MODIFIED RISK TOBACCO PRODUCT APPLICATIONS

CDR Raquel Peat, PhD, MPH
Conrad J. Choiniere, PhD
Office of Science
Center for Tobacco Products
U.S. Food and Drug Administration
DISCLAIMER 1

The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy. The information is being provided to TPSAC to aid the committee in its evaluation of the issues and questions referred to the committee.
This presentation contains statements of preliminary findings and interpretations of the data and information reviewed to date. It must be emphasized that this presentation does not represent final findings, recommendations, or conclusions, and that no final regulatory decision on the status of these applications has been made. Due to the large volume of information contained in the applications, it is not feasible to provide a comprehensive review for discussion at this meeting. Although the entire applications are referred to the Committee, this presentation may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Committee.
OUTLINE

• Statutory framework for Modified Risk Tobacco Products
• Process for review of applications accepted for filing
• Applications under review
STATUTORY FRAMEWORK FOR MODIFIED RISK TOBACCO PRODUCTS
Modified Risk Tobacco Products (MRTPs) are tobacco products sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercial marketed tobacco products; this includes products whose label, labeling or advertising represents (explicitly or implicitly) that:

- The product is less harmful or presents a lower risk of tobacco-related disease than other commercially marketed tobacco products

- The product or its smoke contains a reduced level of, presents a reduced exposure to, or does not contain/is free of a substance
A tobacco product is also considered a Modified Risk Tobacco Product if:

• The words “light”, “mild,” “low” or similar descriptors are used in its label, labeling or advertising; or

• Its manufacturer has taken any action after June 22, 2009 directed to consumers through the media or otherwise, other than by means of label, labeling or advertising, that would be reasonably expected to result in consumers believing that the tobacco product may present a reduced risk of harm, tobacco-related disease, or exposure to a substance than commercially marketed tobacco products
In order for a Modified Risk Tobacco Product to be legally introduced or delivered for introduction into interstate commerce:

• An application must be filed with FDA; and

• FDA must issue an order under section 911(g) with respect to such product allowing it to be introduced or delivered for introduction into interstate commerce.
Types of Modified Risk Orders

Risk Modification Orders
Are for tobacco products that have been shown to significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, and benefit the health of the population as a whole, taking into account both users and non-users of tobacco products. (Section 911(g)(1))

Exposure Modification Orders
Are for tobacco products that reduce or eliminate exposure to a harmful substance and for which the available scientific evidence is not sufficient to meet the standard for a risk modification order but suggests that a measurable and substantial reduction in morbidity and mortality is reasonably likely in future studies. (Section 911(g)(2))
In order for a tobacco product to make claims that the product presents a lower risk of disease, an applicant must make the demonstrations outlined in 911(g)(1):

That the product, as it is actually used by consumers:

• Will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and

• Benefit the health of the population as a whole, taking into account both users and non-users of tobacco products.
FDA must determine whether an MRTP will significantly reduce harm and the risk of tobacco-related disease to individuals and benefit the health of the population as a whole, taking into account:

- the relative health risks to individuals of the MRTP;
- the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the MRTP;
- the increased or decreased likelihood that persons who do not use tobacco products will start using the MRTP;
- the risks and benefits to persons from the use of the MRTP as compared to the use of smoking cessation drug or device products approved to treat nicotine dependence (e.g., nicotine replacement therapies (NRTs)); and,
- comments, data and information submitted by interested persons.
FDA must make MRTPAs (except confidential & trade secret information) available for public comment.  

FDA must refer MRTPAs to the Tobacco Products Scientific Advisory Committee (TPSAC) for recommendations.  

FDA intends to make decision on the application within 360 days.  

MRTP orders are issued for individual products, not for a class of tobacco products.  

MRTP orders are valid for a duration specified by FDA. An applicant may request renewal of the order.  

All applicants who receive orders must conduct postmarket surveillance and studies.
In order for an MRTP to be legally introduced or delivered for introduction into interstate commerce:

- An MRTP application (MRTPA) must be filed with FDA, and
- FDA must issue an order under section 911(g) with respect to such product allowing it to be introduced or delivered for introduction into interstate commerce.

And

Applicants must also satisfy the premarket requirements under section 910 of the FD&C Act. If an MRTP is a new tobacco product, it may be brought to market through any of the following pathways:

- Premarket Tobacco Product Application
- Substantial Equivalence (SE)
- Exemption from SE
Swedish Match North America, Inc. (SMNA) submitted MRTPAs on June 10, 2014 for 10 snus products.

European Smokeless Tobacco Council defines Swedish snus “as a smokeless tobacco product for oral use which is traditionally produced and used in Sweden and manufactured using a heat treatment process.” (page 87, Chapter 2)

The 10 snus products vary in name, flavor, package quantity and portion size. Nine of the products are portioned snus (in pouches), one is loose snus.
The Comprehensive Smokeless Tobacco Health Education Act currently requires that each smokeless tobacco product package and advertisement bear one of four required warnings. The applicant is proposing:

- To keep the “WARNING: Smokeless tobacco is addictive.”
- To eliminate the “WARNING: This product can cause mouth cancer.”
- To eliminate the “WARNING: This product can cause gum disease and tooth loss.”
- To revise the “WARNING: This product is not a safe alternative to cigarettes.”

If granted, the proposed modified risk tobacco products would be required to bear on their packaging and advertising one of two warnings:

- “WARNING: Smokeless tobacco is addictive.”
- “WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.”
MRTPA REVIEW PROCESS

Phase 0
Pre-MRTPA Meetings

Phase 1
Acceptance

Phase 2
Filing

Phase 3
Review
Final Action

Phase 4
Postmarket Surveillance & Studies

Day 0

360 Days

Day 360

Reapplication / Renewal

START

April 9 - 10, 2015 TPSAC Meeting | Modified Risk Tobacco Product Applications
Acceptance is an administrative review of a submission to determine whether it is acceptable for processing and further review.

CTP has jurisdiction under Chapter IX of the FD&C Act

For example:

- Does the product meet the statutory definition of “tobacco product”?
- Is the tobacco product currently regulated?
For filing, a Modified Risk Tobacco Product Application must include:

1. a description of the proposed product and any proposed advertising and labeling
2. the conditions for using the product
3. the formulation of the product
4. sample product labels and labeling
5. all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health
6. data and information on how consumers actually use the tobacco product
7. such other information as the Secretary may require
FDA scientists evaluate data and information to inform a regulatory science decision on the application.

Actions:
- Application is made publically available
- Scientists review application and public comments
- Conduct inspections (clinical and manufacturing)
- TPSAC provides recommendations to FDA

Timeline goal - completion of scientific review results in an order by day 360
Final Decision

Marketing Order (issued for a specified time)

No Marketing Order

Phase 4
If authorized for marketing, Phase 4 activities include:

Actions:

• The applicant submits a postmarket surveillance protocol to FDA
• FDA reviews the applicant’s proposed protocol and determines whether to approve the protocol (under section 911(i)(2))
• FDA monitors and reviews data submitted as part of postmarket surveillance
• If submitted, FDA will evaluate requests to renew an MRTP marketing order
SCIENTIFIC REVIEW PROCESS
In order to determine that a tobacco product meets the criteria for issuance of an order, FDA has recommended to applicants that an MRTPA contain studies and information with respect to the following areas:

• Health risks of the tobacco product;
• The effect the tobacco product and its marketing may have on tobacco use behavior among current tobacco users;
• The effect the tobacco product and its marketing may have on tobacco use initiation among non-users (both never users and former users);
• The effect of the tobacco product’s marketing on consumer understanding and perceptions; and
• The effect the tobacco product and its marketing may have on the population as a whole.
The SMNA MRTPAs contained information addressing each of the areas identified by FDA including evidence from various types of scientific studies:
- Product analyses (chemistry, engineering, microbiology)
- Toxicological assessments
- Pharmacokinetic studies
- Clinical trials (for cessation)
- Epidemiological studies (health and behavior)
- Consumer perception and comprehension
- Statistical modeling
- Plans for postmarket surveillance and studies
Swedish Match North America, Inc. currently markets General Snus tobacco products, however, the snus products included in the MRTP applications are new tobacco products and appear to differ from those on the market in some respects, such as:

- Additives
- Tobacco blends
- Flavors

If FDA issues modified risk orders for any of these products, those orders would only be applicable to the products in the MRTP applications and would not extend to any other snus products currently in the market, including any other snus products marketed by Swedish Match North America, Inc.
TOPICS FOR DISCUSSION

FDA review encompasses the entirety of the materials included in the applications.

Although the entire applications are referred to the Committee, this presentation may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Committee.

Based on its review, FDA has identified several critical scientific issues to bring to TPSAC for discussion, directly related to the factors FDA must consider when taking an action.
With respect to the relative health risks to individuals, FDA brings to TPSAC questions related to:

- The strength of association between snus use and the risk of tooth loss and gum disease
- The strength of association between snus use and the risk of oral cancers.
- The risks of snus use as compared to cigarettes.

With respect to the impacts on initiation and cessation, FDA brings to TPSAC questions related to:

- The applicability of the Swedish experience to infer impacts on the U.S. population.
With respect to the ability of the public to comprehend the modified risk information, FDA brings to TPSAC questions related to:

• The impacts of providing modified risk information in the context of a warning.

FDA also seeks recommendations from TPSAC on postmarket surveillance and studies, should FDA issue an order permitting the marketing of the products as modified risk.
FDA made the MRTPAs available for public comment on August 27, 2014. FDA indicated at the time that comments received prior to November 25, 2014 would be more likely to be considered prior to referring the applications to TPSAC. In total, FDA has received 149 comments, 121 of those were received prior to November 25, 2014.

Comments were submitted by members of the public, including individuals from the tobacco control research community, public health advocacy organizations, and the tobacco industry. Those comments address:

• Legal and policy considerations
• Ethical implications
• Personal experiences
• Scientific issues
Given the scope of this meeting, the comments discussed today are limited to those addressing scientific issues. Many of the issues raised in the comments were also identified by FDA during its review of the applications.

In particular, comments raised concerns about the epidemiological evidence on health and behavioral impacts of snus use, consumer perceptions of the products, and interpretation of the scientific data.
Some commenters expressed concerns about the interpretation of the epidemiological data on the impacts of snus on individual health. In particular, comments raised the potential for the snus use to increase risks of certain health outcomes, as compared to non-users:

- Fatal myocardial infarction and stroke
- Fatal heart disease
- Esophageal and pancreatic cancers
Some commenters expressed concerns about the impacts of marketing snus as modified risk on behaviors. In particular, comments raised the potential for the proposed modified risk messaging to:

- Increase initiation among youth
- Encourage dual use among smokers
- Fail to reach the target population (smokers), and thereby not benefit the population health
Other commenters discussed the applicability of the Swedish experience, highlighting:

• Features in the environment in Sweden that do not exist in the U.S. (e.g., restrictions on the advertising for tobacco products)
• Cultural differences
• Patterns of use of smokeless tobacco products
Other commenters discussed potential impacts on consumer perceptions, that the messaging may:

• Correct perceptions about the relative risks of snus use
• Exacerbate perceptions about the relative risks of snus use
• Mislead consumers into believing all smokeless products carry the same risks as snus
The remaining scientific comments addressed a variety of concerns. Included among those concerns:

- Uncertainty about the similarities between the SMNA products and those traditionally marketed in Sweden
- The proper handling and storage of snus products by U.S. consumers
- Methodological issues with the consumer perception study included in the applications
• With respect to the relative health risks to individual users of these snus products (i.e., the Swedish Match North America, Inc. snus tobacco products that are the subject of these applications):
1. Discuss the evidence regarding the association between the ten snus products and gum disease or tooth loss. Please address the following issues in your discussion.

   • Biological plausibility that gum disease or tooth loss in snus users would differ from those in users of other smokeless tobacco products;
   • Confidence in the information from studies that only include young adults under the age of 25, given that the prevalence of periodontal disease increases with age;
   • Confidence in the information on tooth loss from the use of snus, where the studies presented in the application evaluated the number of teeth between snus users and non-users in cross-sectional studies;
   • Sufficiency of information from studies where the number of snus users in many of the cross-sectional surveys was fewer than 50.

   a. Does the evidence support that these snus products pose risks of gum disease to individual users of these products? (vote)
   b. Does the evidence support that these snus products pose risks of tooth loss to individual users of these products? (vote)
2. Discuss the evidence regarding the association between these ten snus products and oral cancer.
   a. Does the evidence support that these snus products pose risks of oral cancer to individual users of these products? (vote)

3. Discuss the evidence regarding the association between the ten snus products and overall risks to health as compared to cigarettes.
   a. Should the comparison focus on the major smoking-related diseases according to population burden or assess all relevant health outcomes? (vote)
   b. Does the evidence support the statement that health risks to individual users from using these snus products are “substantially lower” than the health risks from smoking cigarettes? (vote)
   c. Does the proposed warning statement adequately communicate the potential health risks to individual users of these snus products? (vote)
4. Assuming that the behavior of U.S. population does mimic those in Sweden with respect to the use of snus, what information would the Committee need to know about the snus products that are used in Sweden and the snus products that are the subject of these applications in order to have confidence that the health outcomes observed in Sweden would also be observed in the U.S.?

For example, would it be sufficient to know that the exposures to individual users of the Swedish products are comparable to the exposures to individual users of these snus products, or would knowledge about other characteristics of the tobacco product be needed to determine that the health outcomes would likely be comparable?
• With respect to the likelihood that existing users of tobacco products who would otherwise stop using those products will instead switch to these snus tobacco products, and the likelihood that persons who do not use tobacco products will start using these snus tobacco products:
5. Discuss the evidence regarding the likely impact of these ten snus products on tobacco use behaviors among tobacco users and non-users.

a. Does the Committee believe that the epidemiological data from Sweden concerning tobacco use behavior provide relevant information on the:

   i. The likelihood that current tobacco users in the U.S. will switch to the use of these snus products? (vote)
   ii. The likelihood that non-users of tobacco in the U.S. will initiate the use of these snus products? (vote)

b. The applications did not include several types of studies that could be useful in order to assess impacts on behavior, such as actual use studies, self-selection studies, or other behavioral studies. Does the Committee believe that the applications include sufficient information on the behavioral aspects of the use of these snus products among the U.S. population? (vote)
QUESTIONS FOR THE COMMITTEE

• With respect to enabling consumers to comprehend the modified risk information and understand its relative significance in the context of total health:

(time permitting)
6. The applicant proposes to include modified risk information within a warning label. FDA has potential concerns that inclusion of information about relative benefits of product use within a warning label may raise additional questions regarding consumer comprehension of the modified risk information and perceptions of the product.

   a. From the perspective of enabling consumers to understand the modified risk information in the context of total health, does the Committee believe it is appropriate to include modified risk information within the context of the required warning label as opposed to in a statement separate from, and in addition to, the warning label? (vote)

   *(time permitting)*
• With respect to postmarket surveillance and studies to be conducted by Swedish Match North America, Inc.:

(time permitting)
7. If FDA were to issue an order allowing the marketing of these snus products as modified risk tobacco products, what recommendations does the Committee have for postmarket surveillance and studies?

a. What elements should Swedish Match North America, Inc. include in a postmarket surveillance and studies program in order to monitor product use transitions for these snus products, which may have a low prevalence of use?

b. What methods does the Committee recommend that Swedish Match North America, Inc. employ for assessing the impact of a specific modified risk tobacco product marketing on perceptions and behavior in a postmarket setting, particularly among youth?

c. What sources of data does the Committee recommend that Swedish Match North America, Inc. use for providing information on impacts resulting from the marketing of the products as modified risk tobacco products?

d. What additional information does the Committee recommend that FDA request from the applicant regarding plans to conduct postmarket surveillance and studies?

(time permitting)
THANK YOU

QUESTIONS?