



# Center for Tobacco Products

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# Draft Guidance on Modified Risk Tobacco Product Applications



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## Disclaimer

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.

# Background

- FDA issued a draft guidance on Modified Risk Tobacco Products (MRTPs) on March 30, 2012.
- CTP is reviewing comments on the guidance and other issues related to MRTPs that have arisen through consultation with other experts including the Institute of Medicine

# Background

- MRTPs are tobacco products sold or distributed for use to reduce harm or the risk of tobacco-related disease; 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 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

# Background

- A tobacco product is also considered an MRTP 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 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

# Background

- In order for an MRTP 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 commercially marketed or introduced or delivered for introduction into interstate commerce.

# M RTP Orders

- Section 911 identifies two approaches for seeking an order from FDA
  - Risk Modification orders (Section 911(g)(1))
  - Exposure Modification orders (Section 911(g)(2))

# Risk Modification Orders

- 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 (g)(1):
  - That the product 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.

# Exposure Modification Orders

- Section 911(g)(2) sets forth the “Special Rule” for MRTPs that present a reduced level of exposure. FDA may issue an order for such products if:
  - The order would be appropriate to promote the public health;
  - The claims for the product are limited to claims that the product does not contain/is free of a substance or presents a reduced exposure to a substance;
  - Scientific evidence to satisfy the (g)(1) standards cannot be made available without conducting long-term epidemiological studies;
  - The available scientific evidence demonstrates that a measurable and substantial reduction in morbidity/mortality among individual users is reasonably likely in subsequent studies

# Exposure Modification Orders

- Applicants seeking an exposure modification order under the (g)(2) pathway must also demonstrate that:
  - The claimed reductions in exposure to harmful substances will actually occur and that users won't be exposed to higher levels of other harmful substances
  - Consumers will not be misled by the product's labeling/marketing into believing the product has been shown to be less harmful than commercially marketed tobacco products
  - Marketing of the product is expected to benefit the health of the population as a whole

# Benefit to Health Standard

In reviewing all MRTPAs, FDA must determine whether the product will offer a benefit to the health of individuals and 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 compared to the use of FDA-approved drug or device products for smoking cessation approved to treat nicotine dependence;
- comments, data and information submitted to FDA<sup>2</sup>

# Additional conditions for MRTP marketing

- If an MRTP is a new tobacco product, applicants must also satisfy any applicable premarket review requirements under section 910 of the FD&C Act

# Additional conditions for MRTP marketing

- As a result, in most cases to market a tobacco product with modified risk claims applicants must file an MRTPA **plus**:
  - a report of substantial equivalence (905(j)(1)(A)(ii));
  - an exemption from SE (905(j)(3)); or
  - a new product application (910(b))
- Applicants have the option to submit a single application for a new tobacco product and an MRTP order

# Procedure for review of MRTPAs

- 360 day review clock (per November 27, 2009 draft guidance)
- MRTPAs must be made publicly available and FDA must request comments from the public on each application
- All MRTPAs must be referred to the Tobacco Products Scientific Advisory Committee (TPSAC) and TPSAC must make a recommendation on each application

# Key Areas of Investigation

- Health Risks of the Tobacco Product
- Effect on Tobacco Use Behavior among Current Tobacco Users
- Effect on Tobacco Use Initiation among Non-Users
- Effect of Marketing on Consumer Understanding and Perceptions
- Effect on the Population as a Whole

# Health Risks of the Tobacco Product

- Risks to users and non-users associated with use of the product;
- Changes in risks to users who switch to using the product;
- Risks as compared to quitting the use of tobacco products;
- Risks of using the product in conjunction with other tobacco products;
- Risks as compared to the use of FDA-approved tobacco cessation medications; and
- Risks as compared to never using tobacco products.

# Effect on Tobacco Use Behavior among Current Tobacco Users

- Likelihood that current users will start using the product;
- Likelihood that individuals who use the product will switch to or switch back to another product of greater individual risk;
- Likelihood that consumers will use the product in conjunction with other tobacco products;
- Likelihood that users will use the product instead of quitting;
- Impact that use of the product may have on overall use behavior;
- Abuse liability of the tobacco product as compared to other tobacco products on the market.

# Effect on Tobacco Use Initiation among Non-Users

- Likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of tobacco products;
- Likelihood that former users of tobacco products will re-initiate use of tobacco products.

# Effect of Marketing on Consumer Understanding and Perceptions

- Ability of consumers to understand the modified risk information and the significance of the information in the context of one's total health;
- Beliefs about the health risks of using the product as compared to other products;
- Beliefs about the health risks of using the product relative to cessation aids; and
- Beliefs about the risks of using the product relative to quitting all tobacco use.

# Effect on the Population as a Whole

Quantify health impact on various segments of consumers:

- Those that are expected to switch from other products;
- Those that are expected to initiate tobacco use;
- Those that are expected to opt to use the proposed product rather than quit;
- Those that are expected to use the product in conjunction with other tobacco products; and,
- Those non-users that may experience health risks from the product.

# Types of Studies and Analyses

- Product analyses
  - e.g., chemical and engineering
- Nonclinical studies
  - e.g., in vitro, in vivo, ex vivo
- Studies in Adult Human Subjects
  - e.g., controlled environments, natural environments, epidemiological, social and behavioral
- Secondary Analyses and Computational Modeling

# Studies to Support an MRTPA

- Product analyses to validate information regarding the formulation of the product;
- Product analyses to assess user and non-user exposure to harmful and/or potentially harmful constituents
- Nonclinical and/or human studies to assess the abuse liability of the product;
- Human studies regarding actual use of the product to determine if users are likely to use the product in a manner that reduces their individual health risks or exposures compared to other commercially marketed tobacco products

# Studies to Support an MRTPA (cont.)

- Human studies regarding consumer perception about the product, including its labeling, marketing and advertising;
- Human studies regarding consumer understanding of the product, including its labeling, marketing and advertising, to assess the ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
- Quantitative estimates of the effect the marketing of the product, as proposed, may have on the health of the population as a whole.

# Additional Studies for a Risk Modification MRTPA

- Human studies that show the product's use will result in a significant reduction in harm and the risk of tobacco-related disease to individual tobacco users.

# Additional Studies for an Exposure Modification MRTPA

- Nonclinical and/or human studies that demonstrate that the substance(s) or exposure(s) that have been reduced are harmful;
- Human studies that demonstrate that the level of exposure to harmful substances has been substantially reduced;
- Nonclinical and/or human studies that demonstrate that use of the product is expected to result in a measurable and substantial reduction in morbidity or mortality to individual tobacco users based on the effects of the product on a validated biomarker of harm or disease;

# Additional Studies for an Exposure Modification MRTPA

- Human studies to evaluate likely impact on the behavior of non-users (initiation/relapse); and
- Human studies that evaluate consumer perception of the proposed labeling and marketing of the product, including beliefs that the product is, or has been demonstrated to be, less harmful, or presents or has been demonstrated to present less risk of disease than one or more other commercially marketed tobacco products.

# Postmarket Studies and Surveillance

- Every MRTP order will require the submission on the part of the MRTP order holder of postmarket data on an annual basis
- Studies must determine the impact on consumer perception, behavior, and health

# Postmarket Studies and Surveillance

- FDA recommends that data be collected from
  - Active surveillance
  - Passive surveillance, and/or
  - On-going studies of impacts on health, behavior and consumer perception

# Issuance of an order under 911(g)

- A modified risk tobacco product may only be marketed using the marketing and labeling specified in the order.
- If an applicant wants to commercially market the modified risk tobacco product with variants of the marketing and labeling, or changes the product design or manufacturing, the applicant must submit an MRTPA and FDA must issue an order before the product may be marketed.

# Renewal of orders

- Both risk modification orders issued under 911(g)(1) and exposure modification orders issued under section 911(g)(2) are effective for a set period of time. An applicant must request renewal of the order by filing a new application to extend commercial marketing.
- FDA will renew such orders if applicable requirements have been satisfied and if FDA finds that the MRTP order is consistent with protection of public health.

# Withdrawal of an order issued under 911(g)

- FDA must withdraw an order under circumstances described in § 911(j), e.g.,
  - Any explicit or implicit representation that the product reduces risk or exposure is no longer valid
  - The applicant fails to conduct or submit postmarket surveillance and studies

# Consultation

- FDA received a report from IOM in December 2011
- In the draft MRTP guidance FDA requests comments from interested parties on the IOM report, including two recommendations:
  - "The FDA should establish guidance that conveys an expected sequencing of studies, such that preclinical work is completed and submitted to the FDA before clinical (human subjects) work commences, and [FDA should establish] that there is a reasonable expectation based on preclinical work that a reduction or lack of harm will be seen in humans."
  - "MRTP sponsors should consider use of independent third parties to undertake one or more key functions, including the design and conduct of research, the oversight of specific studies, and the distribution of sponsor funds for research."

# Consultation

- Public input
  - A public meeting was held August 25-26, 2011
  - An associated docket for public comment closed September 23, 2011
  - Meeting materials and transcripts and comments submitted to the docket were considered in drafting final guidance
- CTP also met with the tobacco industry to learn more about the industry

# Next Steps

- CTP is reviewing the scientific information provided in the docket
- FDA may issue a final guidance or propose regulation once all comments are considered
- FDA will continue to evaluate other scientific issues related to MRTP applications, particularly those raised by the IOM