

## 2.5 Summary

### 2.5.1. Tobacco Use and the Public Health

According to the World Health Organization (“WHO”), tobacco use continues to be the leading global cause of preventable death.<sup>1</sup> Premature deaths attributable to tobacco smoking are expected to rise to 6.4 million in 2015, and 8.3 million in 2030 (Gartner et al. 2007b). In the United States alone, more than 400,000 persons die each year from smoking-related diseases, and approximately 8,600,000 Americans have chronic illnesses related to smoking.<sup>2</sup>

Notwithstanding these alarming statistics, the risk of a man dying from a tobacco-related disease is less in Sweden than in any other European country, despite the fact that total tobacco consumption is comparable to that of other countries in Europe. Researchers refer to this paradox as “the Swedish Experience,” a phenomenon which is most likely explained by the unique form of tobacco use among Swedish men, which largely takes the form of Swedish snus. Swedish men smoke substantially less than their counterparts in other countries with comparable rates of tobacco consumption, and the use of snus among Swedish men is more common than smoking. Moreover, although snus use has increased as smoking has declined, the overall rate of tobacco consumption in Sweden has also steadily declined.

The positive effect of this phenomenon is a very low frequency of tobacco-related illnesses among Swedish men and low smoking-related mortality rates. This unique situation is documented in a large number of epidemiological studies with findings such as the following:

- The incidence of lung cancer among Swedish men has declined over the past 20 years, which researchers link to the fact that Swedish men are smoking less and that many of them have switched to snus.
- There is no demonstrable correlation between the use of Swedish snus and oral cancer.
- Several studies have shown no increased risk of cardiovascular diseases among snus users.

Although the use of Swedish snus may have some negative health effects, research results have shown that health risks are substantially lower for the use of snus compared with smoking. In light of the medical consensus that Swedish snus is approximately 90-95% *less harmful* than smoking (Levy et al. 2004), it would be contrary to both sound science and sound regulatory policy to treat snus and cigarettes as *equally harmful*.

The overall effect from Swedish snus on public health comes down to the balance between its beneficial effect on smoking prevalence and its adverse effects on the overall prevalence of

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<sup>1</sup> World Health Organization, [http://www.who.int/tobacco/health\\_priority/en/](http://www.who.int/tobacco/health_priority/en/).

<sup>2</sup> Family Smoking Prevention and Tobacco Control Act of 2009, Pub. L. No. 111-31, § 2(13), 123 Stat. 1776 (2009) (hereinafter “Tobacco Control Act”).

tobacco use (Lund 2013). Congress rightly recognized this balance when crafting the statutory standard governing the issuance of an order for the commercial marketing of an MRTP under the FDCA, as amended by the Tobacco Control Act. In accordance with Section 911(g) of the Act, FDA shall issue an MRTP order only if the product, as actually used by consumers, will “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.”

Swedish Match asserts that the scientific data and information presented in this Application fully satisfy the statutory standard under FDCA Section 911(g). These data demonstrate that the individual and population-level health risks associated with Swedish snus, as manufactured by Swedish Match, are significantly lower than those of cigarettes. Consequently, Swedish Match believes that its Swedish snus products should be recognized as modified risk tobacco products under the Act. This science-based designation would recognize the important and constructive role that Swedish snus can play in reducing the adverse health consequences of tobacco use, and permit adult consumers to make informed decisions about the relative risks of Swedish snus as part of a pragmatic and effective harm reduction strategy.

### 2.5.2. MRTP Application Overview

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.”<sup>3</sup> In other words, 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” (IOM 2012). Congress recognizes “the compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product”<sup>4</sup> and, thus, authorized FDA “to require that products . . . sold or distributed for risk reduction be reviewed in advance of marketing, and to require that the evidence relied on to support claims be fully verified.”<sup>5</sup>

Swedish Match appreciates the detrimental public health impact that would ensue by permitting manufacturers to make unsubstantiated statements concerning MRTPs, whether express or implied.<sup>6</sup> This danger is particularly acute for those tobacco products that *do not in fact* reduce the risk of harm or tobacco-related disease associated with commercially marketed tobacco

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<sup>3</sup> *Id.* § 3(4) (emphasis added).

<sup>4</sup> *Id.* § 2(40).

<sup>5</sup> *Id.* § 2(43).

<sup>6</sup> *See id.* § 2(42) (emphasis added).

products.<sup>7</sup> However, where the scientific evidence establishes that a tobacco product *does in fact* reduce such risk of harm or disease, it is appropriate for the protection of the public health—and critical to FDA’s fulfillment of its mission<sup>8</sup>—to “ensure that consumers are better informed . . . relating to the health . . . and safety of [the MRTP].”<sup>9</sup>

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. Accordingly, this MRTP Application provides a comprehensive analysis of the relevant scientific evidence relating to the health effects of Swedish snus and the public health impact of the product for users and non-users at both the individual and population levels. The scientific evidence presented in the Application is derived from a collection of rigorous, well-controlled studies conducted by various governments, academic institutions, and private companies. The Application presents two broad categories of scientific evidence, including (i) product-specific information which is derived from studies using Swedish Match’s Swedish snus products and (ii) other relevant evidence from studies that examined products similar to the Company’s products, including other forms of snus and other smokeless tobacco products. What follows is a brief overview of the categories of evidence presented herein, as well as an explanation of how that evidence applies to the recommendations set forth in FDA’s Draft Guidance for Industry: Modified Risk Tobacco Product Applications (the “MRTP Guidance”).<sup>10</sup>

#### **2.5.2.1. Proposed Modified Risk Claim**

This MRTP Application seeks CTP’s approval to make modified-risk claims for ten (10) Swedish snus smokeless tobacco products<sup>11</sup> which are currently marketed in the United States

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<sup>7</sup> See *id.* § 2(40) (emphasis added).

<sup>8</sup> FDA Mission Statement, <http://www.fda.gov/AboutFDA/WhatWeDo/>.

<sup>9</sup> See Tobacco Control Act at § 3(6).

<sup>10</sup> FDA, Draft Guidance for Industry: Modified Risk Tobacco Product Applications, <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf>.

<sup>11</sup> This MRTP Application is being submitted for the following ten (10) Swedish snus products: General Loose (SKU 4852); General Dry Mint Portion Original Mini (SKU 4800); General Portion Original Large (SKU 4880); General Classic Blend Portion White Large – 15 ct (SKU 4877); General Classic Blend Portion White Large – 12 ct (SKU 4878); General Mint Portion White Large (SKU 4352); General Nordic Mint Portion White Large – 15 ct (SKU 4876); General Nordic Mint Portion White Large – 12 ct (SKU 4875); General Portion White Large (SKU 4881); and General Wintergreen Portion White Large (SKU 4882).

(collectively, the “Snus Products”).<sup>12</sup> Specifically, Swedish Match seeks approval to modify the health warnings mandated for the Snus Products pursuant to Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, which requires all smokeless tobacco product labels to bear one of the following general statements:

1. WARNING: This product can cause mouth cancer.
2. WARNING: This product can cause gum disease and tooth loss.
3. WARNING: This product is not a safe alternative to cigarettes.
4. WARNING: Smokeless tobacco is addictive.

Although these warnings may be appropriate for certain customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the net individual and population-level public health risk-reduction benefit of snus. Thus, this Application seeks the following 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:

- The revised labeling will not carry the mouth cancer warning.
- The revised labeling will not carry the gum disease and tooth loss warning.
- The revised labeling will change the “not a safe alternative to cigarettes” warning to “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.”

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<sup>12</sup> On March 17, 2011, Swedish Match submitted SE Reports to FDA for the Snus Products which are the subject of this MRTP Application. The SE Reports, along with their associated amendments, set forth the basis for Swedish Match’s determination that the products are substantially equivalent, within the meaning of Section 910 of the Act, to tobacco products commercially marketed in the United States as of February 15, 2007. Because the SE Reports were submitted prior to March 23, 2011, each of the Snus Products may continue to be legally marketed unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and all ten (10) Snus Products may be lawfully marketed in the United States. Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a “part” of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a “new tobacco product” subject to premarket review. Accordingly, this MRTP Application includes certain SE information for each of the Snus Products, as modified to include, among other things, certain proposed modified-risk claims in their respective labels.

- The revised labeling will keep the current addiction warning.

In other words, there would be two warning labels (and hence, two modified risk claims) subject to the MRTP order, and they would read as follows:

1. WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.
2. WARNING: This product is addictive.

### **2.5.2.2. Description of the Tobacco Product and Scientific Rationale for Its Potential Benefits**

#### **2.5.2.2.1. Description of the Snus Products**

Each of the Snus Products which are the subject of this Application is 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.<sup>13</sup> 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., cooking salt, sodium bicarbonate, etc.) and flavors. In Sweden, the product is classified as food, contains only food-approved ingredients, and is manufactured in premises that are hygienically suitable for food production.

Unlike nasal snuff, which is inhaled through the nasal cavity, Swedish snus is an oral smokeless tobacco product, and it is moist to facilitate use in the oral cavity. Thus, the Snus Products are moist (50-60% moisture) to semi-moist (30-45% moisture) oral tobacco products which are typically placed between the upper lip and the gum and do not require expectoration during use.<sup>14</sup>

The Snus Products are currently marketed in the United States with the statutorily mandated warnings required under Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act. However, this Application seeks to modify these warnings to better convey the product-specific scientific evidence demonstrating the individual and population-

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<sup>13</sup> European Smokeless Tobacco Council, <http://www.estoc.org/about-smokeless-tobacco>.

<sup>14</sup> By contrast, American moist snuff products are typically placed under the lower lip and require expectoration during use.

level public health risk reduction benefit of snus. This scientific evidence, including the rationale for the potential benefits of the Snus Products, is summarized below.

#### **2.5.2.2.2. Scientific Rationale for the Potential Benefits of the Snus Products**

##### **2.5.2.2.2.1. Product-Specific Evidence**

The most applicable evidence submitted in support of this MRTP Application is the result of research conducted using Swedish Match snus products. Typically, such product-specific evidence is only generated by the application sponsor. However, Swedish Match is fortunate to be able to submit an impressive body 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 herein as the “Swedish Experience”—has been widely cited by public health agencies and scientific institutions around the world, and it is fundamental to the FDA Center for Tobacco Products’ (“CTP’s”) analysis of the modified risk claims presented in this Application.

The Swedish Experience evidence is supplemented by additional product-specific evidence collected by Swedish Match, including a series of clinical trials sponsored by the Company just prior to the passage of the Tobacco Control Act and additional research undertaken following the issuance of the MRTP Guidance. Of particular relevance to this MRTP Application is the evidence from two placebo-controlled, double-blind, randomized smoking cessation clinical trials which were conducted during 2008-2010. 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 (US and Serbia) or substantially reduce their smoking (Serbia). These clinical trials—which fulfill many of the key areas of investigation suggested in the MRTP Guidance—were initiated prior to the passage of the Act and are representative of Swedish Match’s longstanding commitment to product stewardship and consumer protection. They are complemented by three Swedish Match trials comparing the nicotine pharmacokinetics and pharmacodynamics of various snus products compared to select nicotine replacement therapies (“NRTs”), which showed that snus is comparable to commercially available NRT products, and is associated with less abuse liability than cigarettes.

To complement the epidemiological evidence and to provide a preclinical, toxicological rationale for the essentially negative findings concerning cancer risks among snus users, Swedish Match also sponsored *in vitro* toxicological testing of extracts of Swedish snus. These tests included the Salmonella reverse mutation assay, mouse lymphoma assay, *in vitro* micronucleus assay, and tests of cytotoxicity. The results of these assays were broadly negative for Swedish snus. There were occasional positive responses, but these were effectively at the highest concentration only (i.e., concentrations well above those suggested by regulatory guidelines) and were often associated with significant cytotoxicity. These data contrast with data reported for combusted tobacco in the form of cigarettes, where strongly positive responses have been routinely reported for mutagenicity and cytotoxicity. These negative findings in a laboratory setting concur with

the large amount of epidemiological data from Sweden, data showing that Swedish snus is associated with considerably lower, if any, carcinogenic potential when compared with cigarettes.

Swedish Match has also conducted premarket consumer perception research designed to address several key areas of investigation set forth in the MRTP Guidance. The research assesses 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 research study protocol was developed over a one-year period and in consultation with the Swedish Match MRTP Advisory Panel (the “MRTP Advisory Panel”) and outside counsel experienced in FDA regulatory science. The protocol was considerably enhanced through a series of meetings with CTP staff, and it was refined by continual review conducted by the MRTP Advisory Panel.

Additional product-specific evidence derives from the results of secondary data analysis and modeling using the Dynamic Population Model (“DPM”). 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. The DPM is a comprehensive and flexible model which provides a useful tool for the development of science-based regulatory policy related to tobacco harm reduction, as it helps to clarify assumptions underlying the arguments for or against the tobacco control policies being considered. Swedish Match financially supported the overall development of the DPM and provided the information to run the applications the results of which are presented herein.

Finally, another key component of the product-specific scientific evidence presented in the MRTP Application is GOTHIA TEK®, the Company’s proprietary quality standard which assures consumers that all Swedish Match products are subject to rigorous controls and maintain the highest quality throughout all the stages from tobacco plant to consumer. GOTHIA TEK® 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 objectives for quality and content beyond that which is required by law. For example, GOTHIA TEK® sets the standards for raw material quality requirements, manufacturing process requirements, consumer product information requirements, and maximum permitted levels of undesirable substances in the finished, snus products.

#### **2.5.2.2.2.2. Other Relevant Evidence**

Although the most compelling evidence presented in the Application is clearly product-specific, there is a vast and ever increasing amount of applicable, non-product-specific studies published in scientific journals that further support the claims made herein. Some of this research is broader in scope and assess smokeless tobacco products in general, or novel products marketed as “snus.”

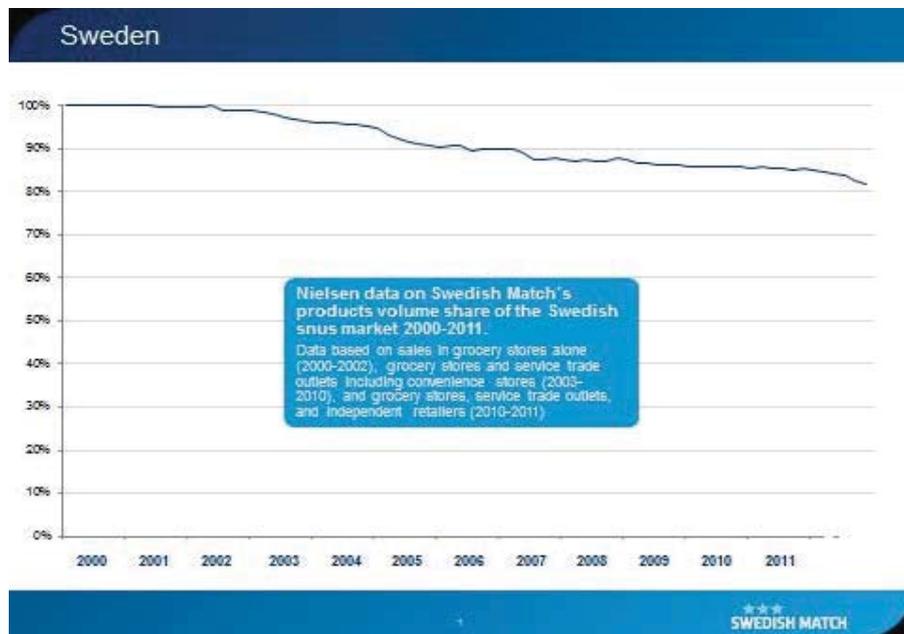
Swedish Match recognized the importance of this information and prior to the passage of the Tobacco Control Act, contracted with ENVIRON International Corporation (“ENVIRON”) to monitor the scientific literature and prepare a comprehensive compendium of the articles pertaining to snus. ENVIRON produced two reports that are particularly applicable to the Application:

- 1) Review of the Scientific Literature on Snus (Swedish Moist Snuff) (the “[ENVIRON Snus Monograph 2013](#)”) and
- 2) Swedish Snus and US Smokeless Tobacco Use Behaviors (the “[ENVIRON TUB Report 2013](#)”).

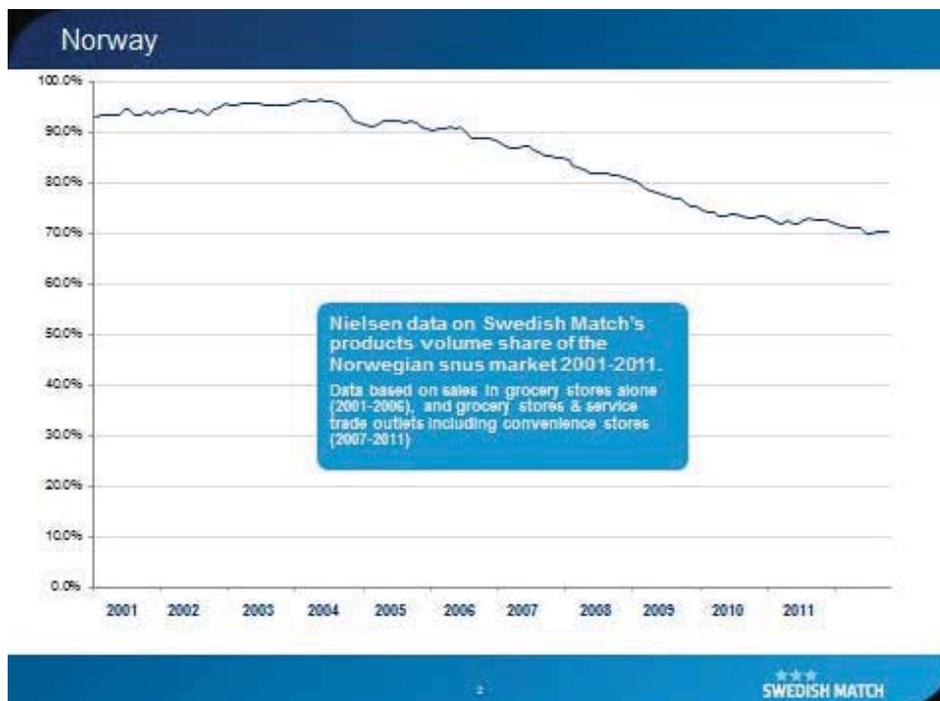
The former report presents a comprehensive review of the scientific literature on the potential health risks associated with the use of Swedish snus. The latter report presents a review of the scientific literature on snus and smokeless tobacco use in the United States and Scandinavia as it relates to tobacco use behaviors, including dual use, gateway issues, and smokeless tobacco as a smoking cessation aid. Both reports are submitted in their entirety for CTP’s review as appendices to this Application ([Appendices 6A](#) and [6B](#), respectively).

In reviewing the scientific literature, it is important to note that snus is and always has been the dominant smokeless tobacco product on the Swedish market, comprising more than 99% of total annual smokeless sales. This means that all Swedish epidemiological studies that have assessed the effects of smokeless tobacco—irrespective of whether the word “snus” or “snuff” was used to qualify the studied product—almost certainly concerned Swedish snus. Swedish Match (including its predecessors in interest, Svenska Tobaksmonopolet, STM, or Svenska Tobaksaktiebolaget, STAB) has always 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. As a practical matter, this means that 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.

**Figure 2-1. Swedish Match Product Volume Share in Sweden**



**Figure 2-2. Swedish Match Product Volume Share in Norway**



### **2.5.2.3. Summary of Information and Scientific Data Being Submitted**

In its report titled *Scientific Standards for Studies on Modified Risk Tobacco Products* (IOM 2012), the Institute of Medicine of the National Academies Committee on Scientific Standards for Studies on Modified Risk Tobacco Products (“IOM”) addressed the type of evidence and studies to be submitted to support modified-risk claims for existing commercially available tobacco products. In these cases, IOM recommended that epidemiologic evidence “weigh heavily in [CTP’s] decision making” and be supported by evidence that “conclusively demonstrate[s] substantially reduced . . . biomarkers of risk.” IOM explained that preclinical studies, though important, “play relatively minor roles (e.g., providing mechanistic context) in justifying a modified-risk claim for a product that is already on the market.” IOM also suggested that “significant emphasis . . . be placed on extensive consumer and non-consumer testing” of the proposed packaging, advertising, and marketing materials in order to ensure the protection of the public health.

Swedish Match has marshalled all the available scientific evidence on Swedish snus in a manner consistent with IOM’s recommendations. Based on the extensive epidemiology and toxicology data presented in this Application, Swedish Match proposes to remove the warnings that these products can cause mouth cancer and gum disease and tooth loss from the labeling for its Snus Products. Swedish Match further proposes to modify the third warning to state that, “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” Finally, Swedish Match proposes to also include an addiction warning. The Company believes that the proposed changes are an important first step in the development of more appropriate, product-specific messages about Swedish snus which are rooted in sound science and tethered to the public health aims of the Tobacco Control Act.

#### **2.5.2.3.1. Epidemiological Cohort Studies and Published Articles**

IOM addressed extensively the evidence and studies needed to evaluate the effect of MRTPs on public health. 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 enhanced by experimental designs, in particular, randomized controlled trials.

IOM’s findings are reflected in the scientific evidence presented in this MRTP Application, which is derived largely from observational epidemiologic studies and enhanced by clinical trials. Swedish Match believes that there are three aspects of the Swedish Experience which are relevant to this Application, namely (i) the epidemiological studies and published articles that form the basis of the experience, including information on the governance of those trials, (ii) the use of the scientific evidence by public health agencies and scientific institutions globally, and

(iii) the applicability of the evidence to the United States market and the requirements for MRTPs more generally.

The scientific claims of the Swedish Experience are set forth in hundreds of published research articles, most of which derive from approximately 10-15 key epidemiological studies of Swedish and Scandinavian cohorts.<sup>15</sup> Like all cohort studies, these studies have their strengths and weaknesses, including varying cohort size, participation rates, and regional characteristics. Nevertheless, these studies are considered to be the most useful and authoritative sources of information globally for the study of Swedish snus, and researchers from academia, government, and industry have relied upon the data to conduct seminal research on this product type.

One of the most significant cohorts applicable to Swedish snus research 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 and 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 Karolinska Institutet ("KI").<sup>16</sup> 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 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 high percentage of participants receiving a follow-up examination. A limitation of the study, and in 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, 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,

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<sup>15</sup> Appendix V of the ENVIRON Snus Monograph (2013) provides an annotated listing of the studies that are the foundation for the Swedish Experience.

<sup>16</sup> Founded in 1810, KI is one of Europe's largest and most prestigious medical universities. It is Sweden's premier medical research institution, accounting for over 40% of the medical academic research conducted in Sweden and offering the country's broadest range of education in medicine and health sciences. See <http://ki.se/en/about/startpage>.

diabetes, high blood pressure, and high cholesterol).

A key element of the evidence of the Swedish Experience that addresses tobacco use behaviors in youths is the Children's Smoking and Environment in Stockholm County, or BROMS cohort. 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 snuff (i.e., Swedish snus) use, including: whether they had ever tried oral snuff, 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.

Numerous scientific articles have been published based on the aforementioned and other Scandinavian cohorts. For example, for several years, researchers in the Department of Medical Epidemiology and Biostatistics at 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 based on the aforementioned Swedish Construction Worker cohort 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. Furthermore, the fact that these studies were funded by either governmental or non-profit organizations, and not by industry, likewise contributes to their relevance and application. All of the foregoing factors make the studies underlying the Swedish Experience (nearly all of which studied Swedish snus products manufactured by Swedish Match) credible and available to be applied in the consideration of this MRTP Application and in CTP's regulatory science decision-making framework more generally.

#### **2.5.2.3.2. Institutional Reports citing the Swedish Experience**

Tobacco harm reduction is a global public policy concern. Governmental and scientific authorities from several countries, including Sweden, Norway, New Zealand, and the United

Kingdom (“UK”), have undertaken studies resulting in published reports that address the key policy issues and recommendations. These scientific analyses have been conducted by a range of entities, including public health agencies, independent scientific advisory committees funded by governmental agencies, and a medical society. The reports have different goals and are intended for different audiences, but they all feature the Swedish Experience and its contribution to the tobacco harm reduction knowledge base and governmental policy and regulatory decisions.

The following seven (7) reports of international authorities are particularly relevant to CTP’s consideration of the modified-risk claims set forth in this MRTP Application:

1. *Scientific Standards for Studies on Modified Risk Tobacco Products*, prepared by the Institute of Medicine Committee on Scientific Standards for Studies on Modified Risk Tobacco Products, 2012 ([Appendix 2A](#));
2. *Health Effects of Smokeless Tobacco Products*, prepared by the European Commission (EC) Scientific Committee on Emerging and Newly Identified Health Risks, 2008 ([Appendix 2B](#));
3. *A Tobacco-Free Society or Tobacco Harm Reduction? Which Objective is Best for the Remaining Smokers in Scandinavia?*, a report by the Norwegian Institute for Alcohol and Drug Research, 2009 ([Appendix 2C](#));
4. *Public Health Status Report: 2005*, a report of the Swedish National Board of Health and Welfare, 2006 ([Appendix 2D](#));
5. *Systematic Review of the Health Effects of Modified Smokeless Tobacco Products*, Marita Broadstock, New Zealand Health Technology Assessment, 2007 ([Appendix 2E](#));
6. *Harm Reduction in Nicotine Addiction: Helping People Who Can’t Quit*, a report by the Tobacco Advisory Group of the UK Royal College of Physicians, 2007 ([Appendix 2F](#)); and
7. *Fifty Years Since Smoking and Health: Progress, Lessons and Priorities for a Smoke-Free UK*, Royal College of Physicians, 2012 ([Appendix 2G](#)).

Two of the studies—the 2012 IOM and 2008 SCENIHR reports—were undertaken at the request of regulatory science agencies and are particularly applicable to decision-making. The reports were initially used to provide scientific input to the regulatory process; however, the reports will undoubtedly also have a long-term impact and will serve as fundamental resources in ongoing policy and regulatory discussions.

The other reports examine public health policy and risk communication issues, and the quality of the evidence relating to tobacco harm reduction. The reports differ slightly in their intent and

application, but all address the complex and controversial issue of tobacco harm reduction, including how to characterize the risks posed by using Swedish snus and whether the product can serve as a smoking cessation aid.

All of the reports have made important contributions to national and regional tobacco control policy, and collectively, they provide a foundation for advancing tobacco harm reduction policy and science. Each report has advanced the current state of the scientific knowledge regarding tobacco use and, therefore, is highly relevant to CTP's consideration of this MRTP Application.<sup>17</sup> A more detailed overview of each report follows, and each report has also been included as an appendix to this Application, in [Appendices 2A – 2G](#), respectively.

#### **2.5.2.3.2.1. Institutional Reports**

##### *Scientific Standards for Studies on Modified Risk Tobacco Products*, Institute of Medicine, 2012

At the request of the FDA, IOM formed a committee to identify the minimum standards for scientific studies that a sponsor should complete to obtain an order to market an MRTP from FDA. Due to FDA's familiarity with the content and recommendations of the IOM Report (2012), it is not necessary to either describe the report or assess how it has contributed to the development of tobacco policy and regulation. However, it is important to underscore IOM's statements about the importance of observational epidemiologic studies in the evaluation of MRTPs. IOM stated that "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 also indicated that such studies should be enhanced by experimental designs, and in particular randomized controlled trials.

##### *Scientific Opinion*, Scientific Committee on Emerging and Newly Identified Health Risks ("SCENIHR"), 2008

In 2004, the EU's Directorate-General for Health and Consumers ("DG SANCO") requested that SCENIHR provide a "scientific opinion" on the health effects of smokeless tobacco products. The request cited the history and justification for the EU's ban on oral tobacco products, and addressed the validity of "claims that the use of smokeless tobacco could reduce harm related to other tobacco products." In response to the request, a SCENIHR working group was formed to evaluate the health effects of smokeless tobacco products ("STPs") with particular attention to

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<sup>17</sup> All of the reports address the health risks of MRTPs and, thus, are highly relevant to CTP's consideration of this Application. In particular, note that three of the reports were written by scientific committees—two of which were charged with addressing particular questions (i.e., IOM and SCENIHR), and a third which had more flexibility to determine the scope and focus of its report (i.e., the Royal College of Physicians' Tobacco Advisory Group).

tobacco for oral use, most notably Swedish snus.

The SCENIHR working group was charged with answering the following five questions regarding the health effects of STP:

1. What are the adverse health effects of smokeless tobacco products?
2. What is the addiction potential of smokeless tobacco products?
3. Do the available data support the claim that smokeless tobacco may constitute a smoking cessation aid comparable to pharmaceutical nicotine replacement products?
4. What is the impact of smokeless tobacco use on subsequent initiation of smoking?
5. Is it possible to extrapolate the information on the patterns of smokeless tobacco use, smoking cessation and initiation from countries where oral tobacco is available to EU countries where oral tobacco is not available?

Following a lengthy assessment and evaluation process, SCENIHR issued a final report and “opinion” on February 6, 2008 (SCENIHR 2008). The report includes an examination of groups of diseases for which cigarette smoking has an effect, and compared the health effects from smoking and from use of snus. A principal conclusion presented in the report is the following:

Overall therefore, in relation to the risks of the above major smoking-related diseases, and with the exception of pregnancy, STPs are *clearly less hazardous*, and in relation to respiratory and cardiovascular disease *substantially less hazardous*, than cigarette smoking. The magnitude of the overall reduction in hazard is difficult to estimate, but as outlined above, for cardiovascular disease at least 50%, for oral and GI cancer and probably also at least 50%, and for respiratory disease close to 100%. (emphasis added)

A number of findings in the report support the characterization of Swedish snus as a potential harm reduction product, including the following:

1. Swedish snus has dramatically fewer adverse health effects than cigarettes. (pp. 113-114)
2. A smoker who switches to snus substantially reduces his or her risk for tobacco-related disease. (pp. 115-117)
3. The availability of snus as a substitute for cigarettes has had positive effects on Swedish public health. (pp. 116-117)

4. Swedish data contradict the hypothesis that snus is a gateway to smoking. (pp. 108, 116, 121)

There is general agreement among stakeholders that the SCENIHR report on smokeless tobacco products provides a useful addition to the scientific knowledge. However, the report has not yet resulted in a change in European Union tobacco harm reduction policy, including lifting of the ban on certain forms of oral tobacco.

*A Tobacco-Free Society or Tobacco Harm Reduction? Which Objective Is Best for the Remaining Smokers in Scandinavia?* Norwegian Institute for Alcohol and Drug Research, 2009

This report was written by Dr. Karl Erik Lund, Norwegian Institute for Alcohol and Drug Research (“SIRUS”) research director and author of several articles related to tobacco harm reduction. The report posits that tobacco harm reduction “should be an additional element in a future disease preventive strategy.” The report provides an overview of current tobacco and harm reduction policies in Norway and other countries, and notes that “[d]espite the fact that measures to prevent smoking have been effective, and the proportion of smokers is decreasing in Scandinavia, the need for harm reduction measures has become greater.” (Lund 2009).

Chapter five of the report examines whether Swedish snus should be considered to be a harm reduction product. More than simply acknowledging that “[r]eviews of the scientific literature show that snus is substantially less hazardous than cigarettes,” the report reaches even bolder scientific conclusions, including that “. . . the pattern of use of snus in Sweden and Norway suggests that availability of snus must have a positive net effect on public health” and that “[t]here is little empirical data from Scandinavia to support the hypothesis that snus increases the risk of starting to smoke.”

The report also includes a chapter addressing the reasons why harm reduction policy should be made “legitimate by the authorities.” Recommendations include “informing people about snus . . . as an alternative to cigarettes in specific population groups” and suggest that “authorities could aim their message to the groups of smokers who cannot manage to quit smoking by any other means.”

The report has generated considerable attention and discussion in Norway, both in the media and in the scientific community. Most significantly, it contributed to a “new attitude to use of snus as a harm-reducing product” by the Norwegian Directorate of Health. Indeed, the report itself includes a Prologue which quotes public health official Knut-Inge Klepp as to when medical professionals should recommend snus to “inveterate smokers.” The Prologue section also contains the following statement from the Norwegian Directorate of Health website:

We know that a large proportion of people who smoke have contact with a dentist or general practitioner, says Klepp. It is important that health care personnel take up the topic of smoking, recommend quitting, and help people who wish to quit. In the first instance they should try established methods such as nicotine chewing gum,

nicotine patches or medicinal nicotine products available on prescription. If patients have tried these methods without being successful, the Norwegian Directorate of Health means that health care personnel in individual cases can consider that the patient should try snus instead.

Public Health Status Report: 2005, Swedish National Board of Health and Welfare, (“SNBH”)

In 2003, the Swedish Parliament adopted a new public health policy that charges the Swedish National Board of Health and Welfare with preparing a public health policy report every five years. The first report was issued in 2006 and focuses on health determinants, or “the factors in the organization of society and people’s living conditions and lifestyles that contribute to health or ill-health.” The 2006 report presents a large number of determinants and clarifies their relationship to health.

The report ([Swedish National Board of Health and Welfare 2006](#)) contains a section titled *Continued Decline for Smoking as Snus Consumption Increases*. The report presents detailed information regarding use patterns, and notes, for example, that snus is used by slightly more than 23% of men and less than 3% of women in Sweden. Furthermore, the percentage of the population aged 16-84 years among whom snus is used on a daily basis rose from 10.3 to 13.0% between 1996/97 and 2004. The report also presents detailed socioeconomic data. For example, snus use is far more common for people born in Sweden, men ages 25-44 years, unskilled workers, and single men with children.

The report also addresses health implications and the ongoing debate about whether snus is a smoking cessation aid or instead a gateway to smoking. It notes that there is general consensus that the health hazards of snus are minor compared with those of smoking. The report also cites contemporary studies showing that snus does not increase the risk of myocardial infarction morbidity. Conversely, the report also cites the scientific literature from the Karolinska Institute indicating that snus may increase the risk of pancreatic cancer and may cause injury to unborn and newborn babies. The report states that the scientific source material for the latter conclusions is not always strong, but the assumption should always remain that snus is not harmless.

The tobacco section of the report also addresses the role of snus in smoking cessation. It poses, but leaves unanswered, the question of whether public health officials should suggest to smokers they switch to snus. The report cites data from the Sweden’s Living Condition Surveys which indicate that, for every person who progressed from snus to smoking, there were four who switched from smoking to snus. It concludes that, apparently, many people have used snus as a means to give up smoking, and that the risk that young adults will progress from snus to smoking is far smaller than the risk that a non-smoker will take up smoking.

Importantly, the report’s tobacco section is part of a broader state of public health report intended for a mass audience. Thus, it provides a risk communication service and addresses a critical health issue—tobacco harm reduction—in a manner which is seldom (if ever) presented to the general public.

*Systematic Review of the Health Effects of Modified Smokeless Tobacco Products, Marita Broadstock, New Zealand Health Technology Assessment (“NZHTA”), 2007*

The NZHTA report focuses on the quality of the international evidence for the health effects of using modified smokeless tobacco products. The report sets forth several conclusions regarding the strengths and limitations of the evidence, including the range of products evaluated, range of health outcomes considered, exposure measurement, confounders and risk modifiers, statistical power and study designs.

The report is primarily snus-oriented. A systematic review of the literature determined that 18 papers were eligible for inclusion in the review, including 16 primary studies which were conducted in Sweden. The report’s Background chapter includes a section titled “Snus as Potential Reduced-Exposure Products” which presents a thorough description of the Swedish experience and addresses the transferability of the experience to New Zealand and elsewhere.

In a section assessing the limitations of current research, the report identifies industry funding as a potential liability. Although funding source is a potential concern that should be considered when examining the evidence, the report notes that research findings and interpretations found in industry-funded studies typically are similar to those in non-industry-funded studies. Furthermore, the report condemns the polarizing positions and statements that often characterize the debate in this arena, as “[n]either stance is an accurate or helpful representation of the complexities of this debate.” (Broadstock 2007).

A principal conclusion stated in the report is that the evidence indicates that “. . . snus use, compared with smoking, has much lower health risks associated with a range of head, neck and gastro-intestinal cancers. Indeed, compared with non tobacco use, snus did not lead to an increased risk for those cancers, although larger studies are required to increase the precision of these risk estimates.”

*Harm Reduction on Nicotine Addiction: Helping People Who Can’t Quit, Tobacco Advisory Group of the Royal College of Physicians (the “Royal College”), 2007*

The Royal College has a long history of addressing tobacco and public health concerns in the UK, including issues related to tobacco harm reduction. Several of the recommendations made by the Royal College have become established international practice. However, the recommendations did not address the problem of the smoker who cannot quit. Thus, in 2007, the Royal College embarked on a project which resulted in the report *Harm Reduction on Nicotine Addiction: Helping People Who Can’t Quit* and makes the “case for harm reduction strategies to protect smokers.”

The report was prepared by the Royal College’s Tobacco Advisory Group, chaired by Dr. John Britton. In the report preface Dr. Britton states, “We demonstrate that smokers smoke predominantly for nicotine, that nicotine itself is not especially hazardous, and that if nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives would be saved.” (RCP 2007). The report is intended to contribute to the national and

global policy debate, and in the preface Dr. Britton laments that “the regulatory systems that currently govern nicotine products in most countries, including the UK, actively discourage the development, marketing and promotion of significantly safer nicotine products to smokers.”

The report provides a comprehensive presentation of the key issues relating to tobacco and nicotine addiction and includes a long list of references, thereby serving as a significant contribution to the scientific literature. However, what sets the report apart from others is the inclusion of clearly stated tobacco control conclusions and recommendations. Many of the conclusions and recommendations are specific to Swedish snus, including the following:

1. “On toxicological and epidemiological grounds, some of the Swedish smokeless (snus) products appear to be associated with the lowest potential for harm to health.”
2. “Some of the smokeless tobacco products also increase the risk of oral cancer, but, if true of Swedish smokeless tobacco, the magnitude of this effect is small.”
3. In Sweden, the available low-harm smokeless products have been shown to be an acceptable substitute for cigarettes to many smokers, while ‘gateway’ progression from smokeless to smoking is relatively uncommon.”

The final recommendation concerns the establishment of a “nicotine regulatory authority to take control of all aspects of regulation of all nicotine products.” Such an approach is consistent with the Royal College’s conclusions that the “regulation of nicotine products, whether medicinal or tobacco-based, thus needs radical reform to ensure that the market forces of affordability, promotion and availability act in a strong and directly inverse relation to the hazard of the nicotine product, and that the marketing and use of nicotine products are carefully monitored to maximize public health benefit.”

*Fifty Years Since Smoking and Health: Progress, Lessons and Priorities for a Smoke-Free UK*, Royal College of Physicians, 2012

In March 2012 the Royal College issued a report titled *Fifty years since Smoking and health: Progress, lessons and priorities for a smoke-free UK*. The report consists of papers from a conference that marked the 50<sup>th</sup> anniversary of its seminal 1962 report *Smoking and health*.

One of the articles—*Reducing harm from nicotine use* by Dr. Ann McNeill—focuses on harm reduction and calls for a “radical change in policy from government and regulators, that will encourage innovation in alternative nicotine products . . . .” The article cites the Swedish experience with snus as “proof” of the concept of tobacco harm reduction. Dr. McNeill cites key statistics from the Swedish experience and concludes that snus “has been proven a viable harm-reduction product because it delivers high doses of nicotine and is as freely available as cigarettes, but also less expensive, as well as being generally socially acceptable. Snus is not a safe product, but its health risks are minimal compared with those of regular smoking.” (RCP 2012).

The article concludes with a series of policy recommendations, many of which relate directly to the provisions governing MRTPs under the Tobacco Control Act and to the Swedish Match quality standard GOTHIA TEK®. For example, Dr. McNeill suggests that harm reduction products should be regulated “to guarantee purity and acceptable safety standards”—which are primary goals of GOTHIA TEK®. Dr. McNeill also calls for more improved risk communication and recommends a program to “inform health professionals and the public about this new strategy; and monitor performance and effectiveness when in place”—an approach which is consistent with the premarket review and postmarket surveillance requirements of the Tobacco Control Act.

#### **2.5.2.3.2.2. Types of Institutions**

Several different types of institutions have played key roles in the ongoing initiatives relating to tobacco harm reduction. Two institutions—IOM and SCENIHR—are scientific organizations that established independent technical committees to examine a specific tobacco regulatory issue for a given timeframe. Two other institutions—SNBH and SIRUS—are national public health agencies, whose responsibilities include understanding the lifestyles and habits of the population they serve and effectively characterizing and communicating the associated risks. The third type of institution (namely, the Royal College) is a medical society, whose mission includes taking part in national debates on medical, clinical and public health issues.

##### Independent Scientific Advisory Committees

Independent scientific advisory bodies (such as the IOM and SCENIHR) have become increasingly instrumental in the United States and European Commission (“EC” or the “Commission”) regulatory science process. These bodies are often essential when a governmental agency must make difficult and complex decisions relating to a controversial subject or product. As CTP is familiar with the IOM committees formed to address tobacco harm reduction-related issues, we therefore focus here on the EC’s SCENIHR process.

In 2004, the Commission established three independent, non-food Scientific Committees, namely (i) the Scientific Committee on Consumer Products (SCCP), (ii) the Scientific Committee on Health and Environmental Risks (SCHER), and (iii) the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). The mission of the committees is to provide the Commission, and through the Commission, other European institutions, with scientific advice in the fields of consumer safety, public health and the environment. The committees are managed by DG SANCO and follow comprehensive rules of procedure. The rules are intended to ensure the committees “perform their tasks in compliance with the principles of excellence, independence, transparency and confidentiality as well as with the principles and standards for scientific advice on risk assessment.”<sup>18</sup> The principle of excellence refers to the performance and

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<sup>18</sup> Scientific Comms. on Consumer Safety, Health & Env’tl. Risks, and Emerging & Newly Identified Health Risks, European Comm’n, Rules of Procedure 5 (Apr. 2013), available at [http://ec.europa.eu/health/scientific\\_committees/docs/rules\\_procedure\\_2013\\_en.pdf](http://ec.europa.eu/health/scientific_committees/docs/rules_procedure_2013_en.pdf).

outcome of the entire process. The principle of independence refers to the organization and results of the process, including in particular the independence criteria and the conditions for the participation of members, advisors and experts.

The EC committees provide advice, but they do not determine policy. According to DG SANCO, “[t]he opinions of the Scientific Committee present the views of the independent scientists who are members of the committees” and “do not necessarily reflect the views of the European Commission.”<sup>19</sup> The term “opinion” refers to the findings and analysis of the committee, not the opinion of an individual member of the committee.

### National Public Health Agencies

Public health agencies, including those in Sweden, Norway, and New Zealand, must understand the lifestyles and habits of the population they serve and effectively characterize and communicate their associated risks. With respect to tobacco, the fundamental message communicated by most public health agencies can be summarized as follows: tobacco products are extremely harmful, consumers should not use the products, and if they do, they should seek help to stop using the products. Although these are appropriate messages for any public health agency to communicate, a truly comprehensive harm reduction strategy requires that an agency communicate a more nuanced message than simply “don’t use tobacco products.”

The Public Health Agencies of Sweden (SNBH and the National Public Health Authority, formerly, the Swedish National Institute of Public Health (“SNIPH”)) and the Norwegian Directorate of Health have confronted the issue of tobacco harm reduction, including how best to characterize the risks posed by using Swedish snus and whether the product should be characterized as a smoking cessation aid. The agencies were compelled to do so, in part, because snus is a widely used in both countries. Further, the public health agencies were obligated to fully consider the increasing body of evidence regarding the health risks of snus. The fact that much of the evidence related to Swedish snus use is based on cohort studies in Sweden and Norway motivated those agencies to fully address if and how the evidence should impact national public health initiatives.

#### *Public Health Agencies of Sweden*

SNBH and SNIPH are state agencies under the Swedish Ministry of Health and Social Affairs. Both agencies work to promote health and prevent ill health and injury, especially for population groups most vulnerable to health risks. A principal task of SNIPH is to monitor and coordinate the implementation of the national public health policy. SNIPH also serves as the national expert agency for the development and dissemination of methods and strategies based on scientific evidence in the field of public health.

In Sweden, SNIPH works closely with other governmental units, academia, and non-governmental organization (NGOs) in determining tobacco usage patterns, and assessing and

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<sup>19</sup> *Id.*

communicating the associated health risks. A key fellow national agency is Statistics Sweden, whose main task is to supply customers with statistics for decision- making, debate and research. Statistics Sweden oversees the Living Conditions Surveys which have been instrumental in determining tobacco usage patterns.

SNBH produces the *Public Health Policy Report* every 5 years. The reports present an evaluation of disease outcomes and offers recommendations for priorities that can improve attainment of the overarching goal of the national public health policy.

*Norwegian Institute for Alcohol and Drug Research (“SIRUS”)*

SIRUS is an independent administrative government body under the Ministry of Health and Care Services.<sup>20</sup> SIRUS conducts social scientific research, compiles documentation, and provides information on substance use and abuse. SIRUS’s work is divided into three areas, each of which is staffed by a dedicated research team. These areas include 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 Lund. Much of Lund’s research has focused on the association between use of snus and quit rates for smoking.

*The New Zealand Health Technology Assessment (“NZHTA”)*

NZHTA was a research unit of the University of Otago that provided analytical services to the New Zealand Ministry of Health. NZHTA is no longer active, but its publications are still relevant and accessible.

*The New Zealand Ministry of Health*

The New Zealand Ministry of Health has traditionally been the key agency for policy development in the tobacco control area and is involved in a large number of policy, service development and operational aspects of tobacco control. The Ministry is currently working on a number of initiatives in its continual efforts to fight the tobacco epidemic. These include the introduction of pictorial warnings on tobacco packages, increased access to NRT, and a review of tobacco displays in New Zealand. In 2006 the Ministry requested NZHTA to undertake a systematic review of the international evidence for health effects of using modified smokeless tobacco in order to inform the Ministry’s policy considerations “regarding harm minimization.”

Medical Societies

Medical societies exist in many countries to support and represent physicians and to further public health goals. In the UK, the Royal College has been in existence for nearly 500 years, supporting physicians during every stage of their careers and seeking to improve the quality of

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<sup>20</sup> Although part of the Ministry, SIRUS is an independent research institution with a scientific council. Other agencies within the Ministry include the Norwegian Directorate of Health.

patient care. The Royal College sets and monitors standards of medical training, establishes evidence-based clinical guidelines, and offers education programs that provide physicians with the knowledge and skills they need for high performance. It is also involved in public health more generally, including campaigning for change, advising government and Parliament, and taking part in national debates on medical, clinical and public health issues.

The Royal College has been a leader in addressing tobacco harm reduction, and its committees prepare reports on tobacco use and other pressing public health issues. These reports have significant impact in the UK and globally, and are comparable in stature to reports issued by the US Surgeon General. The Royal College first addressed tobacco policy in its 1962 report *Smoking and Health* and has remained at the forefront tobacco policy ever since. This seminal report and several of the Royal College's recommended policies have become established international practice.

The Royal College issued the report *Harm reduction in nicotine addiction: Helping people who can't quit* in 2007. In March 2012, it issued a report consisting of papers from a conference that marked the 50th anniversary of the 1962 report. One of the articles, *Reducing harm from nicotine use* by Dr. Ann McNeill, focused on harm reduction and—citing the Swedish Experience with snus—called for a “radical change in policy from government and regulators, that will encourage innovation in alternative nicotine products.”

### **2.5.2.3.3. Transferability of the Swedish and Norwegian Experience to the United States**

#### **2.5.2.3.3.1. Overview**

The previous subsections describe the Swedish epidemiological evidence and how it has been considered by institutional authorities in Sweden, Norway, the UK, New Zealand and the EU. In examining the evidence, researchers from these countries have typically concluded that the use of snus rather than cigarettes significantly reduces individual risk; and the Norway SIRUS articles imply a population benefit. However, researchers have expressed uncertainty regarding the transferability of the Swedish Experience. ([Gartner et al. 2007a](#)).

Comparisons between the effects of snus and cigarettes in the Swedish studies have concerned the type of cigarettes and smoking patterns that have been prevalent in Sweden over the years. Thus, it could theoretically be argued that, since the cigarette brands and smoking patterns that are prevalent in the United States may be different from those in Sweden, the Swedish studies may not be relevant for the US market. However, this is not the case. [Appendix VI](#) to Chapter 5 of the ENVIRON Snus Monograph (2013), compares health outcomes among Swedish smokers to results from several large US cohorts. Notwithstanding the methodological issues associated with comparing different types of studies (which is a point extensively discussed in the review), the results nonetheless illustrate a considerable concordance between the US and Swedish studies in terms of health outcomes (i.e., lung cancer and various other forms of cancer, cardiovascular diseases (“CVD”), stroke, diabetes, and all-cause mortality among smokers). These observations

support the applicability of the Swedish epidemiological data to the US context, and further substantiate Swedish Match's claim that Swedish snus, as manufactured by Swedish Match, is substantially less hazardous than cigarettes.

Notwithstanding the above, assessing the likelihood of the transferability of the Swedish and Norwegian experiences with snus to the United States also 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. In other words, the shift from cigarettes to snus throughout Scandinavia was not the product of a nationally coordinated initiative 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 advertising in Sweden in the 1970s, for the past few decades there has been no advertising in either country. Thus, Norwegian researcher 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 grassroots movement 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, however, snus sales have continued to increase while cigarette sales have significantly declined. During this same time period, smokers increasingly acknowledged the negative health effects of smoking and began considering alternatives. Most smokers were not aware of the 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 (i.e., Norway is not a member of the EU which bans the sale of snus except in Sweden). The transition from cigarettes to snus 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).

#### **2.5.2.3.3.2. Comparing the Swedish and Norway 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 (e.g., 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. 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.

The significance of a word-of-mouth movement cannot be underestimated because governmental authorities are not currently 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.

#### **2.5.2.3.3.3. Contrasting the Swedish and Norwegian Experiences with Snus**

The Swedish and Norwegian experiences with snus have many key 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.

Notwithstanding these similarities, one fundamental difference between the two countries’ experiences concerns when, and over what period of time, the respective 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, which does not allow for epidemiological findings, but nonetheless has focused research attention on the smoking cessation potential of Swedish snus. This public health policy focus in Norway is due to acceptance of the Swedish evidence, the timing of the Norwegian research, and the role of the SIRUS. SIRUS was instructed to evaluate public measures that were initiated in Norway during the period from 2003-2008 to prevent the use of tobacco (Aaro et al. 2009). This coincided with the momentum that the concepts of tobacco harm reduction and continuum of risk (which also happen to be integral elements of the Tobacco Control Act in the United States) were gaining globally. 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.

The report’s principal author and SIRUS director, Dr. Karl Erik Lund, has written follow-up articles (funded by the Norwegian Directorate of Health and by the Norwegian Research Council) that further address the public health benefit of the switch to snus and whether the

Norwegian experience is transferable to other countries. In a 2011 article, Lund and co-authors (Lund et al. 2011) include a section on *The Consequences for Public Health* and state: “The 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 also note that identifying the net effect of snus use from a public health perspective is a “complicated task” but 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).

#### **2.5.2.3.3.4. Summary and Future Prospects for Snus in the United States**

There will always be differences among the experiences with snus in Sweden, Norway, and 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. However, current government-funded research focuses on the use of snus as a 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 Swedish and Norwegian product. This product history greatly contributed to the grassroots movement which not only led to an exponential increase in smokers switching to snus, but also 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 a leading 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. If FDA were to issue MRTP orders for the Snus Products, public awareness and knowledge of this particular type of cigarette alternative is likely to increase substantially,

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. This means that the growth in US market volume for the Snus Products will depend to a large extent on word-of-mouth sales and smokers' response to external influences. Word-of-mouth sales have already contributed to the steady increase in snus sales in the United States, which are expected to continue to rise among current smokers if the Snus Products are permitted to be marketed as MRTPs.

Another factor contributing to the growing awareness of alternatives to smoking in the United States is the increasing amount of tobacco research and resulting scientific articles on the subject. Of particular note are (i) the ongoing FDA/NIH sponsored Population Assessment of Tobacco and Health study ("the PATH Study") that includes, among other things, a thorough and comprehensive examination of knowledge, attitudes, and beliefs toward snus and other smokeless products and (ii) FDA and NIH's joint establishment of fourteen (14) Tobacco Centers of Regulatory Science (TCORS) for tobacco-related research, designed to generate research on reducing toxicity and carcinogenicity, adverse health consequences, marketing and tobacco product risk messaging, and other topics that will inform the regulation of tobacco products. These areas of groundbreaking research will undoubtedly receive considerable media attention, thereby increasing public understanding of the concepts of tobacco harm reduction and continuum of risk for various tobacco products, including Swedish snus.

In short, 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 typically competes for market share with cigarettes and contributes to a growing recognition among smokers of the beneficial harm reduction potential of snus at both the individual and population levels. For that reason, Swedish Match believes that the Swedish and Norwegian Experiences remain highly relevant to CTP's consideration of this Application and the potential public health benefit of the Snus Products discussed herein.

#### **2.5.2.3.4. Swedish Match Clinical Trials and Clinical Studies**

Observational data from Sweden illustrate that, during the past three to four decades, many smokers have switched from cigarettes to Swedish snus. The data also show that, among snus users with a previous history of smoking, daily dual use of both cigarettes and snus is infrequent. These observations confirm that many Swedish smokers have quit smoking cigarettes completely by switching to snus. This transition from cigarettes to snus (which started in the late 1960s-early 1970s and is a fundamental part of the Swedish Experience) has contributed to the internationally record low rates of smoking among Swedish males and their comparatively low rate of smoking-related disease.

Due to methodological issues in cross-sectional survey data on smoking behavior it has been

suggested that—despite the compelling population data noted above—the absence of experimental evidence from randomized clinical trials makes it difficult to draw reliable conclusions as to the effectiveness of snus as an aid to clinical smoking cessation. To address this concern, Swedish Match has since sponsored a number of clinical trials to investigate this and other issues.

#### **2.5.2.3.4.1. 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 clinical smoking cessation to support the compelling population data from the Swedish Experience (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).

In the absence of any previous controlled trials of snus, Swedish Match believed it was reasonable to use a placebo-comparator because this design would generate direct information about the efficacy of snus. Moreover, because a double-blind, placebo-controlled approach is considered to be the gold standard for evaluating clinical interventions, and indeed is typically the first step to establish efficacy, Swedish Match likewise adopted this approach in the conduct of its studies. This design necessarily precluded the inclusion of a second, orally administered comparator (e.g., nicotine gum or lozenges), as use of snus products would interfere with a subject's ability to use gum or other oral products, and vice versa. Theoretically, it might have been possible to include a nicotine patch as an additional comparator, although a placebo-controlled, double-blind study design including snus, placebo snus, nicotine patch, and a placebo patch would have implied significant challenges in terms of study product logistics and may have decreased participant compliance with their allocated treatment.

None of the participating sites in Serbia or the United States had previous experience with smoking cessation interventions. Moreover, with the exception of one site in Serbia, none of the sites had previously been involved in clinical interventions that included use of Swedish snus. Study participants were recruited by word-of-mouth and by advertisements in various local media, not by referrals from other centers. In the United States, potential participants were also identified in a database of healthy volunteers interested in participating in phase 1-4 clinical trials, typically of pharmaceutical products.

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. It would then be possible to assess the relative

efficacy of snus among those with a previous history of NRT exposure versus those without such a history. Information on possible cross resistance between snus and NRT (e.g., “Does snus work among smokers who have failed on NRT?”) might be considered as clinically more relevant than a direct comparison of efficacy with an NRT (e.g., “Is snus more or less efficacious than NRT?”). In the Serbian trial, on the other hand, 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.

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 the primary outcome variable during the first 6 months was smoking reduction. 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. Smokers who have made previous unsuccessful quit attempts might abstain from participating in a program if the requirement is immediate, total abstinence. Initial smoking reduction may facilitate complete cessation later on (Asfar et al. 2011). Only those participants who were found to have substantially reduced their smoking at the week 24 visit were actively followed up to 48 weeks. During weeks 24-48, the main objective was complete cessation. Study products were distributed throughout the study period with no prescribed tapering after a specified time point. The aims of the trial thus focused on smoking cessation but did not include treating the participants’ nicotine dependence. The Serbian design can be described as being naturalistic because clinical experience from Scandinavia indicates that smokers who use snus as a smoking cessation aid typically do not switch abruptly from cigarettes to snus. The transition period of dual daily use can last from weeks to many months. Many successful quitters continue to use snus long term (Gilljam and Galanti 2003).

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. For example, smoking bans in public places and workplaces are uncommon in Serbia. Smokers there have little access to cessation support programs, and pharmaceutical cessation aids are more expensive than cigarettes. Consequently, 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,<sup>21</sup> 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.

A governance structure for the trials was established before the studies were initiated. In the absence of an internationally accepted governance structure for clinical studies of tobacco products or industry-sponsored trials, Swedish Match decided prior to study initiation that the governance and conduct of the two trials should be as similar as possible to the accepted procedures for controlled clinical trials of pharmaceutical products. Thus, the governance structure implemented by Swedish Match included all the following elements:

- Protocols were developed in collaboration between the individual research teams and the sponsor according to internationally accepted guidelines.
- Studies were performed in accordance with International Conference on Harmonisation (“ICH”) guidelines, Declaration of Helsinki guidelines, and all applicable national, state, and local laws.
- Written, full informed consent was obtained from all study participants.
- Conduct of the study was approved by an appropriately constituted institutional review board (“IRB”) or independent ethics committee (“IEC”).
- Trials were conducted according to full Good Clinical Practice (“ICH-GCP”)
- Management of all clinical and other study-related information, including monitoring, conducted by internationally well-reputed Contract Research Organizations (“CROs”) with extensive experience of controlled clinical trials of pharmaceutical products (*Serbian study*: i3 Research, *US study*: Covance).

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<sup>21</sup> See PRISMA guidelines, <http://www.prisma-statement.org>.

- All data handling and statistical analyses were conducted by external contractors according to pre-specified statistical analysis plans (*Serbian study*: i3 Statprobe, *US study*: Covance).
- Prospective registration of the trials was made at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).
- Sponsor committed to publishing results irrespective of trial outcomes.
- Publication in peer-reviewed scientific journals was sought according to the Consolidated Standards of Reporting Trials (“CONSORT”) guidelines.<sup>22</sup>
- Sponsor committed to making individual study data available for systematic reviews and/or meta-analyses conducted according to internationally accepted PRISMA guidelines.

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). As explained below, trial results showed that participants allocated to snus were 2-3 times more likely to quit smoking completely compared to those allocated to placebo:

1. 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).
2. 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).
3. 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.
4. 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.

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<sup>22</sup> See CONSORT guidelines, <http://www.consort-statement.org>.

5. 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.
6. 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.
7. 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 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. Importantly, the observed effects of snus were clearly not limited to a Scandinavian social setting, as the US and Serbian trials showed comparable results. (All study documents, including raw data and relevant reports, are included in [Appendix 2H](#) to this MRTP Application.)

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](#)). Current results on complete cessation are more comparable to those typically seen in smoking reduction trials including smokers with no immediate wish to stop smoking completely. It is also possible that the aforementioned negative cultural connotations of smokeless tobacco in the US contributed to the observed overall success rates. In Serbia there is no traditional use of any form of oral tobacco products, so there are no negative cultural connotations associated with such products. However, the social environment in Serbia with a high smoking prevalence, few smoking restrictions, and a generally low public awareness of the dangers of smoking, is not supportive of quit attempts among smokers who want to stop smoking. 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](#)). This may be due to self-selection of subjects and perhaps due to phasing in STP use over a much longer period. In the current trials use of study products was relatively limited, although in the Serbian study it tended to increase over time. This suggests that it may take some time before smokers become accustomed to using snus

products instead of cigarettes. In the US trial study products were not available to participants after week 16.

In sum, the evidence derived from Swedish Match's smoking cessation clinical trials is applicable to several sections of the MRTP submission as presented in the MRTP Guidance.<sup>23</sup> The clinical trials complement the Swedish Experience research, and together they provide evidence needed to address the five key areas of investigation listed under Summary of All Research Findings. In particular, the questions that the MRTP Guidance poses with respect to the health risks of the proposed MRTPs are primarily addressed by the Swedish epidemiological evidence, with supporting evidence from the clinical trials. The clinical trials also provide much of the relevant evidence for the MRTP Application's discussion of tobacco use behavior.

#### **2.5.2.3.4.2. 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. In addition, 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 putatively 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. These circumstances make it reasonable to study the nicotine pharmacokinetics and subjective effects of snus, particularly in relation to commonly used NRT products.

Swedish Match has sponsored three clinical trials (the 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. (All study documents, including raw data and relevant reports, are included in [Appendices 2I, 2J, and 2K](#), respectively, to this Application.) The governance and conduct of the trials was the same as for clinical trials of pharmaceutical products or medical devices. The trials were conducted by an external contractor with extensive experience in nicotine pharmacokinetics. 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.

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<sup>23</sup> MRTP Guidance at 35.

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).

The products covered by this MRTP Application are substantially similar to the products tested in the nicotine uptake trials. Although the tested snus products are not identical to the Snus Products included in this Application, 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. In particular:

- General Classic Blend Portion Large (SKU 4877 and SKU 4878) is substantially similar to the Catch White Licorice 1.0 g products tested in the SM WS 02 study, the General White Product tested in SM WS 06 study, and the General PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.
- General Dry Mint Portion Original Mini (SKU 4800) is substantially similar to the Catch Licorice Dry Mini product tested in the SM WS 02 study.
- General Mint Portion White Large (SKU 4352) is substantially similar to the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the General PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.
- General Nordic Mint Portion White Large (SKU 4876 and SKU 4875) is substantially similar to the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the General PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.
- General Portion Original Large (SKU 4880) is substantially similar to the General Large product tested in SM WS 02 study.
- General Portion White Large (SKU 4881) is substantially similar to the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.
- General Wintergreen Portion White Large (SKU 4882) is substantially similar to the General Large product and the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.
- 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). Therefore, it is reasonable to conclude that General Loose (SKU 4852) is substantially similar in terms of nicotine uptake to the General Large 1.0 g and Catch White Licorice 1.0 g products tested in the SM WS 02 study, the General White Product tested in SM WS 06 study, and the PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.

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 trials provide a basis for considerations related to the abuse liability of Swedish snus products. 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 is somewhat higher than with NRTs, but clearly significantly lower than for cigarettes. Such a finding comports with a clinical trial 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 STP users, and highest among smokers.

#### **2.5.2.3.5. Biomarkers**

Biomarkers, interpreted carefully and in the context of additional data from clinical and/or epidemiological studies, may be used to assess the actual internal dose of a tobacco component to which a tobacco user might be exposed. While there are certain limitations to the available biomarkers, they can be used to supplement information from product analyses as they reflect total exposure, bypassing differences in routes of exposure and product use behavior. In addition, biomarker levels on a population basis may provide an indication of general trends in internal exposure to certain components of a well characterized product.

A panel of biomarkers to components in tobacco products has been recently proposed for the use in product regulations. Although many biomarkers are less relevant for non-combusted tobacco products such as snus, the panel does include the potentially relevant biomarkers of nicotine,

tobacco-specific nitrosamines (“TSNAs”), polycyclic aromatic hydrocarbons (“PAHs”), aldehydes, cadmium, and acrylamide. To date, published studies (Andersson et al. 1994; Andersson et al. 1995; Bolinder et al. 1997b; Bolinder 1997; Bolinder et al. 1997a; Bolinder and de Faire 1998; Eliasson et al. 1991; Eliasson et al. 1995; Ellingsen et al. 2009; Heling et al. 2008; Holm et al. 1992; Richter et al. 2009b, as cited in Nilsson 2011; Österdahl and Slorach 1988; Post et al. 2005; Wennberg et al. 2006) are available that have investigated the biomarkers of nicotine, TSNAs, cadmium, and selenium in regular users of traditional Swedish snus.

Commonly measured biomarkers of nicotine include cotinine in plasma or serum. However, their levels may be impacted by the route of exposure, as first pass metabolism of nicotine to cotinine via the oral route may result in higher blood concentrations of cotinine that do not necessarily reflect increased exposure to the parent compound, nicotine. This metabolic pathway does not occur following exposure to nicotine via the inhalation route. Thus, total nicotine equivalents in urine are considered to better represent the total nicotine dose absorbed. (Benowitz et al. 2009; Benowitz 2009; Ebbert et al. 2004; Hecht et al. 2010).

Information from nicotine pharmacokinetic parameters is relevant for nicotine delivery, total dose, and abuse liability assessments. The time to maximum plasma nicotine concentrations in snus users appears to be dependent on the usage time, but to a lesser extent on nicotine content or portion size. On the other hand, maximum nicotine concentration (“ $C_{max}$ ”) and areas under the curve (“AUC”) appear mostly dependent on total nicotine content (per pouch or portion size). Whether the tested snus-like product was loose or pouched had no influence on these parameters. (Digard et al. 2012; Holm et al. 1992; Lunell and Curvall 2011; Lunell and Lunell 2005).

A number of studies in regular snus users (Andersson et al. 1994; Andersson et al. 1995; Bolinder et al. 1997b; Bolinder 1997; Bolinder et al. 1997a; Bolinder and de Faire 1998; Eliasson et al. 1991; Eliasson et al. 1995; Ellingsen et al. 2009; Holm et al. 1992; Post et al. 2005) show that mean or median cotinine levels in plasma or serum range from 137 to 399 ng/mL depending on the amount of snus consumed (average 11-32 g/day). In the saliva, average levels ranged from 80 to 343 ng/mL. Urinary biomarkers of nicotine measured in regular users of snus were as follows: for nicotine itself, 29 µg/mmol creatinine; for cotinine, approximately 1000–1210 µg/L; for total cotinine, 5926 µg/L; and for nicotine equivalents, 14.3-35.6 mg/24 hrs.

In addition, TSNAs and their metabolites have been measured in various human bodily fluids, including saliva, blood, and urine, as well as in toenails. Urinary NNAL is the most commonly-measured biomarker of TSNA exposure, and is considered to reflect 12-17% of the NNK dose. Four studies of TSNA biomarkers in users of Swedish snus have been identified. Of those, one publication (Österdahl and Slorach 1988) measured TSNA levels in saliva during snus use. Snus in the 1980s contained higher TSNA concentrations than contemporary snus products. More recently, urinary total NNAL was measured in users of conventional US STPs that were switched to Swedish snus. Of the two clinical studies available (Gray et al. 2008; Hatsukami et al. 2004), only one (Hatsukami et al. 2004) appears to have been of sufficient duration to examine for and detect differences in levels before and after the switch. In this study, total NNAL levels decreased significantly (to half the concentration measured at baseline) by week 4.

Importantly, urinary total cotinine levels in this study did not change significantly, indicating the decreased toxicant exposure could not be explained by a decrease in tobacco intake and mean product use was similar to that reported for regular snus users. No studies measuring biomarkers of NNN in snus users were identified. POB-DNA adducts were significantly increased in oral mucosa of Swedish snus based on information provided in a study abstract (Heling et al. 2008; Richter et al. 2009b, as cited in Nilsson 2011); however, the importance of these adducts in oral cancer development has been questioned.

In the available studies of biomarkers of metals/metalloids, levels of both cadmium and selenium biomarkers in regular users of traditional Swedish snus were similar to those detected in non-tobacco users, indicating that exposure to these constituents from snus use does not result in a significant contribution over background intake from other sources. (Ellingsen et al. 2009; Wennberg et al. 2006).

#### 2.5.2.3.6. Non-Clinical Toxicology Studies

Although epidemiologic evidence, supported by biomarker data, must weigh most heavily in CTP's assessment of a proposed MRTP, non-clinical studies can still play a role in justifying a modified-risk claim. Non-clinical studies with STPs (including Swedish snus) in laboratory animals were reviewed elsewhere (Grasso and Mann 1998). In these *in vivo* studies, test material was administered mixed in the diet, placed in hamster cheek pouches, or inserted into surgical lip canals in rats. No tumors were reported in any of these studies. A lifetime feeding study in rats, with STPs constituting 20% of the diet, was conducted by Homburger (Homburger et al., 1976). No cancer or other systemic effects were observed.

The studies of individual chemicals and STP extracts used include (Kim et al. 2002; Rivenson et al. 1988; Schwartz et al. 2010; Summerlin et al. 1992). In these studies, the test material was administered via hamster cheek pouches, surgical lip canals, swabbing of the oral cavity, and additions to the drinking water. No tumors resulted from treatment with STP extracts, unless the extracts used to swab the oral cavity were enriched by the addition of NNN and NNK. In these cases, small numbers (3) of oral papillomas were reported. Oral tumors were also observed in significant increases over controls with "neat" NNN and NNK, and with use of the positive control, 4-nitroquinoline oxide.

Swedish Match has sponsored *in vitro* toxicological testing of extracts of Swedish snus (Coggins et al. 2012), and all study documents are included in Appendix 2M to this Application. These tests included the *Salmonella* reverse mutation assay, mouse lymphoma assay, *in vitro* micronucleus assay, and tests of cytotoxicity. The results of these assays were broadly negative for Swedish snus. There were occasional positive responses, but these were effectively at the highest concentration only (i.e., concentrations well above those suggested by regulatory guidelines) and were often associated with significant cytotoxicity. These data contrast with data reported for combusted tobacco in the form of cigarettes where strongly positive responses have been routinely reported for mutagenicity and cytotoxicity.

Based on these studies, Swedish snus has minimal activity in state-of-the-art *in vitro* and *in vivo*

toxicology assays. Importantly, these results concur with those from repeated epidemiological studies on Swedish snus use in Sweden and elsewhere, lending further support for the harm reduction potential of the Snus Products which are the subject of this Application, compared to combusted tobacco, most notably cigarettes.

#### **2.5.2.3.7. Premarket Consumer Perception Research**

In support of this Application, Swedish Match conducted a Premarket Consumer Perception Research Study (“the Consumer Perception Study”) to assess the effect and comprehension of the company’s proposed MRTP labels<sup>24</sup> on the public in accordance with Sections 911(g)(1)(B), 911(g)(4)(B) and (C), and 911(h)(1) of the Act.

The Consumer Perception Study is 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.

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 pursuant to Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act. Two test cells (comprised of two 1,100 subject smoker and two 1,100 subject non-user arm) tested the proposed modified risk warning statements for the Snus Products which are the subject of this Application. 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.”

In preparing the research protocol and conducting the study, Swedish Match benefitted greatly from input and recommendations from both FDA and the MRTP Advisory Panel. Swedish Match participated in a series of pre-submission meetings with CTP to discuss and refine the study research concept and protocol. Each meeting provided Swedish Match with a clearer understanding as to how the research should be conducted to ensure the protection of the participants surveyed and enhance the usefulness of the data to the MRTP process. The MRTP Advisory Panel also provided comprehensive reviews of the study protocol, were kept apprised of the discussions with CTP, and reviewed the final version of the protocol.

Pursuant to discussions with CTP, Swedish Match sought the involvement of an IRB to ensure

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<sup>24</sup> Swedish Match proposes only to modify the mandatory warnings featured on the *labels* pursuant to the MRTP order granted; it does not intend to change the *advertising* for the Snus Products.

the protection of human subjects in the study. Accordingly, Swedish Match contracted with (b) (4) a leading provider of independent IRB services for major pharmaceutical companies, universities, individual researchers, academic medical centers, and community hospitals since 1993. (b) (4)

(b) (4) was instrumental in reviewing various aspects of the study protocol and helping ensure that the study was conducted in a manner which provided proper protections for the rights and welfare of the research subjects who participated.

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 which are the subject of this Application, and further supplement the extensive preclinical, toxicology and epidemiology data related to the effects and use of Swedish snus as compared to traditional cigarettes. Study results are discussed extensively in [Section 6.4](#) of this Application and are summarized below:

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Tobacco Use Behavior Among Current Tobacco Users:* The 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 motivate 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.
- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Tobacco Use Initiation Behavior Among 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 proposed 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.
- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Consumer Understanding and Perceptions of the Product:* 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 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 successful in educating consumers about the actual and comparative risks of snus and cigarettes. The results are more consistent with the message conveyed regarding the actual risk as reflected in the clinical and epidemiology studies described in this Application.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Certain Demographic Groups-Minorities:* The results for minority users and non-users of tobacco are similar to those for the total user and non-user populations and do not appear to raise unique issues or concerns for the minority populations. Most of the minority users and non-users found the modified risk claims to be understandable and clear. As with the total population and smokers and non-smokers generally, these results were significantly lower than what was reported for the current claims. Following exposure to the claims the risk perception patterns for minority respondents followed a pattern similar to that reported for total respondents, users and non-users. Again, those exposed to the modified risk claims more likely to report that snus posed a moderate risk and less likely to report that it posed an extremely harmful risk than those exposed to the current claims. The results further suggest that that modified risk claims are unlikely to motivate minority non-users to use or buy snus.
- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Certain Demographic Groups-Low Income:* The perception of clarity, understanding and credibility reported by low income users and non-users of tobacco are similar to what was reported by the total user and non-user populations. Following exposure to the claims the risk perception patterns for low income respondents followed a pattern similar to, but less dramatic than, that reported for total respondents, users and non-users, with those exposed to the modified risk claims more likely to regard snus as a moderate risk and somewhat less harmful than cigarettes. The modified risk claims were also unlikely to cause or motivate low income non-users of tobacco to use or buy snus or initiate cigarette use. Overall, the study does not appear to raise unique issues or concerns for the low income population.
- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Certain Demographic Groups-Youth:* The Consumer Perception 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.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on the Population as a Whole:* The Consumer Perception Study assessed the effects of the modified risk warnings on the total population, including 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 aforementioned subpopulations.

The overall results of the Consumer Perception Study 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 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 proposed modified warning labels changed consumers' perception of the harmfulness of snus, additional measures are needed to more substantially alter consumer risk perception in order to make it more consistent with the scientific evidence.

In sum, the Consumer Perception Study provides several key insights related to intended use of the Snus Products by current users and non-users of tobacco products, and the results of this research supplement the extensive preclinical, toxicology and epidemiology data presented in this Application regarding the effects and use of snus as compared to cigarettes. Survey results significantly contributed to the decision to include the term "substantially" in the proposed label change, 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 2012) and the term "substantially" is supported by the voluminous product-specific scientific evidence from Sweden.

#### **2.5.2.3.8. Dynamic Population Model ("DPM")**

Because of the difficulties inherent in making premarket assessments of the effect of an MRTP's introduction on the population as a whole and the public health, FDA encourages the development and application of innovative analytical methods which estimate the potential health effects expected to result from changes in the distribution and use of different tobacco

products in a given population.<sup>25</sup>

Accordingly, Swedish Match has supported the development and application of a DPM 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 is discussed more fully in [Section 6.5](#) of this Application.

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. The analyses specifically evaluate 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 DPM can also estimate the effects of the MRTP being more attractive than cigarettes to youth who are at risk of becoming tobacco users, the potential effects if the MRTP serves as a gateway to smoking, and/or increases the likelihood of former users (i.e., those who quit all tobacco and those who switched from cigarettes to MRTP) relapsing back to smoking cigarettes.

Analyses using the DPM 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. If introduction of Swedish snus results in more tobacco users compared to the base case, however, a survival deficit may result. However, the latter scenario appears unlikely in this case, given the results of the premarket consumer perception research on the proposed label changes included in this Application.

The size of an effect on overall morbidity, positive or negative, depends on the particular exposure patterns evaluated. For example, tipping point analyses indicate that if some who would have quit smoking in the base case switch to Swedish snus instead, a survival deficit results. This effect is counteracted, however, if a fairly small proportion, 1% or less, of those in the base case who would have continued to smoke instead switch to Swedish snus and don't revert to smoking. Tipping point analyses also indicate a survival deficit results if base case never tobacco users initiate Swedish snus, but this can be counterbalanced by base case smoking initiators initiating Swedish snus instead of cigarettes. If only 1% of base case never tobacco users initiate Swedish snus, less than 5% of base case smoking initiators must initiate Swedish snus to counteract the survival deficit. However, if 5% of base case never tobacco users initiate Swedish snus, at least 20% of base case smoking initiators instead must initiate Swedish snus to counterbalance the survival deficit. These apparently large percent changes must be interpreted in light of the sizes of the exposure groups involved. Because the never tobacco users represent a large subgroup of the whole population, a small percent change affects a large number of individuals. Likewise, there are relatively few individuals who successfully quit smoking in the

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<sup>25</sup> MRTP Guidance at 27.

base case, so a large percentage of that population subgroup must shift to a different exposure for a population-level effect on survival to be observed. In modeling gateway effects, such that base case never tobacco users initiated tobacco use with the MRTP and then switched to smoking cigarettes, there was no statistically significant survival benefit in counterfactual scenarios consisting of base case smoking initiators choosing the MRTP instead of cigarettes. However, other exposure patterns that include additional exposure groups can counterbalance this population-level harm.

This conclusion is corroborated by analyses of counterfactuals based on the Swedish tobacco use patterns estimated for the 1990s compared with a base case defined by US smoking initiation rates from 2008 and cessation rates from 2005-2008. In each of the counterfactual exposure scenarios investigated, in which snus was used with similar frequency and in which snus was 10%, 25% and 50% as popular in the US as in Sweden, there was a substantial and statistically significant survival benefit compared with the US base case. The magnitude of the difference in the number of survivors vs. the base case was not greatly affected by the value selected for the ERR comparing the MRTP to cigarette smoking (0.11 or 0.055), by increasing the gateway effect or by reducing the MRTP initiation rate among those who would have otherwise remained as never tobacco users and those who would have initiated tobacco use with cigarettes. When the rate of switching to the MRTP by those who would have continued to smoke and those who would have quit smoking in the base case was reduced compared to the rates estimated for the “Swedish counterfactual”, there was still a statistically significant increase in the number of survivors in the counterfactual vs. the base case, but the effect was smaller. The greater responsiveness of the results to changes that affected continuing smokers or those who would have quit smoking is a reflection of the relative sizes of the various population subgroups included in the analyses.

#### **2.5.2.3.9. Governance and Oversight**

As noted above, Swedish Match has sponsored a number of studies submitted in support of this MRTP Application. Studies funded by any regulated party are subject to extra scrutiny, but the surveillance that must be applied to research funded by the tobacco industry may be unparalleled. This was one of the findings contained in the IOM Report (IOM 2012) regarding the scientific standards for studies on MRTPs. Chapter 2 of the report details the challenging history of tobacco research and proposes the establishment of an independent third party to oversee such research.

Swedish Match understands why research funded by tobacco companies is subject to greater scrutiny, and the Company conceptually supports the findings and recommendations set forth in the IOM Report. Swedish Match is therefore committed to working toward a long-term solution to tobacco research governance which is characterized by a coordinated effort among FDA, industry, researchers and other stakeholders. In the meantime, Swedish Match is determined to take action on its own, in keeping with the Company’s longstanding history of ensuring that its research is conducted in a credible manner. For example, Swedish Match’s GOTHIA TEK® product standard provides a foundation for a range of product stewardship-related commitments,

including generating and communicating scientific evidence. The GOTHIA TEK® standard was developed in concert with scientists from the Swedish Food Agency (which regulates snus), and it reflects Swedish Match’s historic and ongoing commitment to working with authorities to ensure credibility and transparency.

Swedish Match applied the principles of GOTHIA TEK® and other internationally accepted guidelines when developing the protocols and conducting the clinical trials described in this Application. The protocols were developed in collaboration with individual research teams according to accepted guidelines and the studies were performed 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<sup>26</sup> or IEC, and all trials were conducted according to ICH-GCP.

Management of all clinical and other study-related information, including monitoring, was conducted by CROs with extensive experience of controlled clinical trials of pharmaceutical products (e.g., i3 Research, Covance, and CROel AB). All data handling and statistical analyses were conducted by external contractors according to pre-specified statistical analysis plans, and there was prospective registration in public databases such as [www.clinicaltrials.gov](http://www.clinicaltrials.gov). From the outset, Swedish Match was committed to publishing the results of the clinical trials irrespective of study outcomes, and five (5) peer-reviewed articles based on these studies have been published to date.

In addition to the foregoing, perhaps the most significant action taken by Swedish Match to address concerns relating to tobacco research governance is the establishment of the MRTP Advisory Panel. 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 and operating principles:

- *Mission Statement:* To present advice on matters relating to the FDA Modified Risk

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<sup>26</sup> Swedish Match retained the services of an IRB whenever appropriate. For example, the study protocol for the premarket consumer perception study was subject to oversight by (b) (4), and it was determined that informed consent was not required because the study did not involve the use of test articles (i.e., regulated tobacco products) and, hence, did not constitute a “clinical investigation” for purposes of FDA’s Good Clinical Practice regulations.

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

- *Operating Principles:*

- 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.

In order to ensure that a wide range of perspectives was represented, it was decided the Advisory Panel would not be limited to tobacco experts only, but rather would consist of scientists and science policy experts with extensive backgrounds in toxicology, risk perception and communication, FDA regulations, and research governance. The MRTTP Advisory Panel currently consists of five members,<sup>27</sup> all of whom have had long and accomplished careers in

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<sup>27</sup> In addition to Drs. Fagerström and Hughes, the Panel includes: Dr. Nancy Ostrove, a Principal of EXPRE; Dr. Mark Frankel, the Director of Scientific Responsibility at the Human Rights and Law Program at the American Association for the Advancement of Science (AAAS); and Dr. Daniel Casciano, the Science Advisor at the Center for Integrative Nanotechnology Sciences at the University of Arkansas at Little Rock.

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 Panel's most immediate task was to provide advice regarding Swedish Match's MRTP Application; however, the Panel will continue to operate long after the Application is submitted and tobacco research governance will always remain a priority for Swedish Match.

The MRTP Advisory Panel met via an inaugural 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 and in Washington, DC, on November 13-14, 2013. CTP was notified in advance of the DC meeting and meeting minutes were provided.

Although the MRTP Advisory Panel is not the third-party research governance entity envisioned in the IOM Report, the Panel nevertheless provides important research governance-related services and is representative of the kind of progressive initiative that is needed to reach the Report's stated goals. In particular, the Panel is able to address some of the questions that CTP raised in establishing a public docket<sup>28</sup> and hosting a public workshop<sup>29</sup> on third-party governance of industry-sponsored research on MRTPs. One such question from CTP concerns the aspects of tobacco product research which may properly be subject to third-party governance. The MRTP Advisory Panel now has firsthand experience with this issue. For example, during its initial face-to-face meeting, the Panel reviewed Swedish Match's draft protocol for the premarket consumer perception research. Subsequent to the meeting, panel members provided additional comments on the protocol through a series of email exchanges. Throughout the process, 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.

Swedish Match's science, policy, and marketing staff presented the MRTP Advisory Panel's input during a May 8, 2013 meeting with CTP that was focused solely on the premarket consumer perception study protocol. CTP expressed interest in the Panel's input and suggested that the Company have the Panel conduct a final review of the protocol, which was done during

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<sup>28</sup> FDA published notice of the docket in the Federal Register (78 Fed. Reg. 19713 (Apr. 2, 2013)) and requested data, information, and comments regarding the possible role of independent third parties in industry-sponsored tobacco product research in response to the IOM's recommendations regarding third-party governance. Drs. Fagerström and Hughes submitted comments to the docket on August 14, 2013, explaining why they agreed to serve on the MRTP Advisory Panel and the Panel's relevance to governance concerns. Their submitted comments are included in Appendix 2N of the Application.

<sup>29</sup> FDA held a Public Workshop titled "Third Party Governance of Industry-Sponsored Tobacco Product Research on March 19-20, 2013. The purpose of the workshop was to discuss the recommendation in the IOM Report that sponsors of MRTP applications use independent third parties to undertake one or more key functions in tobacco product research. See <http://www.fda.gov/TobaccoProducts/NewsEvents/ucm336166.htm>.

the June 2013 meeting. Additional input was provided during and following the meeting, and the Panel also provided a final review of the protocol before the research commenced.

The MRTP Advisory Panel has reviewed and commented upon several key components of this MRTP Application, but was not asked to approve the Application. For example, prior to its November 2013 meeting, the Panel received an early draft of [Section 2.5](#) (Summary) and [Section 6](#) (Summary of All Research Findings), and was provided access to the entire Application. The Application was discussed during the two-day meeting and additional comments were received following the meeting. In February 2014, the Panel received the premarket consumer perception data and various drafts of [Section 6.4](#) (Effect of Marketing on Consumer Understanding and Perceptions). The Panel's comments on these materials were incorporated into the final text as appropriate.

#### **2.5.2.4. Concluding Discussion of How MRTPA Meets Relevant Statutory Requirements**

The Tobacco Control Act was enacted to establish a regulatory framework to address the public health and societal problems attributable to tobacco, and to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products.<sup>30</sup> 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.” (IOM 2012)

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. Accordingly, this MRTP Application provides a comprehensive analysis of all the relevant scientific evidence relating to the health effects of Swedish snus and the public health impact of the product for users and non-users at both the individual and population levels. In particular, this Application presents data from numerous observational epidemiologic studies showing that Swedish snus significantly reduces harm and the risk of tobacco-related disease to individual tobacco users—particularly with respect to mouth cancer, gum disease, tooth loss, CVD, and other health outcomes. The Application also summarizes data from a well-run clinical trial demonstrating that *ad lib* provision of Swedish snus to smokers who are interested in quitting (as the majority of smokers in the United States say they are<sup>31</sup>) will result in an increased rate of smoking cessation. Results from a Premarket Consumer Perception Study confirm that current non-users of tobacco products will not be more interested in using the Snus Products simply because of the proposed warning label changes which are the subject of this Application. Finally, dynamic population modeling of reasonable and probable scenarios associated with the of the introduction

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<sup>30</sup> Tobacco Control Act, § 3(4).

<sup>31</sup> CDC Fact Sheet, Smoking & Tobacco Use: Quitting Smoking, Feb. 2014, available at [http://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/cessation/quitting/index.htm#quitting](http://www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting/index.htm#quitting) (last accessed March 4, 2014).

of a new low-nitrosamine MRTP (such as the Snus Products) in the US market evidence a net benefit to public health in every case, including where the proportion of smokers who switched to the MRTP was assumed to be quite low. These data support the conclusion that the Snus Products 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.

This Application meets all the statutory requirements for an MRTP application as set forth in Section 911(d) of the Act. In particular, the Application contains:

- (i) a description of the proposed Snus Products (Section 3.1) and any proposed advertising and labeling (Section 4.1);
- (ii) the conditions for using the Snus Products (Section 3.3);
- (iii) the formulation of the Snus Products (Section 3.2);
- (iv) sample product labels and labeling (Section 4.2);
- (v) 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 (Section 7); and
- (vi) data and information on how consumers actually use the Snus Products (Section 3.4).

Swedish Match has organized and synthesized all the foregoing information—along with the additional information which FDA has suggested be submitted—in accordance with the recommendations found in FDA’s MRTP Guidance.

Swedish Match is confident that this submission provides FDA with conclusive evidence to show that Swedish snus as manufactured by Swedish Match—and hence, the Snus Products which are the subject of this Application—“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, the Company respectfully requests that the Agency grant the requested MRTP orders for the Snus Products pursuant to Section 911(g) of the Act.

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