OVERALL HEALTH EFFECTS OF SWEDISH MATCH SNUS PRODUCTS

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OUTLINE

• Content and format of Applications
• Literature review results
  • Applicant conclusions
  • FDA review comments
• Methodological Issues and Points for consideration
CONTENT AND FORMAT OF APPLICATIONS
• The Applicant is proposing revision of:
  “WARNING: This product is not a safe alternative to cigarettes” to
  "WARNING: No tobacco product is safe, but this product presents
  substantially lower risks to health than cigarettes.”

• In support of this proposed change, the submission included:
  o A comprehensive review of the scientific literature on the health
    effects of Swedish snus
  o A summary of the literature review for selected health effects/disease
    endpoints

• The selected disease endpoints accounted for 90% of smoking-
  related deaths in 2008.
The literature summary included Forest Plots which visually represented the relative risk (RR) of snus and cigarette smoking for each disease endpoint.

Selected disease endpoints were:

- Lung cancer
- Respiratory disease
- Chronic obstructive pulmonary disease (COPD)
- Cardiovascular disease
- Stroke
- Esophageal cancer
- Pancreatic cancer
- Oral cancer
- Stomach cancer
- All-cause mortality
LITERATURE REVIEW RESULTS
APPLICANT CONCLUSIONS:

- Swedish snus users are at no greater risk of developing lung cancer than non- or never-users of tobacco; smokers are 7 to 30 times more likely to develop lung cancer based on two studies of the large Swedish Construction Worker cohort.
- Well-controlled epidemiological evidence indicates that Swedish snus is not associated with lung cancer.

**FDA Review Comment:** The applications provide evidence that these products would not be expected to be significantly associated with risk of lung cancer. This is supported in the submitted data.
APPLICANT CONCLUSIONS:

• There is no known mechanism by which snus could cause nonmalignant respiratory disease.
• Based on mechanistic considerations, Swedish snus is widely accepted not to be associated with chronic lung disease, even in the absence of epidemiological confirmation.
• Statistically significant but inconclusive positive association between snus use and subsequent respiratory death was observed in individual studies.

FDA Review Comment: The applications provide evidence that chronic respiratory disease would not be expected to be significantly associated with use of these products.
APPLICANT CONCLUSIONS:

• It is widely accepted that COPD results from long term exposure from airborne irritants such as tobacco smoke and air pollution. Swedish snus is widely accepted not to be associated with COPD or any other acute or chronic non-malignant lung disease, even in the absence of supportive epidemiological evidence.

FDA Review Comment: The applications provide evidence that without the smoke, these products are unlikely to be a significant risk factor for COPD or other respiratory diseases.
LITERATURE REVIEW RESULTS: CARDIOVASCULAR DISEASE

APPLICANT CONCLUSIONS:

• The observed increased risk in smokers is 1.5 to 3 times that observed among nontobacco users. Overall CVD risk was not increased among snus users.

• There are known acute effects of nicotine on the cardiovascular system, but no increased risk of cardiovascular disease has been detected epidemiologically with respect to snus use, with the possible exception of a moderate increased risk of death due to a CV event.

FDA Review Comment: Increases in blood pressure and heart rate were seen in subjects using these products. There were studies which included snus users who were former or current smokers; this complicated the analysis; adjusting for confounders (e.g., diet, smoking) was an issue.
LITERATURE REVIEW RESULTS: STROKE

APPLICANT CONCLUSIONS:

• The stroke risk among Swedish snus users appears to be no different than that of non-users of tobacco. No studies found an increased risk of all stroke types among current or former snus users. Two recent reviews of stroke reported no increased risk of stroke incidence.

• The risk is consistently at least 40% greater among smokers compared to non-users of tobacco.

FDA Review Comment: One study found an increased risk of stroke in current heavy snus users and others showed elevation of blood pressure and heart rate in users of these products; this could increase risk of stroke. A complete smoking history was not always available making study interpretation challenging.
LITERATURE REVIEW RESULTS: ESOPHAGEAL CANCER

APPLICANT CONCLUSIONS

• The summary RR estimate among snus users is 1.6. Even if this is accurate, the risk among snus users is several fold lower than that for current smokers.

• Epidemiology studies suggest no association between snus use and esophageal cancer, but limitations in the available studies and inconsistent results of the meta-analyses indicate a need for additional study of this outcome.

FDA Review Comment: Data are consistent with a possible relationship between use of these products and esophageal cancer. Although the risk is less than for cigarette smokers, it is elevated over the risk for those with no history of tobacco product use.
APPLICANT CONCLUSIONS

• Evidence suggests that the risk of stomach cancer among snus users is no different than non-users of tobacco. The risk of stomach cancer among smokers is increased.

• No studies found that use of snus was associated with any significant increase in risk of overall or cardia (upper portion of the stomach) stomach cancer but one study found an elevated risk for the non-cardia subtype of stomach cancer.

FDA Review Comment: The applicant acknowledges these products are a source of nitrosamines. Product use patterns may vary by culture; however, saliva produced during use of these products may be swallowed instead of expectorated leading to concerns the nitrosamines could increase the risk of gastrointestinal cancers.
LITERATURE REVIEW RESULTS: PANCREATIC CANCER

APPLICANT CONCLUSIONS

• Uncertainties and inconsistencies exist as to whether the risk of pancreatic cancer among snus users is increased; pancreatic cancer is consistently increased among smokers.

• Two cohort studies suggest that use of Scandinavian ST could be associated with increased risk of pancreatic cancer among some population subgroups. Despite inconsistencies, available evidence suggests that snus and other ST forms are not associated with pancreatic cancer.

FDA Review Comment: The level of risk noted in published literature is variable. The studies have inadequacies, particularly in dealing with possible confounders (e.g., alcohol use, dietary habits, cigarette smoking).
APPLICANT CONCLUSIONS

- Two studies observed small increases in risk of all-cause mortality among snus users, however, the potential for residual confounding from or misclassification of smoking in these studies remains a concern before strong conclusions from these studies can be drawn.

**FDA Review Comment:** The confounding and misclassification issues make these studies difficult to interpret and a definitive conclusion cannot be made.
Based on the literature review, the applicant concludes:

1. Use of snus presents a much lower risk of the diseases that results in the highest number of deaths among smokers, namely lung cancer, respiratory disease/COPD, CVD, and stroke.

2. Overall there is very little evidence that current use levels of snus in Sweden are associated with any long-term health effects. Firm conclusions cannot yet be drawn regarding the relationship between Swedish snus and possible weight gain issues, metabolic syndrome and diabetes, hypertension, and fatal myocardial infarction.
METHODOLOGICAL ISSUES AND POINTS FOR CONSIDERATION
FDA COMMENTS AND POINTS FOR CONSIDERATION

Methodological Issues

1. The comparison of health risks was based on a visual inspection rather than hypothesis testing.

2. The process for selecting studies for inclusion resulted in only a subset of the data; this could lead to different conclusions.

3. Some publications provided analyses conducted on the same study population.

4. The full range of health risks due to smoking was not presented (e.g., bladder cancer, aortic aneurysm).

5. The applications do not include a specific definition of “substantially lower risks to health.”
Additional Points for Consideration

1. Conclusions drawn from a largely homogeneous Swedish population may present challenges for generalizability to a diverse U.S. population.

2. The Applicant provided published literature with studies that use both American snus or snuff and Swedish snus; variations in product formulation were generally not described in the publications.

3. In many studies, the number of snus-only users was small; this could affect study results and interpretation.
Additional Points for Consideration

4. U.S. users of smokeless tobacco products may use Swedish products differently in terms of product placement in the mouth, exposure time in the oral cavity, and expectoration.

5. As a whole, the body of evidence around health risks that may or may not be associated with use of these products is considerably smaller than that for cigarettes.
1. The applications provide evidence that use of these products is not likely to be associated with lung cancer, COPD, and chronic respiratory disease.

2. In contrast, the applications do not provide adequate data to support a lack of association for use of these products with the other disease endpoints explored (i.e., esophageal, stomach, and pancreatic cancers, CVD, stroke, and all-cause mortality).

3. “Substantially lower risks to health” does not have a clear definition. There is evidence that use of these products has some negative health effects and that users are exposed to carcinogens.
THANK YOU

QUESTIONS?