

TOBACCO PRODUCT APPLICATION REVIEW: MODIFIED RISK TOBACCO PRODUCT APPLICATIONS (MRTPAs)

Presented by:

Benjamin Apelberg, PhD, MHS

Director, Division of Population Health Science

Office of Science

Center for Tobacco Products

U.S. Food and Drug Administration

Disclaimer: This is not a formal dissemination of information by FDA and does not represent Agency position or policy.

- Modified Risk Standard
- Approach to Scientific Review
- Opportunities for Clarification & Improvement

RISK MODIFICATION ORDER STANDARD – 911(G)(1)

The FD&C Act requires FDA to determine if a proposed MRTP, as it is actually used by consumers, will:

- (1) Significantly reduce harm and the risk of tobacco-related disease to individuals and
- (2) Benefit the health of the population as a whole



For products that cannot receive an order under 911(g)(1), FDA may issue an order under 911(g)(2) if it determines that the applicant has demonstrated that, among other things:

- it is appropriate to promote the public health;
- the label, labeling, and advertising is limited to a claim that the product does not contain or is free of a substance or contains a reduced level or presents a reduced exposure;
- scientific evidence is not available, and cannot be made available without conducting long-term epidemiological studies, for an application to meet the standard for a 911(g)(1) order;
- scientific evidence that is available demonstrates that a substantial reduction in morbidity or mortality is reasonably likely; and
- testing shows that consumers will not be misled into believing that the product has been demonstrated to be less harmful or present less risk.

QUESTIONS RELEVANT TO THE MRTP EVALUATION



These questions are relevant to the evaluation of whether the applicant has met the applicable 911 standard:

1. Is there adequate scientific substantiation of the proposed modified risk information?
2. What are the health risks of the MRTP to individual tobacco users?
3. How do consumers perceive and understand the modified risk information?
4. What are the potential benefits and harms to the health of the population as a whole?

ADDITIONAL CONSIDERATIONS

- An MRTP order is for a specific product, not for a class of products
- Evaluations are in the context of a specific product and specific modified risk claim
- Form and wording of the claim have a critical impact on the final decision



- In April 2012, FDA announced availability of the “Draft Guidance for Industry: Modified Risk Tobacco Product Applications” for public comment
- Draft guidance discusses, among other things,:
 - Who submits MRTPAs
 - When to submit a MRTPA
 - **Contents of an MRTPA under Section 911(d) of the FD&C Act**
 - **Scientific evidence to support a MRTPA**
 - **Postmarket surveillance and studies**
 - **How to organize and submit a MRTPA**
- When final, the guidance will represent the Agency’s current thinking on modified risk tobacco applications

APPROACH TO SCIENTIFIC REVIEW

- Scientific review includes the following key areas of focus:
 - Identification of modified risk information
 - Substantiation of modified risk information
 - Relative health risks to individuals
 - Consumer understanding and perception
 - Impact to the population as a whole
 - Product description and characterization
 - Environmental review and NEPA
- Reviews are based on all available scientific evidence related the product(s) — both the information provided by the applicant, as well as any other relevant information available to the Agency, including from the general scientific literature.

REVIEW OF MODIFIED RISK INFORMATION

- FDA evaluates all information and statements on the proposed label, labeling, and advertising as part of its scientific review.
- This review includes, but is not limited to, an evaluation of the applicant's label, labeling, and advertising for modified risk claims even if those claims were not specifically identified by the applicant in its request for authorization.



SUBSTANTIATION OF MODIFIED RISK INFORMATION



EXAMPLE OF QUESTIONS FOR CONSIDERATION DURING REVIEW

- Is the proposed modified risk information scientifically accurate?

POTENTIAL LINES OF EVIDENCE

- Chemical analyses
- Toxicological
- Clinical
- Epidemiological

RELATIVE HEALTH RISKS TO INDIVIDUALS

EXAMPLE OF QUESTIONS FOR CONSIDERATION DURING REVIEW

- What does the evidence suggest about the potential health risks of the product?
- How do the risks of the product compare to: never use? cigarette smoking? other products in tobacco product category?
- How do the risks of complete switching (to the product) compare to: continued smoking? quitting altogether? FDA-approved cessation aids?
- Is there any evidence of the potential for reduced exposure or risk among dual users?
- What are the health risks to individuals not using the product, who may be involuntarily exposed to the product?

POTENTIAL LINES OF EVIDENCE

- Toxicological
- Epidemiological
- Clinical (e.g., biomarkers)

CONSUMER UNDERSTANDING & PERCEPTION



EXAMPLE OF QUESTIONS FOR CONSIDERATION DURING REVIEW

- What does the available evidence suggest about consumers' understanding of the modified risk information on the product's label, labeling, and advertising and their perceptions of the product?
- What are consumers' beliefs about the health risks of using the product relative to:
 - Other tobacco products, including those within the same class of products?
 - Use of the product in conjunction with other products?
 - Cessation aids?
 - Quitting all tobacco use?

POTENTIAL LINES OF EVIDENCE

- Consumer perception studies

IMPACT TO THE POPULATION AS A WHOLE



EXAMPLES OF QUESTIONS FOR CONSIDERATION DURING REVIEW

- From the available evidence, what do we know about who is likely to use the product—including both intended and unintended users—and how they are likely to use it?
- How is the product likely to be actually used by consumers (e.g., frequency, intensity of use)?
- How likely is it that consumers will not use the product as intended or designed, either intentionally or unintentionally, and what are the implications of that type of use?
- Under what combinations of product use behavior would we expect a net public health benefit or harm?
- Are there specific populations that would be at increased risk of using this product?

POTENTIAL LINES OF EVIDENCE

- Actual use studies, which may assess: abuse liability, nicotine and metabolite exposure, topography, subjective effects
- Consumer studies that assess intentions to use
- Epidemiological
- Population modeling

- When considering the “population as a whole”, it is useful to think about intended vs. unintended (but potentially likely) users of the proposed MRTP
 - Examples of intended users:
 - Current cigarette smokers who are unable or unwilling to quit
 - Examples of unintended users:
 - Never users, most notably youth, who are at particular risk of tobacco use initiation
 - Recent former users, who are at particular risk of relapse to tobacco product use
 - Current users of tobacco products that may have a lower toxicity profile than the proposed MRTP, including those in the same general product category
- By “intended” users, we mean those users who stand to benefit from complete switching to the product. “Unintended users” are all others.



PRODUCT DESCRIPTION & CHARACTERIZATION

EXAMPLE OF QUESTIONS FOR CONSIDERATION DURING REVIEW

- Are the product design and composition sufficiently described to allow for full understanding of what it is, how it is made, and whether it is a product that can be manufactured and distributed in a consistent manner?
- Does the product design and composition raise any additional concerns about individual health risk or injury?

POTENTIAL LINES OF EVIDENCE

- Chemical analyses
- Engineering
- Microbiological

FDA may also conduct independent laboratory testing and site inspections

- FDA is required to refer all MRTPAs to TPSAC
- TPSAC provides recommendations to FDA on MRTPAs
- 12 members with knowledge in the fields of medicine, medical ethics, science, or technology involving the manufacture, evaluation, or use of tobacco products
 - 9 voting members, including 1 employee of a state, local or the Federal Government and 1 representative of the general public
 - 3 non-voting industry representatives, including 1 representative of the tobacco manufacturing industry, 1 representative of small business, and 1 representative of tobacco growers
- Additional experts may be invited by FDA as needed
- Most meetings are public and provide the public with the opportunity to communicate to the FDA and TPSAC members

- FDA brings to the committee select scientific issues from the applications, for example:
 - Substantiation of modified risk information
 - Relative health risks to individuals
 - Consumer understanding and perceptions of modified risk information
 - Likelihood of use
- FDA and the applicant prepare briefing materials for the committee and present at the TPSAC meeting
- FDA is not required to follow TPSAC recommendations or votes; however, FDA takes into consideration TPSAC members' insights before issuing a determination
- As of October 2018, FDA has held 3 TPSAC meetings on specific MRTPAs

PUBLIC AVAILABILITY



- FDA posts the application materials, including current and future amendments, on a rolling basis
- Applications are reviewed for commercially confidential information and are redacted accordingly prior to posting
- To date, over 1 million pages have been posted publicly

The screenshot shows the FDA website's 'Tobacco Products' section. The main heading is 'U.S. Smokeless Tobacco Company Modified Risk Tobacco Product (MRTTP) Application'. Below the heading are social media sharing options (Share, Tweet, LinkedIn, Pin It, Email, Print). The text on the page states that on September 14, 2018, the FDA filed for substantive scientific review one Modified Risk Tobacco Product (MRTTP) Application from U.S. Smokeless Tobacco Company for its Copenhagen Snuff Fine Cut, a moist snuff smokeless tobacco product. It notes that this product is grandfathered and not subject to premarket review under section 910 of the FD&C Act. A notice establishing a formal docket for public comments on regulations.gov is mentioned for a later date. A section titled 'The following application materials have been redacted in accordance with applicable laws:' lists five redacted items:

- [FOIA Cover Letter](#) (PDF – 45 KB) – posted **September 14, 2018**
- [Executive Summary](#) (PDF – 1.6 MB) – posted **September 14, 2018**
- [Module 1: Cover Letter](#) (PDF – 1.2 MB) – posted **September 14, 2018**
- [Module 2: Table of Contents, Glossary, Summary & References](#) (zip – 2.7 MB) – posted **September 14, 2018**
- [Module 3: Descriptive Information](#) (zip – 11.1 MB) – posted **September 14, 2018**
- [Module 4: Labels, Labeling and Advertising](#) (zip – 10.4 MB) – posted **September 14, 2018**
- [Module 5: Environmental Assessments](#) (zip – 40.4 MB) – posted **September 14, 2018**

- FDA makes available for public comment all MRTPAs
- Any individual or organization may submit electronic or written comments to the open docket
- The public comment period will be open for at least 180 days on all applications under scientific review; FDA will issue a notice in the Federal Register announcing when the comment period will close, which will be at least 30 days from the date the last application documents are posted
- FDA receives both summary reports of submissions as well as all individual comments; comments are reviewed and taken under consideration during the review process

- FDA receives comments in a range of areas, both scientific and non-scientific, including: support or opposition for marketing orders, legal issues, critiques of scientific studies or information submitted, potential impact on state or local policy, published and unpublished data
- Comments are submitted from a variety of sources, including: academia, private citizens, healthcare professionals, public health/advocacy groups, state governments, trade associations, tobacco manufacturers, and tobacco retailers
- FDA has received over 300 public comments across the MRTPA dockets



WEIGHING THE EVIDENCE

- Evaluation of the evidence requires an assessment of the impact of a marketing authorization on both the individual, as well as the population as a whole. Elements include...
 - Effect of modified risk information on tobacco use behaviors (e.g., complete switching, dual use) of particular tobacco user groups (e.g., current smokers, youth)
 - Toxicity of the product
 - Changes in health risks based on tobacco use behaviors and toxicity of the product
- MRTP marketing order issued when the evidence supports a public health benefit

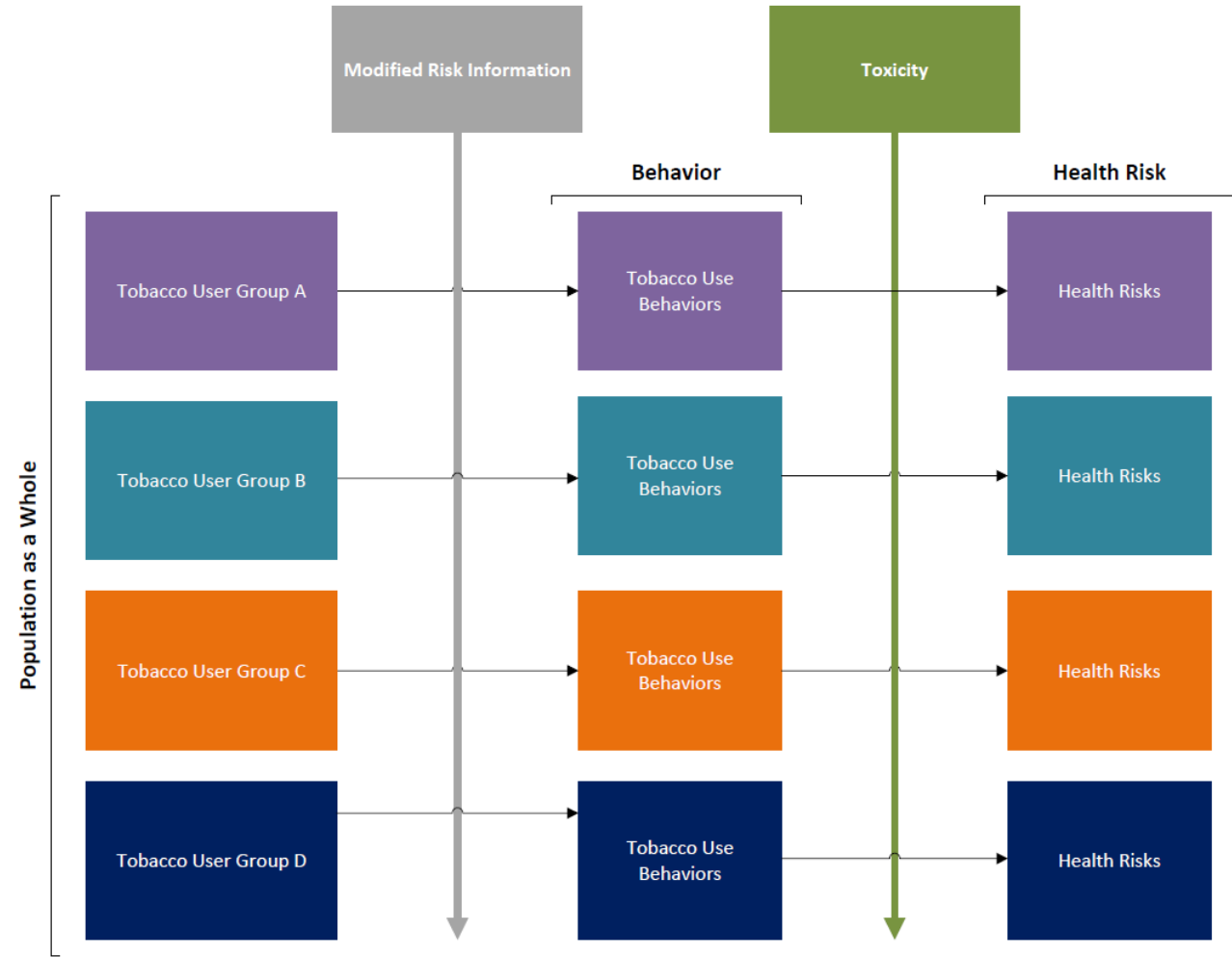


Image used for illustration purposes only

POSTMARKET SURVEILLANCE AND STUDIES (PMSS)

- As stated in Section 911(g)(2)(C)(ii) and (i)(1) of the FD&C Act, each applicant who receives a risk modification or exposure modification order must conduct postmarket surveillance and studies (PMSS)
- PMSS allow for evaluation of the effect of an order on consumer perception, behavior, and health
- As described in the draft guidance available for public comment, FDA proposes that an applicant submit an initial plan for postmarket surveillance and studies that describes the approach that the applicant would undertake, if granted a modified risk order
- As stated in Section 911(g)(2)(C)(iii) and (i)(1) of the FD&C Act, results must be submitted annually



OPPORTUNITIES FOR CLARIFICATION & IMPROVEMENT

- As stated in the draft guidance available for comment, FDA proposes inclusion of the following to facilitate scientific review of applications:
 - Cover letter with information such as company, manufacturer, and contact information, brand/sub-brand name of proposed modified risk product, previous submissions to CTP, satisfaction of premarket review requirements, dates of prior meetings with FDA, and the type of order being sought (i.e., risk modification or exposure modification order)
 - Comprehensive table of contents that precedes a summary of the application
 - Summary of the application with enough detail to provide reviewers with a general understanding of the data and information in the application
 - Tabulated index of all studies and analyses organized by study type (e.g., product analyses, nonclinical studies, human studies, secondary data analyses, modeling) with hypertext link to each study and analysis

ORGANIZING SUBMISSIONS



As stated in the draft guidance available for comment, FDA describes major sections of the application as follows:

Application Section	Description
Descriptive Information	Includes subsections describing: 1) proposed product; 2) formulation of product; 3) conditions for using the product; 4) how consumers will actually use the product
Label, Labeling, and Advertising	<ul style="list-style-type: none">• How applicant intends to communicate the proposed modified risk claims(s) to the public• Copies of proposed advertising and labeling• Sample product labels and labeling
Environmental Impact	Environmental assessment under 21 CFR Part 25
Summary of All Research Findings	Includes key areas such as: 1) health risks; 2) effect on tobacco use behavior among current users; 3) effect on tobacco use initiation; 4) effect on consumer understanding and perceptions; 5) effect on population as a whole
Scientific Studies and Analyses	<ul style="list-style-type: none">• Includes documents related to the research referenced elsewhere in the MRTPA as well as any other documents related to research findings• Organized by study type: product analyses, nonclinical and human studies, secondary data analyses, modeling
Postmarket Surveillance and Studies Plan	<ul style="list-style-type: none">• Includes plans for conducting postmarket surveillance and studies

- Under 911(d)(5) of the FD&C Act, an MRTPA must include:
 - “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 disease 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.”
- Studies relating to the effect of the proposed product on tobacco-related diseases and health-related conditions can include, but are not limited to:
 - Studies conducted on the product itself or components of the product (e.g., product design and information about HPHCs)
 - Studies conducted with users of the product (e.g., market research/consumer insight research; consumer perceptions and understanding studies; those related to population effects)
 - Clinical studies with the product or related products
- As stated in the draft guidance, if any of this information is not available, it is useful for applicants to provide an explanation for the omission(s)

ALL DOCUMENTS: EXAMPLES OF WHAT IS INCLUDED



As communicated to industry through meetings and letters, FDA proposes inclusion of the following:

Examples of What to Include	Examples of What NOT to Include*
Study reports	Cover documents or emails that merely describe the transmission of scientific information (e.g., attached study or protocol)
Protocols and investigator instructions	Case report forms from clinical studies (except those related to participant deaths, other serious and unexpected adverse experiences, or discontinuation)
Analyzable datasets (including a description of how raw data were converted into an analyzable dataset and disposition for all study participants)	Raw chromatograms/spectra/mass spectra arising from analytical chemistry testing
Study instruments and stimuli (e.g., images)	Unprocessed raw data
Statistical analysis plans (if used)	
Statistical software programming code	
Full copies of any published articles and other reference materials	
Individual case report forms related to participant deaths, serious and unexpected adverse experiences, withdrawals where participant was exposed to modified risk product	

*may be asked to submit upon request; FDA expects that any underlying information will still be available for review during Agency inspections of clinical and/or non-clinical study sites

ALL DOCUMENTS: EXAMPLES OF MISSING DOCUMENTS



- In its review of MRTPAs, FDA has noted the following types of missing documents...
 - Full descriptions of quantitative method procedures, including method validation information, for all HPHC testing methods
 - Study protocols, including but not limited to study design, objectives, recruitment, inclusion/exclusion criteria, and study reports
 - Focus group study protocols, study reports, and transcripts/recordings
 - Underlying datasets
 - Statistical program(s) used

SUBMITTING LABELS

- Section 911(d)(4) of the FD&C Act requires submission of sample product labels and labeling
- To facilitate FDA's review of the labels, it is helpful to include:
 - Copies of all labels for all products included in the MRTPAs that reflect the actual size and color proposed
 - Images of the labels that provide a view of the full label



PRODUCT NAME AND VERSION NUMBER



- Section 911(d)(1) of the FD&C Act and 21 CFR § 1105.10(a)(7) require a description of the product that includes the product name of the proposed MRTPs, including brand and sub-brand (if applicable)
- As communicated to industry through meetings and letters, if different versions of the product have been tested, it is useful to clearly identify versions across the application. For example...
 - Clearly identifying and explaining differences in brand name if proposed product was marketed differently in other non-U.S. markets
 - Thoroughly describing differences in product versions, including if/how the product(s) differ from the proposed MRTPs

BRIDGING ACROSS PRODUCTS

- MRTPAs may include a variety of evidence, ranging from product specific studies of the proposed MRTPs to epidemiologic studies that report disease risks of product classes (e.g., smokeless tobacco)
- As communicated to industry through meetings and letters, if applicants provide data from only a subset of the products under review (e.g., studies only include selected sizes or flavors) or a class of products, it is useful to provide bridging data or a scientific rationale for why the findings are relevant to the product(s) under review



PUBLIC AVAILABILITY AND PROPOSED REDACTIONS

- Under 911(e) of the FD&C Act, FDA is required to make applications public
- As described in the draft guidance available for comment, submitting a version of the application that identifies trade secrets, confidential commercial information (CCI), and privacy information for redaction facilitates FDA's ability to make applications available to the public
- Applicants may want to consider the following for proposed redactions:
 - Marking proposed redaction in the text so that the text remains legible (e.g., place a box around the content)
 - Submitting an index that lists the location of each proposed redaction by page number, including (for information that is not privacy information), a statement explaining how content of each proposed redaction qualifies as trade secret or CCI under § 20.61
 - Including a description of competitive harm that would result from disclosure



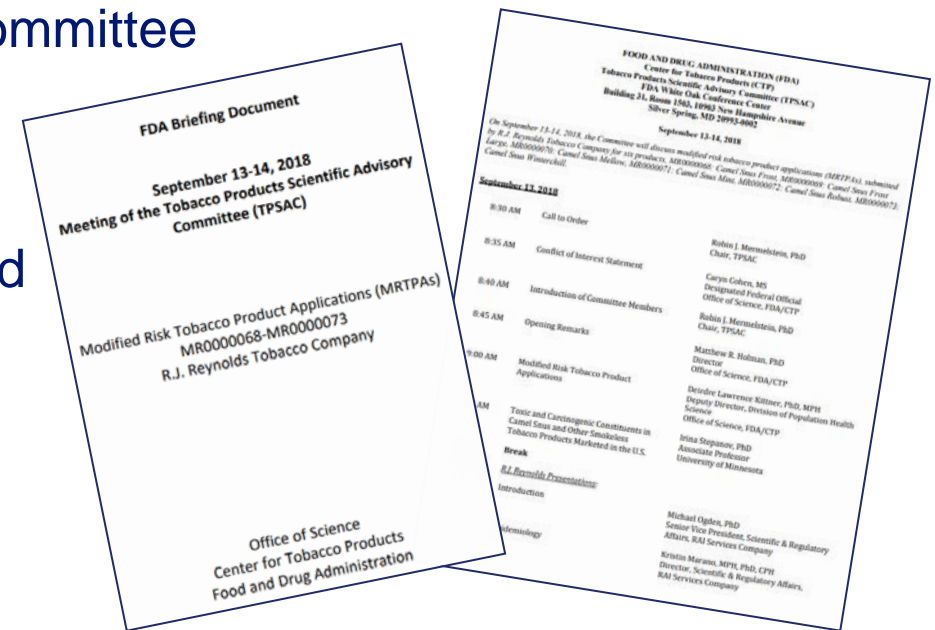
As described in the draft guidance available for public comment, FDA suggests applicants submit all data used to conduct analyses in their MRTPA

- Data may include public use datasets and/or restricted use datasets
- It is helpful for FDA to have the exact dataset that was used by the applicant
- Full datasets, methodology reports, questionnaires, codebooks and programming code facilitate a comprehensive scientific review of applications

TPSAC MEETINGS



- FDA has held 3 TPSAC meetings on MRTPA specific issues
 - Learnings from each meeting have been applied to subsequent meetings
- FDA seeks to maximize the efficiency and productivity of TPSAC meetings by...
 - Focusing the scope of the meeting to select scientific issues from the applications
 - Producing focused FDA background materials for the committee
 - Streamlining FDA presentations
 - Crafting clear, focused questions for the committee
 - Bringing in additional subject matter expertise as needed



THE END

