products in cool storage differ based on product category (e.g., loose snus v. dry portion snus). Selected sample products are tested at the end of their shelf lives (i.e., the “best before” date) as part of the Company’s Quality Analysis Program.

6.2. Manufacturing Standards

6.2.1. Raw Tobacco

Two types of tobacco species are used in the production of snus: *Nicotiana tabacum* and *Nicotiana rustica*. A tobacco blend for production is a mixture of selected tobacco qualities. The quality differs depending on country of origin, curing procedure, and plant position. It is characterized by taste, aroma, texture and chemical content. At present the tobacco used for snus production originates from several countries including USA.

The final quality of the raw tobacco is determined by a combination of factors including seed variety, growing and curing conditions, and knowledge/ handling by farmers as well as by suppliers. Swedish Match has developed proprietary procedures to handle and supervise these variables in order to obtain high quality tobacco to ensure consistency, integrity, consumer acceptance, and regulatory compliance of the final products.

Swedish Match has a longstanding commitment to reduce TSNAs and other undesired constituents in raw tobaccos through research and development and in cooperation with suppliers and growers. This commitment has resulted in a range of recommendations and instructions governing the production of the tobacco at several locations around the world.

To meet the GOTHIA TEK® standard for snus products, Swedish Match has established maximum tolerance levels for constituents and agrochemicals in raw tobacco, along with tolerance levels for constituents and agrochemical residues in finished products.

After approval of the chemical testing results, the tobacco is shipped to Sweden. When the tobacco arrives at Swedish Match’s facilities, the quality of the delivered tobacco is inspected according to codified routines. The tobacco is then stored under controlled conditions until released for grinding and use in snus production.

6.2.2. Ingredients

Swedish Match defines ingredients as raw materials, additives and flavors (i.e., essential oils, flavor compounds or compounded flavors). A processing aid is not regarded as an ingredient since it is not intended to remain in the finished product. Each ingredient in Swedish Match’s snus products complies with external regulations and internal policy.

- *Raw Materials:* All raw materials comply with Swedish Match’s raw material specification requirements.

- *Additives:* The additives legally permitted to be used in snus are governed by LIVSFS 2012:6 Livsmedelsverkets föreskrifter om snus och tuggtobak (*Swedish National Food Agency Directive on snus and chewing tobacco*). Specific purity criteria for additives are regulated in Commission regulation (EU) No231/2012. In addition to compliance with the regulated purity criteria, all additives in snus products comply with Swedish Match's additive specification requirements.
- *Flavors:* Flavors are regulated in the directive LIVSFS 2012:6 Livsmedelsverkets föreskrifter om snus och tuggtobak (*Swedish National Food Agency Directive on snus and chewing tobacco*). This directive refers to Regulation (EC) No 1334/2008 and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. Further, the "Swedish Match Negative List for Flavors" is sent to each flavor supplier with whom Swedish Match conducts business. The list includes additional restrictions on the flavors that, according to Swedish Match's internal ingredient policy, are allowable in snus recipes.
- *Pouch Material:* According to Swedish Match's internal pouch material policy, snus pouch material must comply with legislation concerning materials and articles intended to come in contact with food. All materials in the portion pouch fabric are in compliance with applicable FDA requirements in Title 21 of the Code of Federal Regulations.
- *Can Material:* Loose snus is packed in cans made of cardboard, which is the material traditionally used for snus cans in Sweden for more than 100 years. Portion snus is packed in cans made of plastic. The materials of the can are approved for food contact.

6.2.3. Manufacturing

To meet the GOTHIA TEK® standard, all tobacco qualities are bought in lots which are analyzed chemically.

Snus production consists of three manufacturing steps, namely tobacco flour grinding, snus blend processing, and packing of finished product.

- *Grinding:* A blend of different raw tobacco qualities, specified by a tobacco blend recipe, is ground and blended to tobacco flour.
- *Snus Blending:* Tobacco flour is mixed with other ingredients and heat treated.
- *Packing:* The packing of finished products consists of packing of the snus blend into cans as loose snus products, or packing of pouches which are packed into cans as portion snus products.

6.2.4. Hygiene

In Sweden, snus is regulated as a food product according to the Swedish Food Law. Swedish law requires a manufacturer to follow "Codex Alimentarius, General Principles of Food Hygiene CAC/RCP 1-1969", which is an internationally recognized process for food safety. The Hazard Analysis Critical Control Point (HACCP) based quality assurance system ensures that

employees are HACCP qualified, each critical control point of the production chain is identified, and the critical control limits are determined, monitored and recorded. A HACCP program according to “Codex Alimentarius CAC/RCP 1-1969” is implemented in each different production stage, including grinding, heat-treatment, and packaging. In accordance with GOTHIA TEK®, Swedish Match takes all necessary steps and precautions to comply with the hygiene requirements set by food regulations, as well as the Company’s additional internal rules.

6.2.5. Track and Trace

The GOTHIA TEK® standard stipulates that the manufacturing process must comply with Swedish law on food production and meet the requirements of the quality standard ISO 9001:2000. Accordingly, Swedish Match’s snus traceability processes comply with Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002, Chapter II General Food Law, Section 4, General Requirements of Food Law, Article 18, Traceability and the Swedish Food Agency directives on snus and chewing tobacco LIVSFS 2012:6, §12 Traceability.

6.3. Consumer Information

Swedish Match believes that consumers and the public are entitled to accurate and important information about the Company’s products. The Company maintains a public website with brand-specific product information and, in accordance with country-specific regulations, provides detailed scientific information about the health effects of snus use.

Moreover, to meet GOTHIA TEK® requirements, all snus package labeling includes the “best before” date, recommended storage conditions, and a declaration of ingredients in accordance with requirements for labeling of processed food stuffs in Sweden.

7. INDIVIDUAL RISK REDUCTION

Section 911(g)(1)(A) of the Act provides that in order to issue an MRTP order, FDA must determine that the product, “as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users....” The MRTP Guidance states that an MRTPA must provide scientific evidence regarding the effect of the product on the health of individuals so that FDA can determine whether the MRTP does, in fact, modify risk as claimed by the applicant. The Applications’ demonstration that the Snus Products provide a significant reduction in individual risk includes the following three key components:

- The Snus Products are manufactured in a manner that eliminates or reduces HPHCs and follows a product standard that seeks to achieve ever lower harmful constituent levels. Swedish Match believes the quality standard GOTHIA TEK® (described in Section 6 above) achieves these goals.
- There are sufficient product-specific human health studies, undertaken by credible institutions and supporting peer-reviewed scientific articles, to address individual risk

reduction. The Company believes the Swedish Experience evidence is exceptional in this regard and is unique in tobacco research.

- There is evidence from clinical trials, conducted in accordance with good clinical practices and applicable regulatory and international standards to assess the individual risk-reduction potential of the proposed MRTPs. Swedish Match believes that the five clinical trials that are described in Section 5.2 above, and presented in full in the Applications, provide the clinical evidence to complement and support the Scandinavian epidemiological evidence.

The MRTPAs propose three changes in the current warning labels related to individual risk reduction. First, the Applications propose to replace the warning labels stating that the Products are “not a safe alternative to cigarettes” with the statement “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” This change is intended to provide tobacco consumers with accurate, science-based information about the relative risks of snus and cigarettes. The Applications also propose to eliminate two of the current warnings that relate to individual risk: “WARNING: This product can cause mouth cancer”; and WARNING: This product can cause gum disease and tooth loss.” Although these warnings may be appropriate for certain customarily marketed smokeless tobacco products, they are inconsistent with the scientific evidence demonstrating the individual risk-reduction benefit of snus. Therefore, the Applications seek product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of Swedish snus as compared to other commercially marketed tobacco products.

7.1. Substantially Lower Risk than Cigarettes

It is generally accepted that switching from cigarette smoking to a low nitrosamine smokeless product such as General snus results in a 90% reduction in individual risk (Levy et al. 2004). The MRTPAs feature extensive data regarding the great extent of individual risk reduction that occurs when a cigarette smoker switches to Swedish snus. In particular, the section on *Health Risks Associated with the Use of Snus as Compared to Using Cigarettes* (Section 6.1.1) of the Applications provides narrative description and forest plots (i.e., graphical displays of individual study results and findings of systematic reviews and meta-analyses) relating to the following health outcomes:

- Lung cancer
- Cardiovascular disease
- Stroke
- Respiratory disease
- COPD
- Esophageal cancer
- Pancreatic cancer

- Oral cancer
- Stomach cancer
- Diabetes
- All-cause mortality

The MRTPAs propose, among other things, that the following warning label statement be added to the Snus Products: “No product is safe, but this product presents substantially lower risks to health than cigarettes.” Swedish Match proposes this warning label for two reasons. First, the modified warning is consistent with the widely accepted evidence demonstrating reduced individual risk for a smoker who switches to Swedish snus. Second, the proposed language would benefit the health of the overall population by providing consumers with more accurate information about the relative risks of cigarettes and Swedish snus.

Warning labels are widely accepted regulatory communication tools used to inform the public about potential hazards in order to minimize or avoid undesirable consequences. Though changed warning labels alone will likely not result in a US experience similar to that in Scandinavia, the use of accurate, science-based warnings is a foundational step in the process of educating consumers about the continuum of risk in nicotine-containing products. These changes may encourage smokers familiar with the hazards of combustible products to consider switching to snus, or may introduce unfamiliar smokers to the notion that there are alternative nicotine-delivery products to cigarettes.

Importantly, the results of Swedish Match’s Consumer Perception Study demonstrate that the proposed new warning labels for the Snus Products are unlikely to produce unintended negative consequences for the population as a whole, or the former smoker, imminent quitter, minority, low income, or youth subgroups. Study results demonstrate subjects’ comprehension and understanding of the proposed warning labels and support the conclusion that the modified risk claims are not misleading, but rather promote a better understanding of the actual health risks of snus as compared to cigarettes. These results are consistent with the scientific literature on relative risk perception of snus (Lund 2012), and underscore the need for additional measures to more substantially alter consumer risk perception in order to make it more consistent with the scientific evidence.

7.2. Disease-Specific Claims

7.2.1. Oral Cancer

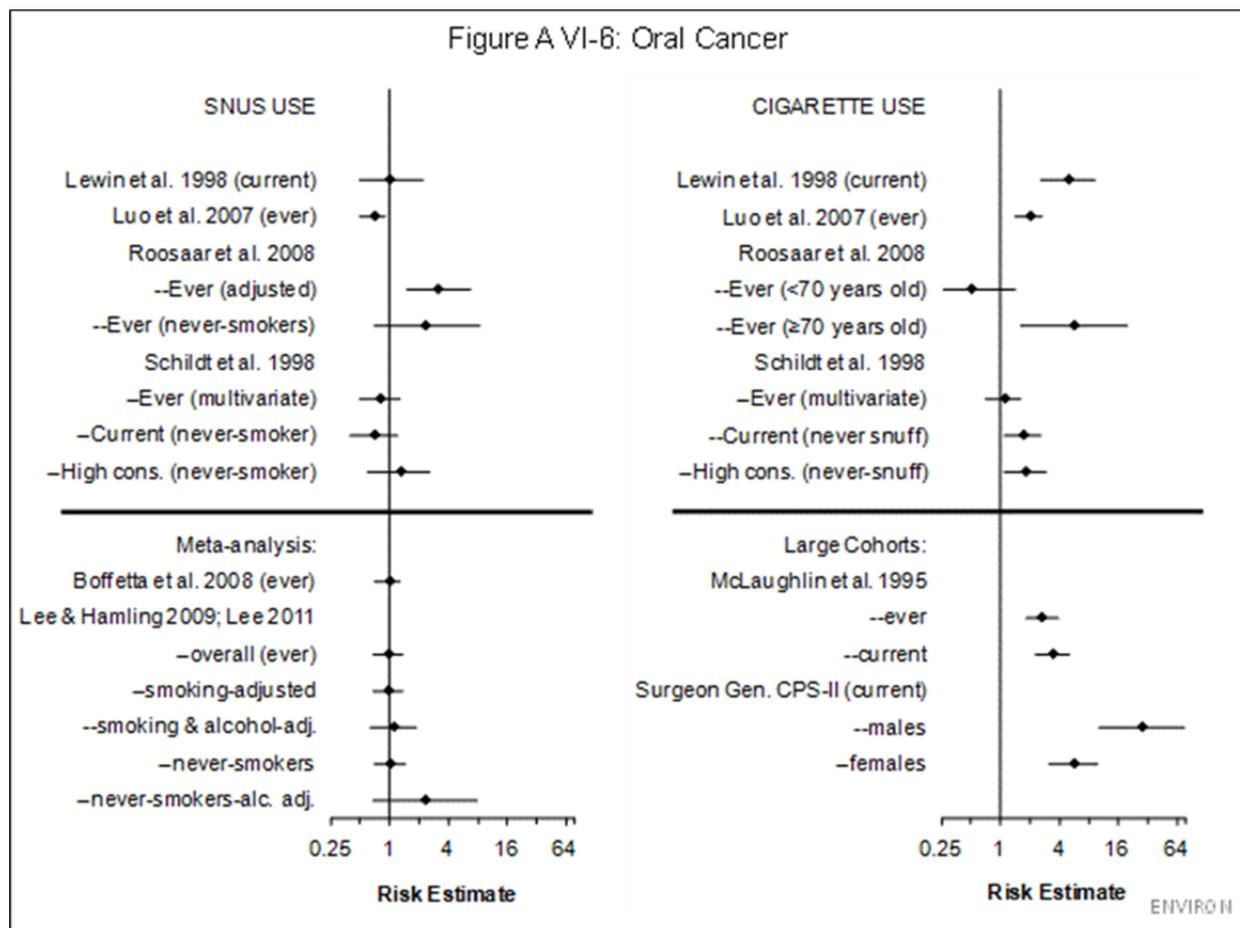
The available evidence suggests that use of Swedish snus is not associated with an increased risk of oral cancer. Results of high-quality epidemiology studies that specifically examined the possibility that use of snus causes oral cancer found no relationship; only one study found a significant association with oral cancer (Lewin et al. 1998; Rosenquist et al. 2005; Schildt et al. 1998). Several meta-analyses restricted to Swedish snus did not find a significantly increased risk of oral cancer, and other public health committees have agreed that snus does not increase the risk of oral cancer.

In 2004, Rodu and Jansson (2004) concluded in a review of smokeless tobacco and oral cancer that “the use of Swedish moist snuff is associated with no demonstrable risk.” The IOM's 2001 report “Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction,” states that, based on recent epidemiologic studies, “Swedish snus does not increase the risk of oral cancer” (Stratton et al. 2001).

Weitkunat and colleagues (2007) and Boffetta and colleagues (2008) conducted meta-analyses that examined the risk of oral cancer from the use of a range of smokeless tobacco and snuff products (both snus and traditional smokeless tobacco products) and these researchers concluded that no increased risk from use of snus was observed. Other meta-analyses (Lee 2011; Lee and Hamling 2009) also did not show an elevated risk of oropharyngeal cancer among smokeless tobacco users generally, or specifically among snus users in Scandinavia. The SCENIHR Working Group (2008), charged with assessing the health risks of smokeless tobacco use, also concluded that the available literature indicates that “an increased risk of oral cancer has not been proven in snus users.”

Three population-based case-control studies carried out specifically to study the relationship between snus and oral cancer (Lewin et al. 1998; Rosenquist et al. 2005; Schildt et al. 1998b) have found no evidence that use of snus was associated with a statistically significant increased risk of oral cancer.

Figure 7.1 Oral Cancer Risk Estimates for Snus and Cigarettes



7.2.2. Non-Cancer Oral Effects (gum disease and tooth loss)

In examining the studies of potential non-cancer oral effects, methodological considerations, such as study design, samples sizes, detail on product identification and exposure levels, data control or comparison population (i.e., non-tobacco or non-snus users), definitions of the dental and oral conditions, and consideration of important confounders (e.g., dietary and oral hygiene habits, and socioeconomic status), are important considerations in drawing conclusions. For example, in an investigation of individuals from Jönköping, Sweden, Hellqvist and colleagues (2009) reported that nonusers of snus visit the dentist more and brush their teeth more frequently than users, while Hirsch and colleagues (1991) reported that snus use is more common among groups with lower socioeconomic status. There are known associations between socioeconomic status and dietary and oral hygiene habits, and dental conditions such as periodontitis. (Juliñ and colleagues 2008).

Lee (2011) presented a review of the available studies that examined dental-related outcomes and concluded that a relationship of snus to periodontal and gingival diseases is not clearly established, and that a possible relationship with tooth loss and dental caries is not established.

His conclusions are consistent with an earlier review conducted by Kallischnigg and colleagues (2008) in which the authors evaluated the relationship between smokeless tobacco products and non-cancerous oral diseases in both Europe and the U.S. The authors concluded that the Swedish cohort studies reveal no clear relationship between snus use and periodontitis or gingivitis, and described the evidence of an association between snus use and gingival recession as limited. The available studies conducted to evaluate potential non-carcinogenic oral effects in snus users are summarized below.

Several studies identified in the literature address the effects of snus on the teeth and the periodontal tissues. These effects can be generally divided into the following categories: (1) dental conditions (plaque, caries, tooth wear, and tooth loss); (2) gingivitis (inflammation of the gums); (3) gingival recession (receding gums); and (4) periodontal disease (periodontitis) (often preceded by gingivitis, an infection of the tissues surrounding and supporting the teeth and indicated by alveolar bone loss, pocket depth, attachment loss, bone height), though many outcomes are examined within the same study.

- *Dental Conditions:* Eight cross-sectional studies assessed the dental effects of snus. Five of these studies accounted for potential confounding factors, including socioeconomic status or dietary or oral hygiene habits (Bergstrom et al. 2006; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004). None of these studies found a relationship between the use of snus and dental caries (Hugoson et al. 2012; Rolandsson et al. 2005) or tooth loss (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005), and none reported a significant relationship between dental plaque and snus use. Two older studies that reported a significant association between snus use and dental caries and tooth loss (Hirsch et al. 1991) and tooth wear (Ekfeldt et al. 1990) did not account for the potential confounding effects of socioeconomic status, or dietary or oral hygiene habits.
- *Gingivitis:* Six cross-sectional studies assessed the relationship between snus use and gingivitis, gingival index, or gingival bleeding. Five of the studies reported no association between snus use and gingivitis or other endpoints associated with gingivitis (Bergstrom et al. 2006; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004). Three of these studies accounted for either oral hygiene habits and/or socioeconomic variables (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005). The one older study that reported a significant association between a higher gingival index and the use of snus (Modeer et al. 1980) did not report whether oral hygiene habits or sociodemographic variables differed between snus users and nonusers of tobacco.
- *Gingival Recession:* Three cross-sectional studies compared gingival recession among snus users and non-users of tobacco. One of the studies found that the prevalence of gingival recession among snus users and nonusers was not significantly different (Wickholm et al. 2004), one reported a significantly lower percentage of sites with gingival recession ≥ 1 mm among snus users compared to nonusers (adjusted for sociodemographic variables) (Hugoson and Rolandsson 2011) and one reported that participants with gingival recessions had significantly increased odds of using snus (Monten et al. 2006) (with no significant differences in oral hygiene habits between users and nonusers of snus). A fourth study found that loose snus was significantly associated with gingival recession compared to the use of portion-bag snus, but provided no

comparison of the effects of loose or portion-bag snus use with non-use of tobacco (Andersson and Axell 1989).

- *Periodontal Disease*: None of six cross-sectional studies nor one case-control study (Kallestal and Uhlin 1992) reported a significant association between the use of snus and periodontal disease, or individual indicators of periodontal disease. Most of the studies, with only two exceptions (Bergstrom et al. 2006; Kallestal and Uhlin 1992), adjusted or accounted for either socioeconomic factors (Hugoson and Rolandsson 2011; Julihn et al. 2008; Wickholm et al. 2004) or oral hygiene habits (Monten et al. 2006; Rolandsson et al. 2005).

8. PUBLIC HEALTH BENEFIT

Section 911(g) of the FDCA states that, in order to receive a MRTP order, the applicant must demonstrate that the product, as actually used by consumers, will “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.” FDA’s MRTP Guidance elaborates on the statutory language and describes key areas of investigation that should be submitted to demonstrate a population health benefit. It also suggests the applicant address the effect the product and its marketing may have on tobacco use behavior.

The demonstration of a public health benefit requires consideration of the following three key issues:

- the health risks associated with using the Product in conjunction with other tobacco products, commonly referred to as “dual use”;
- the health risks associated with switching to the Product as compared to quitting the use of tobacco products (i.e., whether dual use or snus only use delays smoking cessation); and
- the health risk associated with initiating use of the Product as compared to never using the Product, including importantly, whether adolescents initiate tobacco use via the Product.

The MRTP Guidance recommends that two types of evidence be submitted to address the population health benefit standard: human studies, and quantitative estimates or dynamic population modeling. The Norwegian SIRUS evidences and the premarket consumer perception data are human studies that relate directly to the population benefit of snus on humans. Much of the Swedish Experience human evidence also addresses population benefit, as does the snus smoking cessation clinical trials funded by Swedish Match and the DPM co-funded by the Company.

8.1. Norwegian SIRUS Evidence

The Norwegian snus-related studies were conducted by SIRUS, an independent administrative government body under the Norwegian Ministry of Health and Care Services that conducts

social scientific research, compiles documentation, and provides information on substance use and abuse, including tobacco research.

In recent years SIRUS funding has resulted in a number of scientific articles authored by SIRUS researcher Dr. Karl Erik Lund and others. Much of the SIRUS funded research has focused on the association between use of snus and quit rates for smoking and resulted in the following articles:

- Lund, K.E. (2009), "A Tobacco-Free Society or Tobacco Harm Reduction? Which Objective is Best for the Remaining Smokers in Scandinavia?" SIRUS-Report 6/2009, Norwegian Institute for Alcohol and Drug Research, Oslo.
- Lund, K.E. and McNeill, A, and Scheffels, J. (2010a), "The use of snus for quitting smoking compared with medicinal products", *Nicotine & Tobacco Research*, Vol. 12 No.8, pp. 817-22.
- Lund, K.E. and McNeill, A, and Scheffels, J. (2010b), "The association between use of snus and quit rates for smoking: results from seven Norwegian cross sectional studies", *Addiction*, Vol. 106 No 1, pp 162-7.
- Larsen, E., Rise, J. and Lund, K.E. (2012), "The relationship between snus use and smoking cognitions", *Addictions Research & Theory*, Vol. 20 No. 6, pp. 447-55.
- Lund, K.E. (2012), "Association between willingness to use snus to quit smoking and perception of relative risk between snus and cigarettes", *Nicotine & Tobacco Research*, Vol. 14 No. 10, pp. 1221-8.
- Lund, I and Scheffels, J. (2012), "Perceptions of the relative harmfulness of snus among Norwegian GPs and their effect on the tendency to recommend snus in smoking cessation", *Nicotine & Tobacco Research*, Vol. 14 No.2, pp. 169-75.
- Lund, K.E. and McNeill, A. (2013), "Patterns of dual use of snus and cigarettes in a mature snus market", *Nicotine & Tobacco Research*, Vol. 15 No. 3, pp. 678-84.

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 SIRUS-funded snus studies. In its Introduction, the article states, "SIRUS...has published a series of studies illustrating the role of snus in smoking cessation and reduction, and how availability to snus has affected the magnitude and concomitant use of snus and cigarettes. In this case study, the aim is to sum up the findings from this research." The SIRUS researchers understand the unique perspective provided by the snus-related studies and further state, "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."

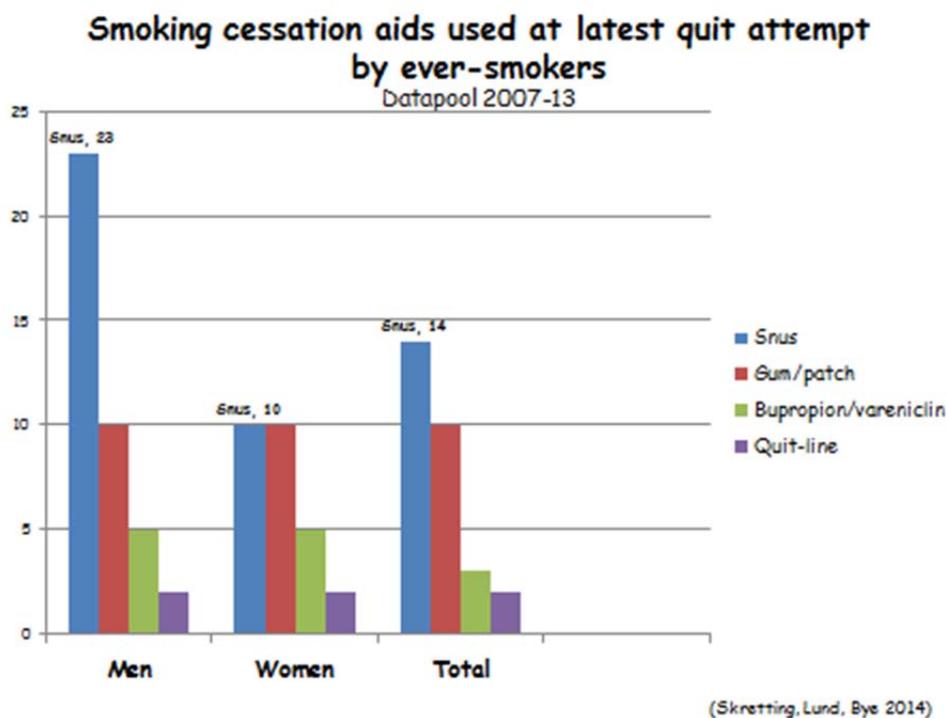
The SIRUS studies seek to address the same fundamental public health questions that are posed in the Tobacco Control Act, including dual use, initiation (particularly by youth), and impact on quitting tobacco use altogether. However, the SIRUS studies also address the role of snus as a cessation aid, which is not part of the MRTPA claim.

Dr. Lund's 2013 summary article provides an overview of the evidence in three areas of interest: the role of snus in smoking cessation; dual use of snus and cigarettes and the magnitude of dual use; and snus use among young people. In the article's Conclusions section, the author makes the following points:

Cessation

- "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."
- "Moreover, those using snus are more likely to have quit smoking completely or considerably reduce 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."

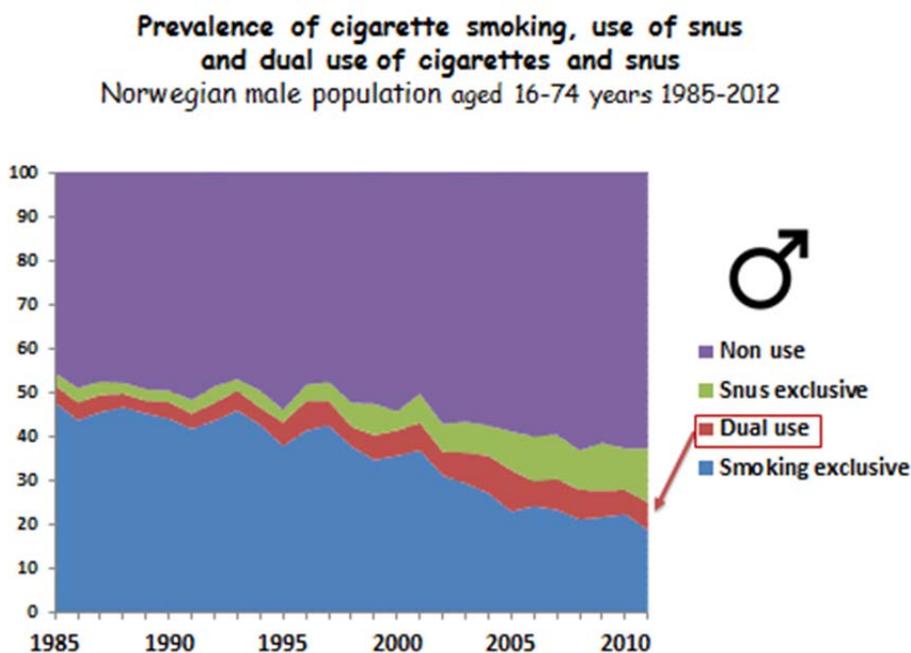
Figure 8.1



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, and there is no evidence that dual use lessons 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.”

Figure 8.2



Adolescent Initiation

- “Availability to snus may lead to use among young people who would not otherwise have used a tobacco product, or lead to snus use by smokers who would have managed to quit by other means.”
- “Any public health impact from this is likely to have been more than offset by the substantial numbers of Norwegian smokers who have switched from cigarettes to snus.”

8.2. Dual Use

Adults

Norway presents “natural laboratory” for the study of dual use of snus and cigarettes. Lund and McNeill (2013) used data from a time-series covering the period 1985-2010, a period in which the market share of snus increased from five percent (5%) to more than 30 percent. They found that, among men, the segment of dual users of cigarettes and snus varied between four (4%) and seven (7%) percent for the whole period. The overall percentage of male tobacco users decreased from 54 to 37 percent, and the share of Norwegian men who reported daily or occasional use of cigarettes, but no other tobacco product, declined from approximately half in 1985 to fewer than one in five in 2010. Women in Norway have been late adopters of snus, and the prevalence of dual use was less than one percent (1%) for the whole period.

The most typical pattern of dual use is a combination where daily use of one product was paired with occasional use of the other. One study showed that 22 percent of male daily snus users reported to smoke occasionally while 10 percent were using cigarettes on a daily basis (Lund and McNeill 2013). Among occasional snus users, 41 percent smoked daily, while 16 percent smoked occasionally.

In a Norwegian study not funded by SIRUS, Grotvedt et al. (2013) examined patterns of tobacco use among tenth graders living in Oslo County who were surveyed as part of the Oslo Health study in Norway (n=1395), with a three-year follow-up. Prevalence of dual use was 10%, where 6% of respondents were snus users, and 13% of respondents smoked.

The Swedish evidence provides additional data on dual use. According to the 2011 Swedish National Tobacco Survey, the prevalence of daily snus and daily cigarette use is two percent (2%), a rate which has remained stable since 2004. Cross-sectional studies in Sweden and Norway have reported similar prevalence rates, ranging from two percent (2%) to approximately ten percent (10%). Among adult male participants in the Swedish “Your Country and Your Life” survey, dual daily use of both snus and cigarette was low (2%), and no such use was observed among female tobacco users (Ramström and Foulds 2006). When occasional dual use of combustible tobacco products among snus users was considered, Digard et al. (2009) found that 12.6% reported dual use of a smokeless tobacco product and a combustible tobacco product and 9.8% of daily snus users also smoked cigarettes (whether daily or occasionally), among male and female study participants. Among dual users of daily snus and occasional or daily use of cigarettes, 53.5% reported that they smoked daily.

In the northern Sweden-based MONICA cohort study of 25-64 year-olds, dual use was reported among two to five percent (2-5%) (Rodu et al. 2002; Stegmayr et al. 2005). This prevalence of dual use was stable for the study period, from 1986 to 1999. According to the authors, dual use reflects a temporary transition between cigarette and snus as an unstable and transient period.

Rodu et al. (2003) examined the stability of dual users compared to other tobacco use groups to assess whether participants who were dual users at baseline remain in the dual use category at follow-up. They reported that combined use (smoking and snus) was the least stable category (39%), as 43% switched to snus and six percent (6%) switched to cigarettes. Former users of both products were also much less stable than former users of either cigarettes or snus.

In the Malmö study conducted in southern Sweden, Janzon and Hedblad (2009) reported an overall prevalence of snus use of seven percent (7%) among men (mean age 59 years) and less than one percent (1%) among women (mean age 57 years). Among the male snus users, 34% were also current smokers, 57% were ex-smokers, and nine percent (9%) were never smokers.

Among all age groups (16-74 years) surveyed as part of the Norway Tobacco Statistics (n = 3,145), 27% of respondents were exclusive smokers, eight percent (8%) were exclusive snus users, and seven percent (7%) both smoked and used snus (Lund and Lindbak 2007; SCENIHR 2010). In addition, in a meta-analysis by Lund et al. (2011) of seven cross-sectional data sets from Norway, 3.1% to 10.6% of snus users smoked daily, while a higher percent of participants reported that they smoked occasionally (16-35%). Tobacco consumption was not quantified and the authors noted that it is difficult to draw conclusions about whether this combined use was more or less damaging than the amount of smoking that would have taken place without the influence of snus.

Youth

Hamari et al. (2013) conducted a study among young male military recruits (n = 1174) living in Northern Finland. The prevalence of daily snus use in this study was 15.6%, which was higher than the 2.1% rate observed in the general male population (Statistics Finland 2008). The authors found daily use of both snus and cigarettes to be 6.9%. Occasional smokers were twice as likely to be daily snus users than daily smokers, at rates of 30.1% vs. 15.1%, respectively. The authors concluded that concomitant snus use seemed to increase cigarette dependence in dual users, albeit not to a statistically significant extent. The study did not collect information on duration of use and daily tobacco consumption.

A study of adolescents in the BROMS cohort found that tobacco consumption did not differ significantly among snus, cigarette, and mixed starters (Galanti et al. 2008).

Summary

Overall, dual use was more common in all age groups among men than women (Norberg et al. 2011; Ramström and Foulds 2006; Rodu et al. 2002; Stegmayr et al. 2005). Norberg and colleagues examined other factors that affected dual tobacco use, and concluded that being male and having a low educational background seemed to increase the likelihood of being a dual user. This was also observed by Engstrom et al. (2010). Additionally, as compared to non-tobacco users, dual users were more likely to be skilled and/or unskilled workers, binge drink, and engage in risky alcohol consumption. Compared to smokers, dual tobacco users were less likely to be binge drinkers, and more likely to engage in other risky alcohol consumption (Engstrom et al. 2010). There were no significant differences in dual use prevalence across all age groups (Engstrom et al. 2010; Ramström and Foulds 2006). Digard et al. (2009) reported a slightly higher prevalence of cigarette smoking among pouched snus users (10.5%) in comparison with loose snus users (8.7%).

There is evidence to suggest that the amount of tobacco consumed by dual tobacco users may differ from that used by exclusive users of either product (Galanti et al. 2008; Gilljam and Galanti 2003; Rodu et al. 2002). In particular, dual users appear to consume less tobacco than exclusive snus or cigarette users. In one study (2002), exclusive snus users reported average daily consumption of 0.41 packages of snus among ex-smokers and 0.44 packages amongst

those who never smoked. Former snus users averaged 15.1 cigarettes daily and those who never used snus smoked 16.0 cigarettes. In comparison, dual users consumed 0.25 packages of snus daily and smoked an average of 10.8 cigarettes daily (Rodu et al. 2002). Digard et al (2009) also investigated the frequency of cigarette use among daily snus users; all daily snus users who also smoked reported doing so at least once per week, and 53.5% of them did so daily. In the Malmö study, Janzon and Hedblad (2009) reported that male dual users smoked significantly less (12.3 cigarettes per day) than exclusive smokers (16.1 cigarettes per day). This trend was also observed among female dual users, who smoked on average 7.8 cigarettes per day compared to 12.9 cigarettes per day among exclusive smokers. Similarly, Gilljam and Galanti reported that the proportion of current smokers smoking fewer than 10 cigarettes per day was nearly twice as high among users of snus than among nonusers (44% versus 24%, respectively) (Gilljam and Galanti 2003).

By contrast, when tobacco consumption was considered among adolescents in the BROMS cohort, tobacco consumption was not found to differ significantly among snus, cigarette, and mixed starters (Galanti et al. 2008). Similar results were also observed in the Finnish study of male military recruits (Hamari et al. 2013). However, mixed starters were over-represented in the highest category of tobacco consumption (85 or more cigarettes and/or snus portions per week).

In summary, the frequency of daily dual use has been assessed in several studies, and has been reported to be approximately 2% in men and less than 1% in women. However, these rates appear to vary slightly depending on whether the criterion is daily dual use or occasional use of one tobacco type. Other studies have reported a slightly higher prevalence of dual use in Sweden. For example, 3.2% of male and 4.4% of female snus users in northern Sweden were found to smoke regularly in the VIP cohort (2009), and Digard et al. (2009) reported a prevalence of about 9.8% (for daily and/or occasional use). Taken together, among adults and adolescents, the range of dual use appears to be less than 10% in the Swedish population of snus users and some evidence suggests slightly lower overall tobacco use among dual tobacco users.

8.3. Delay in Smoking Cessation

There are studies in the US (not specific to the MRTPA Products) that indicate that some smokeless tobacco products may have the potential to delay cessation of tobacco use. Some studies indicate that dual users of cigarettes and smokeless tobacco products were less likely to achieve abstinence from tobacco over a four-year period compared with exclusive users of either product (Wetter et al., 2002). However, in Norway, no such difference was observed.

Norwegian studies observed no difference in intention to quit smoking within six months between exclusive smokers and dual users of snus and cigarettes. (Lund and McNeill, 2013). There are also Norwegian studies (Lund, 2009; Lund et al., 2010a; Scheffels et al., 2012) that address how many smokers who quit smoking with the help of snus, continue to use snus. In one study, 62% of those smokers who reported that they had tried to quit by using snus reported that they still used snus at the time of the survey, either daily (44%) or occasionally (19%). Those who had quit smoking completely or greatly reduced their cigarette consumption with the help of snus were more likely to use snus on a daily basis than people whose attempt to quit had resulted in less change in cigarette consumption. A substantial percentage (38%) of those using snus as a method for quitting, in fact, achieved complete tobacco cessation.

In another study from Norway comprising more than 2,300 male quitters under the age of 45 years, Scheffels et al. (2012) observed that 46% of those who had used snus on their last attempt to quit were current non-smokers, while 26% of those who had used NRT were current non-smokers. In total, 60% of successful quitters and 20% of unsuccessful quitters who had used snus as a method for quitting smoking had continued to use snus on a daily basis after quitting.

The Norwegian evidence is consistent with a study from Sweden (Ramstrom and Foulds, 2006). Another Swedish study (Wikmans and Ramstrom, 2010) had similar observations. Expectancies of being smoke-free five years into the future were significantly more prevalent among dual users than exclusive smokers.

The smoking cessation results from Norwegian and Sweden are encouraging, where a study conducted in some US test markets for snus indicated that smokers who had no immediate plans to quit were more likely to try snus (Biener et al., 2011).

8.4. Initiation by Youth and Adolescents

A fundamental concern regarding use of snus or any potential MRTP is whether it will be used by people (youth and adolescents, in particular) with no previous experience with nicotine, or by people who would have managed to quit smoking by other means. A Norwegian prospective study found that snus enabled few of the cognitions which usually increase the desire to smoke among young people (Larsen, et al, 2012).

Another fundamental concern is whether the increase in snus use in Norway (and Sweden) is caused by an influx of young non-smokers who, in the absence of snus, would have remained abstinent from all tobacco. In one Norwegian study (Larsen et al 2012) a significant segment of the young users had social and demographic characteristics most typical of non-tobacco users. However, an equally large segment of snus users had characteristics that typically predispose for smoking, which might indicate that they otherwise would have started to smoke in a situation where snus was unavailable.

8.5. The Premarket Consumer Perception Study and the Dynamic Population Modeler

The Consumer Perception Study provided several key insights related to intended use of the Snus Products by current users and non-users of tobacco products. As discussed in Section 5.3 above, study results demonstrate that the proposed warning labels for the Snus Products are unlikely to produce unintended negative consequences for the population as a whole, or the former smoker, imminent quitter, minority, low income, or youth subgroups. Study subjects' ability to comprehend and understand the proposed warning labels support the conclusion that the modified risk claims are not misleading, but rather promote a better understanding of the actual health risks of snus as compared to cigarettes. The results of this premarket research supplement the extensive preclinical, toxicology and epidemiology data presented in the MRTPAs regarding the effects and use of snus as compared to cigarettes.

Evidence supporting the expected population benefit of the Snus Products is further buttressed by the results of the Dynamic Population Modeler. The DPM specifically evaluated effects due

to use of the MRTP (i.e., Swedish snus) by those who, in the absence of the MRTP, would have remained tobacco-free (i.e., non-smokers) and those who would have quit smoking. The DPM accounted for the potential effects of Swedish snus being more attractive than cigarettes to youth who are at risk of becoming tobacco users, the potential gateway effects of Swedish snus to smoking, and the potential effects of an increased likelihood that former users (i.e., those who quit all tobacco and those who switched from cigarettes to Swedish snus) may relapse back to cigarettes. The results confirm that the introduction of Swedish snus can result in a net population-level benefit, particularly if the product is adopted by a sufficient number of smokers. Taken together with the results of the premarket research, the DPM suggests that a scenario in which introduction of Swedish Match snus results in more tobacco users compared to the base case (giving rise to a survival deficit) is unlikely.

8.6. Public health benefit of accurate relative risk information

There is an increasing need for effective communication on the relative risks of the range of nicotine-containing products. Public awareness of the Tobacco Control Act and the growing popularity of electronic cigarettes, with the resultant media coverage, have contributed to increased public knowledge of the changing landscape of nicotine delivery products. CTP has demonstrated a willingness to address complex and somewhat controversial concepts such as continuum of risk; but determining and communicating the relative risk of a specific product must be done through scientific evidence-based processes that take time and judgment and in accordance with governing law.

Section 911 of the Tobacco Control Act specifies the evidence to be provided to permit FDA to make an MRTP determination. The Act is less clear regarding how to communicate a modified risk finding to consumers. Implicit, however, is the notion that accurate, science-based warning labels are fundamental to communicating the risk of any product. Research has shown that warnings can communicate benefits and risks to consumers successfully, but only if (i) the warnings contain the information needed for effective decision-making, (ii) users can access that information, and (iii) users can comprehend what they access.⁴ Warning labels for tobacco products are particularly challenging, and it is essential that the warnings accurately reflect the science and communicate clear messages.

Swedish Match's MRTPAs propose changes to the existing warning labels for the Snus Products to more accurately reflect the science. The Applications present compelling data evidence that the switch from cigarettes to Swedish snus reduces individual risk for a number of health outcomes, including oral and lung cancer, heart disease and non-cancer oral effects (i.e., gum disease and tooth loss). This evidence necessitates the removal of the current warnings regarding mouth cancer, and gum disease and tooth loss. In addition, meeting the reduced individual risk standard in itself warrants a warning label change—namely, that the label reflect the fact that snus poses substantially lower risks than cigarettes.

Swedish Match applauds CTP's leadership in communicating the concept of continuum of risk for nicotine-containing products. CTP Director Mitch Zeller has publicly addressed the topic on several occasions, and the preamble to CTP's proposed Deeming Regulation includes

⁴Baruch Fischhoff, *Duty to Inform*, in FDA, Risk Communication Advisory Committee, Communicating Risks and Benefits: An Evidence-Based User's Guide 19 (Aug. 2011), available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf>.

compelling and insightful statements about continuum of risk, tobacco harm reduction, and the science of nicotine. The risk continuum ranges from cigarettes, the most risky product, to NRTs, the least risky nicotine delivery devices. Swedish Match believes that Swedish snus should be placed at the far lower end of the risk scale, next to NRT products, and that the warning label for the Snus Products should reflect that distinction.

Swedish Match's Consumer Perception Study considered (and tested) two warnings that would reflect the risk reduction that occurs by switching from cigarettes to Swedish snus. The primary difference in the two warnings relates to the presence of the term "substantially", as in "No tobacco product is safe, but this product presents *substantially* lower risks to health than cigarettes." The term "substantially" accurately reflects the extent of risk reduction that actually occurs with a switch from cigarettes. Moreover, study results demonstrated that this warning was clear and understood by the public. It also resulted in a more accurate understanding of the relative risks of snus and cigarettes. For that reason, we believe that the proposed warning conveys the concept of continuum of risk, indicating that the Products are at the opposite end of the risk scale as cigarettes.

9. GOVERNANCE

9.1. The Challenges of Governance

In the IOM Report, the IOM's Committee on Scientific Standards for Studies on Modified Risk Tobacco Products articulated certain concerns, shared by governmental authorities and stakeholders, regarding the scientific studies conducted and funded by tobacco companies. The conclusions and suggestions presented in the IOM Report chapter titled "Governance and Conduct of Studies" resonated with Swedish Match and reinforced the Company's approach to the conduct of research to support the MRTPA. It also provided the impetus for the Company to take incremental steps toward improving the regulatory science environment for tobacco research.

Swedish Match has a strong tradition of product stewardship and research governance, perhaps best embodied in the Company's development of its voluntary quality standard, GOTHIA TEK®. The Company's commitment to governance is further reflected in the manner in which it undertook the clinical trials. The Company developed the clinical trial protocols according to internationally-accepted guidelines and performed the studies in accordance with local and national laws, ICH guidelines, and the guidelines of the Declaration of Helsinki. Further, the studies were approved by an appropriately constituted IRB or IEC, and all trials were conducted according to ICH-GCP.

The studies undertaken to support the MRTPAs afforded Swedish Match a unique opportunity to build on past accomplishments and further demonstrate its commitment to governance. Most notably, the Company established an independent advisory body to provide advice during the development of the MRTP Applications. Although the MRTP Advisory Panel does not meet all of the criteria of the third-party research governance entity envisioned in the IOM Report, the Panel nevertheless provides important research governance services and Swedish Match believe that it represents the kind of progressive initiative that is needed to reach the Report's stated goals.

The IOM Report states that “[t]he role of governance is to ensure the proper conduct of research.” The committee devoted an entire chapter to this issue because, as stated in the report, “There is profound distrust of the tobacco industry and of research supported by the tobacco industry.” The governance chapter offers suggestions for establishing “...the tobacco industry as a legitimate participant in tobacco research as an important consideration in the overall goal of producing evidence on the effects of MRTPs.” In particular, the Committee recommends strategies to “...create an environment conducive to the production of reliable and credible evidence...” including “An independent third party that conducts research, provides oversight of research, distributes funding for research or manages research contracts, or otherwise provides governance of research...” The committee suggests that such an independent third party would be particularly useful for “...research involving populations with a high risk for tobacco use such as behavioral research, studies of adolescents, research on abuse liability, and observational studies of health effects will be very challenging for the tobacco industry.”

Swedish Match understands that research funded by tobacco companies is subject to greater scrutiny than that conducted by other FDA regulated industries, and the Company supports the findings and recommendations set forth in the IOM report. The Company also understands that it benefits greatly from the “observational studies of health effects” that have already been conducted in Sweden by highly credible authorities. The evidence from Sweden and Norway, collected through studies undertaken by governmental and public health authorities, provides a strong and credible scientific basis for the claims made in the MRTPAs.

One of the most sensitive issues in establishing an MRTP is adolescent use of the tobacco product. The MRTPAs include product specific evidence from Sweden and Norway regarding adolescent use. This evidence, which was collected through government or academics studies, rather than by a tobacco company comports with the position taken in the IOM Report that it is essential that governmental authorities and/or credible third parties take the lead in documenting adolescent tobacco use. Swedish Match supports this position and publicly stated that it is contrary to Company policy to conduct research on “sensitive subpopulations such as adolescents...” due to “...ethical and product stewardship concerns.”

While the Swedish and Norwegian adolescent-use evidence may be sufficient to support the MRTPAs, going forward, for example when conducting postmarket surveillance, it will be necessary to involve external experts and organizations in gathering such data. Ideally, in the near future, an independent third party will be established to implement this and other IOM Committee suggestions.

9.2. Swedish Match MRTP Advisory Panel

Following on the suggestions in the IOM Report, Swedish Match established the MRTP Advisory Panel to address concerns relating to tobacco research governance. The Company initiated the advisory panel process by soliciting advice from leaders in the research, tobacco control, and public health communities. In early 2013, Swedish Match 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:

- 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 also developed the following operating principles that define the role of the body and provides guidance for operation:

- The Advisory Panel is an independent body that develops its own mission statement and operating procedures. Members do not have a contractual arrangement with Swedish Match and do not sign confidentiality agreements.
- The Advisory Panel does not offer a consensus position; rather the members express their individual views.
- Swedish Match staff provides administrative services to the Advisory Panel; including offering background information, arranging for calls and meetings, and providing meeting follow-up. Swedish Match staff and the Panel members work closely together in preparing meeting agendas and identifying work tasks with the Advisory Panel having the final decision.
- Advisory Panel members are informed of Swedish Match operations in the US and globally and are encouraged to ask questions regarding policies and performance.
- The Advisory Panel will serve as a model for how a tobacco company can interact with an external science-based group. Accordingly, it is essential that the operations of the Advisory Panel are as transparent as feasible and members continually seek opportunities to communicate its goals and operations. The Advisory Panel has an interest in informing the tobacco enterprise and the broader scientific and public health communities of its actions and principles.
- The Advisory Panel is a new and evolving body. The members are committed to the mission statement and operating principles but the approach used to accomplish the mission will continually evolve.

To ensure that a wide range of perspectives was represented, Swedish Match did not limit membership in the Advisory Panel solely to experts in tobacco science and policy. Rather, Panel members would include scientists and science policy experts with extensive backgrounds in toxicology, risk perception and communication, FDA regulations, and research governance. The MRTP Advisory Panel currently consists of five members, all of whom have had long and accomplished careers in their scientific fields and are seeking to apply their experiences and insights to improve the exchange of information and concepts in the area of tobacco regulatory science.

The MRTP Advisory Panel first met via conference call on March 1, 2013, and the first face-to-face meeting followed two weeks later. During that period, the Panel finalized its mission statement and operating principles and discussed how best to communicate its work to the tobacco community. The Panel met again for two-day sessions on June 24-25, 2013 in Stockholm and in Washington, DC, on November 13-14, 2013. CTP was notified in advance of the DC meeting and meeting minutes were provided.

The Advisory Panel provided advice and comments on the premarket consumer perception study and on several key components of the MRTPAs. The Panel was not asked to approve the study protocol or the Applications and the Panel did not seek a consensus view, but rather endeavored to be as transparent as possible and ensure that each member shared his or her comments with the entire group. Specific Panel activities included the following:

- During its initial face-to-face meeting in March 2013, the Panel reviewed the draft protocol for the premarket consumer perception research. Following the meeting, several members provided additional comments on the protocol through a series of email exchanges.
- In a meeting in May 2013, CTP staff expressed interest in the Panel's input on the Consumer Perception Study protocol. At CTP's suggestion, the Company requested that the Panel conduct a final review of the protocol during the June 2013 Panel meeting. Panel members provided additional input following the meeting, the protocol was revised and the Panel provided a final review of the protocol before the research commenced. Prior to its November 2013 meeting, the Company provided the Panel with early drafts of Section 2.5 (*Summary*) and Section 6 (*Summary of All Research Findings*), and access to the entire MRTPAs. The Panel discussed the application during the two-day meeting and members provided additional comments to the Company following the meeting.
- In February 2014, the Panel reviewed and provided comments on the premarket consumer perception data and various drafts of Section 6.4 (*Effect of Marketing on Consumer Understanding and Perceptions*). At a meeting in Stockholm in July 2014, following submission of the MRTPAs, the Panel decided to write a scientific article based on further analysis of the premarket consumer perception data. Dr. Fagerström and Dr. Hughes offered to take the lead in writing the article and Swedish Match agreed to facilitate access to the data and the provide additional assistance. Indeed, the premarket consumer perception data are publicly available via the FDA CTP web site, and the Company encourages all researchers to access and utilize the data.
- Members of the tobacco control community were invited to the Panel's November 2014 meeting in Washington, DC providing an opportunity for the Panel to describe their role in the MRTP process and discuss issues of interest to the guests.

9.3. Swedish Match Outreach Efforts

Swedish Match believes that transparency is a fundamental tenet of governance and, with the support of its Board of Directors, has reached out to a wide range of stakeholders and given presentations in various forums to describe the submitted MRTPAs, receive feedback, and

answer questions. During every presentation, the audience was urged to submit comments to the federal docket established for the MRTPAs.

In light of its “trailblazing” role as the submitter of the first MRTPAs accepted for filing by FDA, Swedish Match is committed to sharing its experiences with other companies that may be considering preparing a MRTPA. A presentation was made at the largely industry attended Global Tobacco Network Forum in October 2014 and at two Food Drug Law Institute conferences which attracted many industry representatives in Washington (October 2014) and Brussels (November 2014).

On October 21, 2014, Swedish Match gave a 1-hour presentation during the Strategic Dialogue II conference held in Washington, DC, by the Legacy Foundation for Health and the Schroeder Institute for Tobacco Research and Policy Studies. The presentation attracted approximately 40 leaders in tobacco research and public policy and was followed by a 30-minute question and answer session which provided a constructive exchange of views between Swedish Match and tobacco control advocates and researchers.

10. POSTMARKET SURVEILLANCE

Swedish Match has established the foundation for a postmarket surveillance and study program (“Postmarket Program”) to satisfy the requirements of Section 911(g)(2)(C)(ii) of the Act and to address the recommendations set forth in the MRTP Guidance. Swedish Match considers the Postmarket Program to be part of a broader product stewardship effort that is based on traditional Company practices, such as GOTHIA TEK®; the funding of health and safety research, including clinical trials; and an enduring commitment to transparency and inclusiveness, including the involvement of external, independent reviewers.

The primary objective of the Postmarket Program is to evaluate the benefit to the population as a whole of the labeling changes proposed in the Applications. The Postmarket Program will collect evidence to address the key public health questions of who is using the Swedish Match Snus Products and, importantly, how the products are being used. Swedish Match intends to collect evidence on consumer behavior indicators and perceptions using a series of large-scale surveys.

A second objective of the Postmarket Program is to monitor and collect information regarding unanticipated and undesired events related to the Snus Products once they are introduced to the market, and to contribute to the establishment of an adverse event reporting mechanism. If the requested MRTP orders are granted, Swedish Match is committed to working with CTP and serving in a pilot capacity in the building and testing of a reporting mechanism.

Swedish Match’s Postmarket Program for the Snus Products will build on the processes established in preparing the Applications. In particular, Swedish Match will continue to seek the input of external experts, including most importantly, the Swedish Match MRTP Advisory Panel. In addition, postmarket surveys will build on the information and experience derived from Swedish Match’s Premarket Consumer Perception Study, as described in Section 5.3 of this Briefing Document. The postmarket surveys will include several questions used in the premarket survey, as well as incorporate additional questions assessing consumer perception about different types of tobacco products and their effects on individual health. The Postmarket

Program will also seek to benefit from and complement ongoing research initiatives, including the ongoing FDA/NIH sponsored Population Assessment of Tobacco and Health (PATH) Study.

In sum, the Postmarket Program, and the postmarket surveys in particular, will be comprehensive and will include a range of elements and influences. As with the premarket consumer perception research, Swedish Match will use its considerable market research experience and expertise to develop and implement a Program that blends marketing concepts with regulatory science principles, resulting in a collection of evidence that will support decision-making and future research. In accordance with Section 911(i)(2) of the Act, Swedish Match will submit a final protocol for the Program within 30 days following the issuance of the MRTP orders.

11. CONCLUSION

Swedish Match is confident that the comprehensive scientific evidence submitted in support of the MRTPAs, and further summarized in this Briefing Document, permit CTP to issue an MRTP order permitting the use of the Company's proposed modified risk statements. Swedish Match considers these warning label adjustments wholly appropriate given the global acceptance of the Swedish epidemiological and other data which demonstrate the reduced risk to individual users and the population-level public health benefits of Swedish snus.

Based on the totality of the evidence presented, Swedish Match has demonstrated that the Snus Products "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" and also "benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." Therefore, FDA should grant the requested MRTP orders for the Snus Products pursuant to Section 911(g) of the Act. In so doing, FDA would not only give effect to Congress's intent in enacting the Tobacco Control Act, but would also fulfill the Agency's public health mission of ensuring that consumers are better informed relating to the health and safety of tobacco products.

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APPENDIX I

Swedish Match’s MRTPA meets all the statutory requirements for an MRTP application as set forth in Section 911(d) of the Act. Moreover, Swedish Match has organized and synthesized the compelling scientific evidence and information presented in the MRTPAs in accordance with the recommendations in FDA’s MRTP Guidance.

Statutory Requirements for MRTP applications

FDCA Requirements	SMNA MRTP Application Section
FDCA § 911(d)(1): description of the proposed product and any proposed advertising and labeling;	Section 3.1: Description of proposed Snus Products
FDCA § 911(d)(1): description of the proposed product and any proposed advertising and labeling	Section 4.1: Description of proposed Snus Product advertising and labeling
FDCA § 911(d)(2): conditions for using the product	Section 3.3: conditions for using the Snus Products
FDCA § 911(d)(3): formulation of the product	Section 3.3: formulation of the Snus Products
FDCA § 911(d)(4): sample product labels and labeling	Section 4.2: sample Snus Product labels and labeling
FDCA § 911(d)(5): all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health	Section 7: all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by Swedish Match relating to the effect of the Snus Products on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the Snus Products to reduce risk or exposure and relating to human health
FDCA § 911(d)(6): data and information on how consumers actually use the tobacco product	Section 3.4: data and information on how consumers actually use the Snus Products); and
FDCA § 911(d)(7): such other information as the Secretary may require	N/A