7.5.1.: LITERATURE SELECTION AND SUMMARY

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7.5.1. LITERATURE SELECTION AND REVIEW PROCESS

7.5.1.1. Purpose

Altria Client Services LLC ("ALCS") on behalf of U.S. Smokeless Tobacco Company LLC ("USSTC") submits this Modified Risk Tobacco Product Application (MRTPA) to seek authorization for a proposed modified risk claim - "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." This proposed claim will apply to Copenhagen® Snuff Fine Cut (candidate product), a moist smokeless tobacco (MST) product.

The candidate product is a grandfathered product (FDA Grandfather Status # GF1200194) (Appendix 2.3-1), commercially marketed in the U.S. as of February 15, 2007. As such, it is not a new tobacco product as defined by FDCA Section 910(a)(1) and does not require premarket review and authorization[1].

The Food and Drug Administration (FDA) Modified Risk Tobacco Product Application (MRTPA) Draft Guidance (2012) lists several questions related to a variety of health risk and tobacco use behavior topics for the candidate product. Smokeless tobacco products (ST) and cigarettes have been in the U.S. market for many years and are the subject of numerous peer-reviewed scientific publications. We rely on this literature to support our conclusions regarding the substantial risk differential between ST use and cigarette smoking and other topics addressed in the MRTPA Draft Guidance.

We believe that this U.S. epidemiologic dataset represents the health risks from long-term exposure to ST and the moist smokeless tobacco (MST) products discussed in these studies and is representative of the candidate product (Section 7.5.6-1 and Section 7.5.6-2).

7.5.1.2. Literature Review Process

This section outlines the process we used to conduct a comprehensive review of the published literature in order to identify scientific publications related to the health risks and population effects of ST, with particular attention to studies using MST products.

The goal of our literature review process was to provide a comprehensive assessment of the available literature on the specific topics.

The protocol we developed consists of clearly identified inclusion and exclusion criteria based on published best practices for reviewing scientific literature. The protocol was based on recommendations set forth in the Institute of Medicine report "Finding What Works in Health Care: Standards for Systematic Reviews"(Institute of Medicine, 2011), the Cochrane Handbook for Systematic Reviews of Interventions ("Cochrane Handbook for Systematic

[1] Copenhagen® Fine Cut and variants thereof have been on the market since 1822. Since 2007, USSTC made minor modifications to Copenhagen® Snuff Fine Cut, which are the subject of a separate pending Substantial Equivalence review. The candidate product subject to the MRTPA is the product for which FDA granted grandfathered status (Grandfather Number – GF1200194) on November 1, 2012.

Reviews of Interventions," 2011), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The modifications were incorporated to minimize potential exclusion of papers that may be considered relevant. Unlike the practice adopted by Cochrane Collaboration and the Institute of Medicine, we did not exclude research papers based on an assessment of bias. We also did not assign a weight of evidence score due to the lack of a consensus in many fields of research regarding appropriate objective scoring methods. Additionally, we included peer-reviewed published literature identified through EMBASE/Medline and SCOPUS, and did not include 'Gray'[2] literature, except for publications from authoritative bodies such as the U.S. Surgeon General or International Agency for Research on Cancer reports.

The steps used to conduct the literature review are:

1. develop the review objective;
2. identify the data sources;
3. define the search terms;
4. select a time frame spanning the literature search;
5. select inclusion and exclusion criteria; and
6. execute the literature assessment.

7.5.1.2.1. Developing the Review Objective

The objective for our literature review was to identify and review published scientific literature relevant to the multiple specific topics of interest indicated by FDA in the MRTPA Draft Guidance.

The MRTPA Draft Guidance recommends that the manufacturer provide the scientific evidence for significant reduction in tobacco-related disease to the individual user and demonstrate that the candidate product will benefit the population health as a whole, including users and nonusers. To provide relevant scientific information to the FDA, we concentrated on literature that characterized the health and behavioral effects of ST products. We employed broad search terms in order to identify the largest body of literature possible. While our primary objective was to obtain information related to U.S.-produced MST, our wide search strategy included many ST products. Our inclusion and exclusion criteria were designed to include as many relevant publications as possible, regardless of study outcome.

[2] *Gray literature* is information generated by a variety of sources, including "trial registries, conference abstracts, books, dissertations, monographs, and reports held by the FDA and other government agencies, academics, business, and industry"(Institute of Medicine, 2011). However, it is not peer-reviewed or typically published through traditional commercial channels, and for those reasons is excluded from this comprehensive literature review. As outlined in the Cochrane Handbook: "The inclusion of data from unpublished studies can itself introduce bias. The studies that can be located may be an unrepresentative sample of all unpublished studies. Unpublished studies may be of lower methodological quality than published studies."("Cochrane Handbook for Systematic Reviews of Interventions," 2011).

7.5.1.2.2. Identifying the Data Sources

We used both EMBASE/Medline[3] and SCOPUS[4] to identify candidate publications for review since these databases provide comprehensive coverage of a wide range of scientific topics.

7.5.1.2.3. Defining Search Terms

Our initial search terms were intentionally broad at the outset to capture the widest possible range of literature results. The initial search terms included the following: (1) "Tobacco, Smokeless," "Smokeless Tobacco"; (2) "snuff" OR "snus" OR "stem tobacco*" AND "oral," "plug," "smokeless," "Swedish"; and (3) "loose leaf" OR "stems chew*" OR "spit*" OR "dip*."

Medical subject heading (MeSH) terms, Boolean operators, and free-text strategies were internally designed and used to combine the search results into a Reference Manager 12 database (Thomson Reuters) for documentation and removal of duplicate entries.

7.5.1.2.4. Selecting a Time Frame Spanning the Literature Search

Our search period covered the years 1960 to December 2014 (initial review). This search was repeated on February 6, 2017 (update review) using the same search terms and databases as previously described. Due to recent interest in the reduced risk potential of ST, we modified the inclusion criteria to incorporate Swedish-manufactured Snus used and/or tested in U.S. populations, covering the period between December 2, 2014 and February 6, 2017.[5]

7.5.1.2.5. Selecting Inclusion and Exclusion Criteria

Selecting inclusion and exclusion criteria is a critical element in accumulating any publication dataset for review. We designed our criteria to develop a dataset of publications representing studies among U.S. tobacco users using ST products representative of the candidate product.

Publications identified were screened against inclusion and exclusion criteria at two stages during both the initial and the update review process:

1. In stage 1, we reviewed the title and abstract to ensure that the publications were within the scope of the review (Table 7.5.1-1).

[3] MEDLINE consists of more than 25 million citations for biomedical literature from life science journals, and online books. https://www nlm nih.gov/pubs/factsheets/medline.html
[4] According to the website, SCOPUS is the largest abstract and citation database of peer-reviewed literature, scientific journals, books, and conference proceedings. https://www.elsevier.com/solutions/scopus
[5] We conducted a supplementary literature search covering the period between February 2017 and December 2017. Relevant citations were discussed in specific sections of this application. A full review will be conducted as part of the postmarket assessment plan as described in Section 8.1.

Table 7.5.1-1: Initial and Update Summary – Inclusion and Exclusion Criteria

Criteria - Inclusion or Exclusion	Initial Review – 1960 Through December 2014 Update Review – December 2, 2014 Through February 6, 2017
Inclusion	original research, including secondary analyses and meta-analyses
	studies of smokeless tobacco products sold in the U.S.
	published in the English language
Exclusion	studies of ST products sold in other countries than the U.S.
	studies of non-U.S. populations (e.g., Swedish snus epidemiology)
	published in a foreign language
	not peer-reviewed, except for reports from authoritative bodies (e.g., U.S. Surgeon General, IARC, etc.)

2. In stage 2, we conducted an additional in-depth review of the full-text publications for both in-scope articles and for articles where scope was difficult to determine based on the title and abstract. We assessed these publications and assigned them into specific categories based on topics addressed in the MRTPA Draft Guidance, which included the following:
    - dual use: current use of ST and other tobacco products;
    - intercepting quitting: use of ST in place of complete cessation;
    - switching: transitioning from cigarettes to ST;
    - gateway: ST users initiating to higher risk products like cigarettes;
    - initiation: onset of use, and reasons for, in previous nonusers;
    - chemistry: product characteristics and constituents such as pH, nicotine, tobacco-specific nitrosamines;
    - exposure: biomarkers of exposure;
    - health risks: epidemiology, case reports, linked mortality data;
    - preclinical: all *in vitro*, *in vivo*, and *ex vivo* studies;
    - ST vs. cigarettes: health risk comparisons between ST and cigarettes;
    - ST vs. nicotine replacement therapy: health risk comparisons between ST and nicotine replacement therapy;
    - perceptions: consumer perceptions of risk of ST, or ST compared to other commercial products;
    - topography: patterns of use such as cans per week, dips per day, duration of dip use; and

- abuse potential/abuse liability: pharmacokinetic data, subjective effects, craving, withdrawal.

ALCS scientists with relevant subject matter expertise used the publications included in these categories to develop the following literature summary narratives and evidence tables (initial and update):

- Section 7.5.2-1 and 7.5.2-2, Users' Behavior
- Section 7.5.3-1 and 7.5.3-2, Nonusers' Behavior
- Section 7.5.4-1 and 7.5.4-2, Chemistry
- Section 7.5.5-1 and 7.5.5-2, Exposure
- Section 7.5.6-1 and 7.5.6-2, Health Risks
- Section 7.5.7-1 and 7.5.7-2, Perceptions
- Section7.5.8-1 and 7.5.8-2, Topography
- All original references compiled (1960-December 2014) and all updated references compiled (December 2, 2014-February 6, 2017)

Many of the publications we considered relevant often related to multiple topic categories. In such cases, the same publications were included in the multiple reviews between topics as appropriate. In addition, in the process of reviewing the literature, ALCS authors made note of additional, relevant publications by using cross-referencing techniques. Any publications that were found by reviewing cited references, but not identified in our search strategy, were included according to ALCS authors' best scientific judgment.

7.5.1.3. Comprehensive Review Results

Figure 7.5.1-1 and Figure 7.5.1-2 show the review process and the number of publications included or excluded for the initial and the update searches, respectively.

Figure 7.5.1-1: Initial Publication Search and Review (1960 – December 2014)

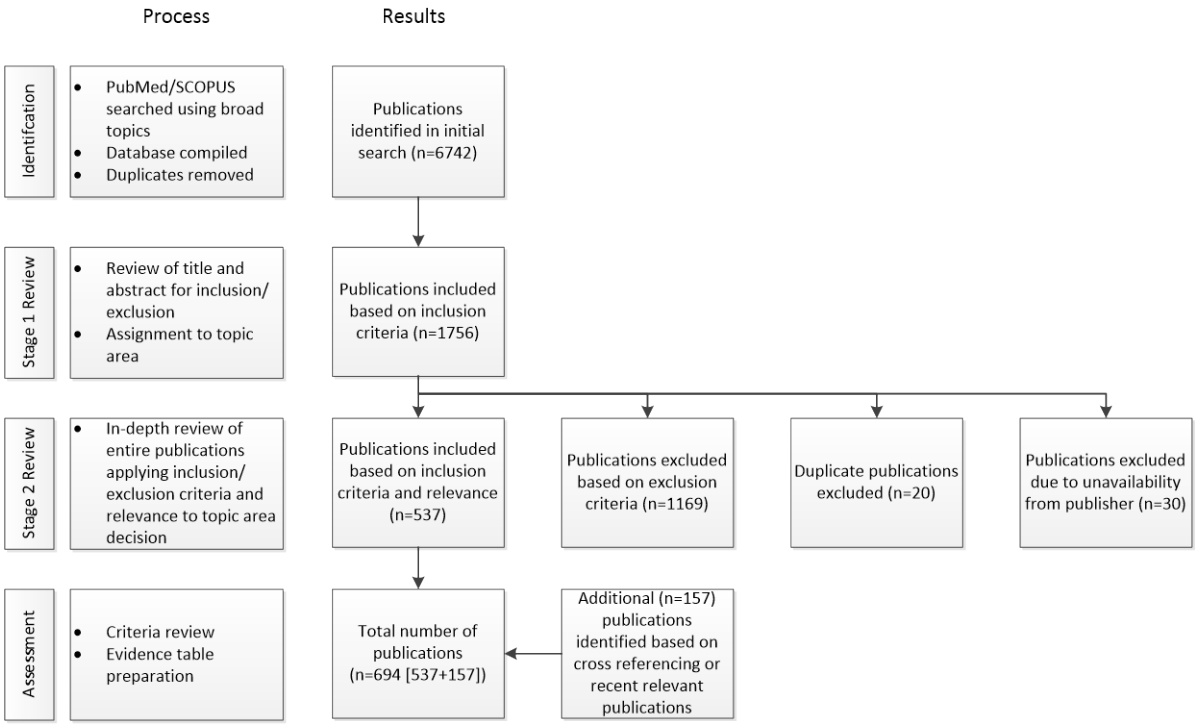
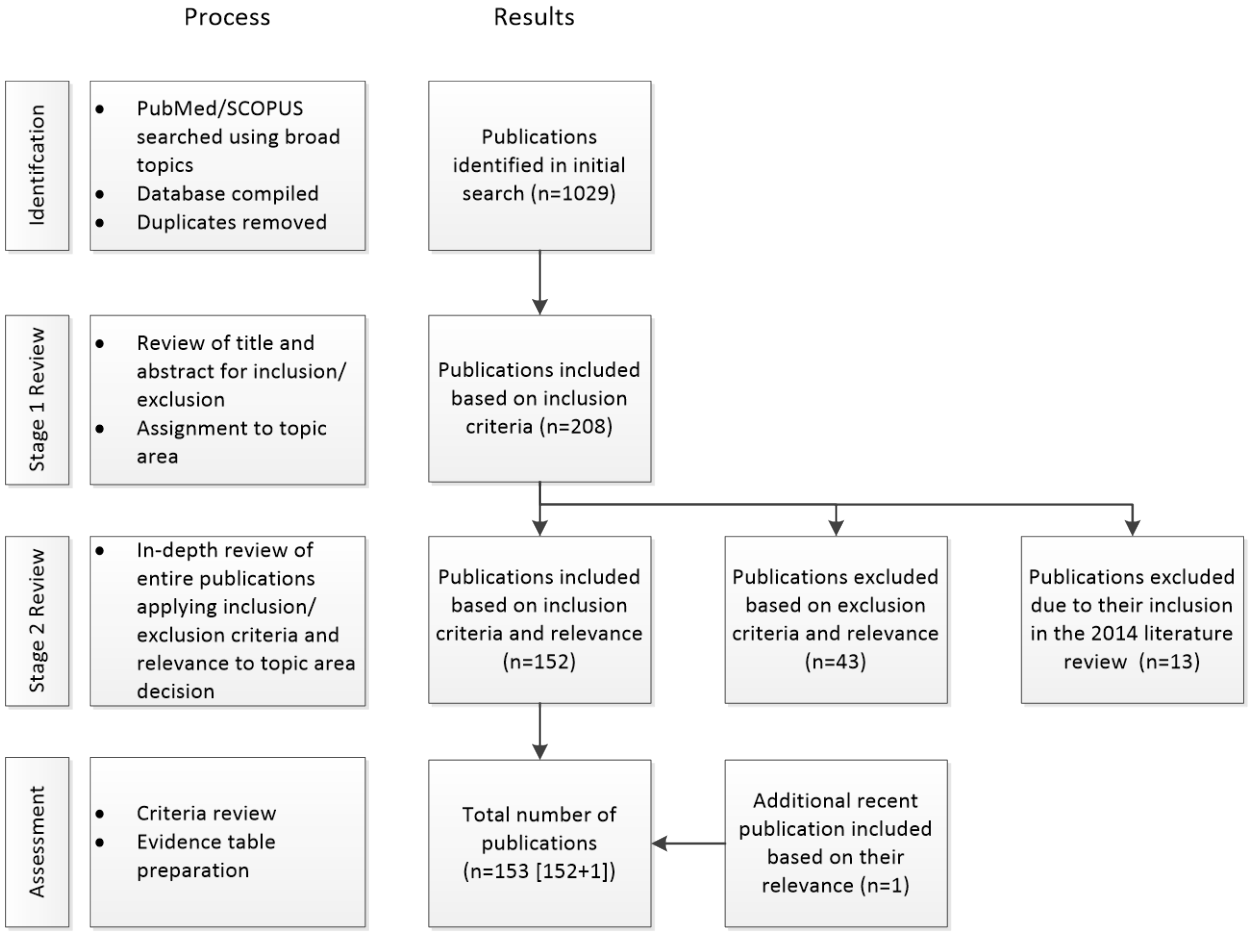


Figure 7.5.1-2: Update Publication Search and Review (December 2, 2014 – February 6, 2017)



7.5.1.4. Literature Cited

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Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med, 6*(7), e1000097. doi:10.1371/journal.pmed.1000097