EPIDEMIOLOGICAL EVIDENCE RELATED TO THE SMNA MRTPA SNUS PRODUCTS AND GUM DISEASE OR TOOTH LOSS

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OUTLINE

- Introduction
- Study characteristics and results
- Select methodological issues
- Summary
INTRODUCTION
“No effects of snus use on gingivitis, gingival recessions, and other dental conditions were consistently identified among studies that controlled for important confounders such as socioeconomic status (SES) and oral hygiene habits.

“The use of snus is not associated with periodontal disease or any individual indicators of periodontal disease based on the results of seven studies, five of which accounted for the potential confounding effects of SES or oral hygiene habits.”

(page 442 section 6.1.1.7 of the applications)
INTRODUCTION: FDA ASSESSMENT

- Twelve epidemiological studies
  - Full evidence tables (see FDA Briefing Document)
  - Study design
  - Results (focus on study aims, applicant included additional outcomes)
  - Select methodological issues
- Systematic review conducted
  - No additional studies identified
- The slides that follow are all based on FDA’s independent assessment of the literature
STUDY CHARACTERISTICS AND RESULTS
FDA EVALUATION OF STUDY POPULATIONS

• All 12 studies were conducted in Sweden

• Six cross-sectional studies in adults
  • Two of the studies used the same population
  • One adult study included only snus users and no non-users

• 5 cross-sectional studies and 1 case-control study in adolescents and young adults under the age of 25
**Current Snus Use Yes/No**
- Hirsch 1991
- Ekfeldt 1990
- Monten 2006
- Kallestal and Uhlin 1992

**Lifetime (Current, Former, Never)**
- Bergstrom 2006
- Wickholm 2004

**Frequency of Snus Use**
- Daily snus users
  - Hugo2012
  - Hugoson and Rolandsson 2011
  - Julihn 2008
- Every day or almost every day
  - Rolandsson 2005
- Took snus regularly
  - Modeer 1980

Andersson and Axell 1989 included only snus users, comparing loose snus to portioned snus users
Three studies with aims to examine dental outcomes

- **Caries**: Hirsch 1991, Hugoson 2012
- **Individual Tooth Wear Index**: Ekfeldt 1990

Five studies with aims to examine gum disease or precursors

- **Periodontal Disease**: Wickholm 2004
- **Periodontal Bone Loss**: Bergstrom 2006
- **Lesions and Gingival Recessions**: Andersson and Axell 1989
- **Incipient Alveolar Bone Loss**: Julihn 2008
- **Buccal attachment loss**: Kallestal and Uhlin 1992

Four studies broad aims (oral health status or periodontal conditions)

- **Oral Health Status**: Rolandsson 2005, Modeer 1980
- **Periodontal Health**: Monten 2006, Hugoson and Rolandsson 2011
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Significant Association</th>
<th>No Significant Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caries</td>
<td><em>Hirsch 1991 (unadjusted, youth)</em></td>
<td>Hugoson 2012 (adults)</td>
</tr>
<tr>
<td>Tooth Wear</td>
<td>Eklfellt 1990 (adults)</td>
<td></td>
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<tr>
<td>Gum Disease or Precursors of Gum Disease</td>
<td><em>Modeer 1980 Gingival Index (youth)</em></td>
<td><em>Youth and Young Adult</em></td>
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<td></td>
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<td>Julihn 2008</td>
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<td></td>
<td></td>
<td>Kallestal and Uhlin 1992</td>
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<tr>
<td></td>
<td></td>
<td><em>Rolandsson 2005 (unadjusted)</em></td>
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<td>Adults</td>
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<tr>
<td></td>
<td></td>
<td>Bergström 2006</td>
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<td></td>
<td></td>
<td>Wickholm 2004</td>
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<td></td>
<td></td>
<td>Hugoson &amp; Rolandsson 2011</td>
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<tr>
<td></td>
<td></td>
<td>(Association with PPD in 1983 only)</td>
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<tr>
<td>Gingival Recessions</td>
<td>Monten 2006 (19 year olds)</td>
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</tbody>
</table>

Unadjusted (italics) only presented in this table when no adjusted results were given in the paper. Andersson and Axell 1989 not included in the table because no non-user comparison group.
SELECT METHODOLOGICAL ISSUES
SELECT METHODOLOGICAL ISSUES: STUDY DESIGN

• 11 of 12 studies were cross-sectional
  • Inability to establish temporality
  • Snus users may quit as health problems occur
• No cohort studies included
• Heterogeneity in exposure/outcome definitions
• No studies included outcomes of tooth loss
• Six studies in adolescents or adults under age 25
  • But many oral health outcomes are not seen until later in life
SELECT METHODOLOGICAL ISSUES: PRECISION

- Only 3 studies included more than 50 snus users per comparison
  - Wickholm 2004
  - Hirsch 1991
  - Juhlin 2008
- Two studies did not mention number of snus users
  - Kallestal and Uhlin 1992
  - Ekfeldt 1990
- Studies may lack statistical power to detect a significant difference
METHODOLOGICAL ISSUES: CONFOUNDING

- Risk factors for gum disease include age, gender, tobacco use, systemic disease and oral hygiene
- None of the studies adjusted for comorbid diseases
- Treatment/inclusion of smokers unclear in many studies and rarely adjusted for
- Adjustment factors not clearly stated for the relationship between snus and attachment loss in the case-control study

<table>
<thead>
<tr>
<th>Cross-Sectional Studies</th>
<th>Adjusted or restricted for Gender</th>
<th>Adjusted or restricted by Age</th>
<th>Adjusted for SES</th>
<th>Adjusted for Dental Health or Hygiene</th>
<th>Dual Use of Cigarettes and Snus Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rolandsson 2005</td>
<td>Males</td>
<td>Age 16-25</td>
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<tr>
<td>Hugoson and Rolandsson 2011</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<td>Dual users excluded</td>
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<tr>
<td>Hugoson 2012</td>
<td>√</td>
<td>√</td>
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<td>Dual users excluded</td>
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<tr>
<td>Wickholm 2004</td>
<td>√</td>
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<td>√</td>
<td>√</td>
<td>Dual users Separated group</td>
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<tr>
<td>Hirsch 1991</td>
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<tr>
<td>Monten 2006</td>
<td>Males</td>
<td>Age 19</td>
<td></td>
<td>√</td>
<td>Only included Non-Smokers</td>
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<tr>
<td>Modeer 1980</td>
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<td>√</td>
<td></td>
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<tr>
<td>Bergstrom 2006</td>
<td>Males</td>
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<tr>
<td>Ekfeldt 1990</td>
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<tr>
<td>Julihn 2008</td>
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</table>

Andersson and Axell 1989 not included
SUMMARY
Despite these methodological limitations, several of the studies in youth populations found an association between snus use and:

- Dental caries (Hirsch et al., 1991)
- Gingival recession (Monten et al., 2006)
- Gingival index (Modeer et al., 1980)

One study found an association between snus and tooth wear in adults (Ekfeldt et al., 1990).
SUMMARY

• Almost all of the studies presented were cross-sectional
• Half included only adolescents and young adults
• Many were small in size (most had fewer than 50 snus users)
• Most did not control for all appropriate potential confounding factors
• Applicant does not provide a justification as to why it is biologically plausible that effects of snus on gum disease and tooth loss would be significantly different from other smokeless tobacco
THANK YOU

QUESTIONS?