Guidance for Industry

Modified Risk Tobacco Product Applications

DRAFT GUIDANCE

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For questions regarding this draft guidance, contact the Center for Tobacco Products at (Tel) 1-877-CTP-1373 (1-877-287-1373) Monday-Friday, 9:00 a.m. – 4:00 p.m. EDT.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products

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Guidance for Industry[1]

Modified Risk Tobacco Product Applications

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This draft guidance provides information about submitting applications for modified risk tobacco products under section 911 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387k), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31). Congress found that "[u]nless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause substantial harm to the public health . . . ." Section 2(37) of the Tobacco Control Act. Furthermore, Congress noted that "[t]he dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that [FDA must] ensur[e] that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product." Section 2(40) of the Tobacco Control Act. Thus, Congress recognized that manufacturers must "demonstrate that such products . . . meet a series of rigorous criteria, and will benefit the health of the population as a whole" before marketing tobacco products for use to reduce harm or the risk of tobacco-related disease or to reduce exposures to harmful substances associated with tobacco products. Section 2(36) of the Tobacco Control Act.

The modified risk tobacco product provisions of the FD&C Act may be valuable tools in the effort to promote public health by reducing the morbidity and mortality associated with tobacco use, particularly if companies take advantage of these provisions by making

[1] This guidance was prepared by the Office of Science and Office of Regulations in the Center for Tobacco Products at FDA.

bold, innovative product changes that substantially reduce, or even eliminate altogether, either the toxicity or addictiveness of tobacco products, or both.

Section 911(l)(1) of the FD&C Act directs FDA to issue regulations or guidance (or any combination thereof) on the scientific evidence required for assessment and ongoing review of modified risk tobacco products. This draft guidance, issued pursuant to section 911(l)(1), explains, among other things:

- Who may submit a modified risk tobacco product application under section 911 of the FD&C Act;
- When to submit a modified risk tobacco product application;
- What information the FD&C Act requires you to submit in a modified risk tobacco product application;
- What scientific studies and analyses FDA recommends you submit in a modified risk tobacco product application;
- What information should be collected through postmarket surveillance and studies; and
- How to organize and submit a modified risk tobacco product application.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

This document provides extensive information about the types of scientific studies and analyses FDA recommends that applicants consider conducting in order to provide the evidence needed to support issuance of an order under section 911(g) of the FD&C Act. As with all guidance, applicants can use an alternative approach if that approach would provide the evidence needed to support issuance of an order. FDA encourages anyone who is considering development of, or preparing an application for, a modified risk tobacco product to meet with FDA to discuss what studies would be appropriate for your product, so that you can best use your resources to conduct studies that will support your application. We request comment on the extent of information needed to support FDA's decision-making process under section 911(g) of the FD&C Act.

II. Background

Modified risk tobacco products (MRTPs) are tobacco products that are sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products (see Definitions).

Before an MRTP can be introduced or delivered for introduction into interstate commerce, an order from FDA under section 911(g) of the FD&C Act ("risk

modification order" or "exposure modification order" – see Definitions) must be in effect with respect to the tobacco product. Section 911(a) of the FD&C Act. If the modified risk tobacco product is a new tobacco product within the meaning of section 910(a)(1), any applicable premarket review requirements under section 910 of the FD&C Act must also be satisfied. Section 910(a)(2)(A) of the FD&C Act.

Section 911(g) of the FD&C Act describes the demonstrations applicants must make to obtain an order from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two bases for FDA to issue an order.

In general, FDA shall issue an order under section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated 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 of tobacco products and persons who do not currently use tobacco products.

Section 911(g)(1) of the FD&C Act.

FDA has the authority to require with respect to tobacco products for which risk modification orders are issued that the product comply with requirements relating to advertising and promotion of the tobacco product. Section 911(h)(5) of the FD&C Act.

In the alternative, for products that cannot receive a risk modification order from FDA under section 911(g)(1) of the FD&C Act, FDA may issue an order under section 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Section 911(g)(2)(A) of the FD&C Act.

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

Section 911(g)(2)(B) of the FD&C Act.

In evaluating the benefit to health of individuals and of the population as a whole under sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Section 911(g)(4) of the FD&C Act.

In reviewing any MRTPA and making its determination whether to grant an order under section 911(g) of the FD&C Act, FDA will consider the scientific evidence submitted by

the applicant as well as other scientific evidence or information made available to FDA. Section 911(g)(3) of the FD&C Act.

Furthermore, FDA must ensure, for a risk or exposure modification order, that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions. Section 911(h)(1) of the FD&C Act.

A risk modification order issued under section 911(g)(1) of the FD&C Act will be effective for the period of time specified in the order issued by FDA. Section 911(h)(4) of the FD&C Act. An applicant to whom a risk modification order is issued under section 911(g)(1) must conduct postmarket surveillance and studies and submit the results of such surveillance and studies to FDA annually. Section 911(i)(1) of the FD&C Act.

An exposure modification order issued under section 911(g)(2) of the FD&C Act will be effective for a term of not more than 5 years. FDA may renew an exposure modification order if the applicant files a new application and FDA finds that the requirements for such order under section 911(g)(2) continue to be satisfied. Section 911(g)(2)(C)(i) of the FD&C Act. Further, an exposure modification order will be conditioned on the applicant's agreement to conduct postmarket surveillance and studies and to submit the results of such surveillance and studies to FDA annually. Section 911(g)(2)(C)(ii), (iii) of the FD&C Act.

III. Definitions

This section provides definitions of certain terms used in this guidance.

A. Tobacco Product

"Tobacco product" means "any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)." Section 201(rr)(1) of the FD&C Act (21 U.S.C. 321(rr)(1)). Thus, the term is not limited to products containing tobacco, but also includes components, parts, or accessories of tobacco products, whether they are sold for further manufacturing or for consumer use. For example, cigarette rolling papers and filters are tobacco products, whether they are sold to consumers for use with roll-your- own tobacco or are sold for further manufacturing into a product sold to a consumer, such as a cigarette. This term does not include an article that is a drug, a device, or a combination product as defined in the FD&C Act. Section 201(rr)(2) of the FD&C Act (21 U.S.C. 321(rr)(2)).

B. New Tobacco Product

"New tobacco product" means "any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007." Section 910(a)(1) of the FD&C Act (21 U.S.C. 387j(a)(1)).

C. Modified Risk Tobacco Product

"Modified risk tobacco product" means any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. Section 911(b)(1) of the FD&C Act. Sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products means a tobacco product

(1) that represents in its label, labeling, or advertising, either implicitly or explicitly, that:
    i. the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
    ii. the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
    iii. the tobacco product or its smoke does not contain or is free of a substance;
(2) that uses the descriptors "light", "mild", "low", or similar descriptors in its label, labeling, or advertising;[2] or
(3) for which the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, after June 22, 2009, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially

[2] While cigarettes had been marketed with such descriptors before the Tobacco Control Act was enacted, as of June 22, 2010, manufacturers were prohibited from manufacturing for sale or distribution any tobacco products for which the label, labeling, or advertising contains the descriptors "light," "low," or "mild," or any similar descriptor, without an FDA order in effect under section 911(g) of the FD&C Act. Section 911(b)(3) of the FD&C Act. Furthermore, as of July 22, 2010, manufacturers, including importers of finished tobacco products, were prohibited from introducing into the domestic commerce of the United States any tobacco product for which the label, labeling, or advertising contains the descriptors "light," "low," or "mild," or any similar descriptor, irrespective of the date of manufacture, without an FDA order in effect under section 911(g) of the FD&C Act. *Id.*

marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances.

Section 911(b)(2) of the FD&C Act.[3]

A product that is intended to be used for the treatment of tobacco dependence, including smoking cessation, is not a modified risk tobacco product if it has been approved as a drug or device by FDA and is subject to the requirements of chapter V of the FD&C Act. Section 911(c) of the FD&C Act.

D. Risk Modification Order

A risk modification order is an order permitting the introduction or delivery for introduction into interstate commerce of a modified risk tobacco product that FDA has found meets the criteria for an order under section 911(g)(1) of the FD&C Act. In order for FDA to issue a risk modification order under section 911(g)(1) of the FD&C Act, the applicant must demonstrate 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 of tobacco products and persons who do not currently use tobacco products.

FDA intends to describe in the risk modification order the claim(s) for the tobacco product covered by the order.

E. Exposure Modification Order

An exposure modification order is an order permitting the introduction or delivery for introduction into interstate commerce of a modified risk tobacco product that reduces or eliminates exposure to a substance and for which the available scientific evidence suggests that a measurable and substantial reduction in morbidity and mortality is reasonably likely to be demonstrated in future studies. In order for FDA to issue an exposure modification order, the applicant must satisfy all of the criteria for issuance of an order under section 911(g)(2) of the FD&C Act. An applicant may file an application seeking an exposure modification order only if scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies, for an application to meet the standards set forth in section 911(g)(1).

[3] No smokeless tobacco product shall be considered to be sold or distributed for use to reduce harm or the risk of tobacco-related disease solely because its label, labeling, or advertising uses the following phrases: "smokeless tobacco," "smokeless tobacco product," "not consumed by smoking," "does not produce smoke," "smokefree," "smoke-free," "without smoke," "no smoke," or "not smoke." Section 911(b)(2)(C) of the FD&C Act.

If an applicant is seeking an exposure modification order, any aspect of the label, labeling, and advertising that would cause the tobacco product to be an MRTP must be limited to an explicit or implicit representation that:

- The tobacco product or its smoke does not contain or is free of a substance;
- The tobacco product or its smoke contains a reduced level of a substance; or
- The tobacco product presents a reduced exposure to a substance in tobacco smoke.

FDA intends to describe in the exposure modification order the claim(s) for the tobacco product covered by the order.

IV. General Information

A. Who Submits an MRTPA?

Any person may submit an application seeking an order under section 911(g) of the FD&C Act. The requirements of section 911 of the FD&C Act apply to any tobacco product subject to Chapter IX of the FD&C Act that meets the definition of an MRTP.

Tobacco products subject to Chapter IX of the FD&C Act include the products named in section 901(b) (i.e. cigarettes, cigarette tobacco, smokeless tobacco and roll-your-own tobacco) and tobacco products that have been or may be deemed by regulation to be subject to Chapter IX of the FD&C Act (section 901(b) of the FD&C Act), as well as the components, parts, and accessories of such products (e.g., cigarette rolling papers, filters, or filter tubes sold separately or as part of kits) sold or distributed for consumer use or for further manufacture.

At this time, FDA does not intend to enforce the requirements of section 911 of the FD&C Act for components, parts, or accessories of regulated tobacco products that are both (1) sold or distributed for further manufacturing into finished tobacco products, and (2) not sold or promoted to consumers.

B. When Should You Submit an MRTPA?

Before you may introduce or deliver for introduction into interstate commerce an MRTP, there must be in effect an order under section 911(g) of the FD&C Act. FDA encourages persons to meet with FDA early in their process of developing an MRTP to discuss MRTPA submission and investigational requirements and recommendations. See section IX.B.

Other Required Submissions

If your proposed MRTP is a new tobacco product within the meaning of section 910(a)(1), it is subject to any applicable premarket review requirements under section 910 of the FD&C Act, *in addition to* any requirements under section 911 of the FD&C Act. To introduce or deliver for introduction a new tobacco product into interstate commerce there must be:

- A substantial equivalence order under section 910(a)(2)(i) of the FD&C Act in effect for the tobacco product;
- An exemption of the tobacco product from the requirement to obtain a substantial equivalence order under section 910(a)(2)(i) of the FD&C Act pursuant to a regulation issued under section 905(j)(3) of the FD&C Act; or
- A marketing authorization order issued by FDA for the tobacco product under section 910(c)(1)(A)(i) of the FD&C Act.

The label and packaging of a tobacco product are considered a "part" of that product. A change to any part of a tobacco product after February 15, 2007, makes that product a "new tobacco product."[4] Adding modified risk claims to the label or packaging of a tobacco product that is already commercially marketed makes the tobacco product a new tobacco product. Therefore, in addition to obtaining an order from FDA under section 911(g) of the FD&C Act, the applicant must satisfy the applicable premarket review requirements under section 910 of the FD&C Act.

For details on how to submit a substantial equivalence report under section 905(j) of the FD&C Act (21 U.S.C. 387e(j)), see FDA's Guidance for Industry *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products* (http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM239021.pdf) and FDA's Draft Guidance for Industry *Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions* (http://www.fda.gov/downloads/TobaccoProducts/ResourcesforYou/ForIndustry/UCM271239.pdf). For details on how to request an exemption from the substantial equivalence requirements, see FDA's final rule – *Exemptions from Substantial Equivalence Requirements for Tobacco Products* (76 FR 38961; July 5, 2011) (http://www.gpo.gov/fdsys/pkg/FR-2011-07-05/pdf/2011-16766.pdf). For details on how to submit a Premarket Tobacco Product Application (PMTA) under section 910(b) of the FD&C Act (21 U.S.C. 387j(b)), see FDA's Draft Guidance for Industry *Applications for Premarket Review of New Tobacco Products*

[4] See FDA's Draft Guidance for Industry *Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions.* As discussed in this draft guidance, however, we do not intend to enforce the premarket requirements of sections 905(j) and 910 of the FD&C Act for certain limited modifications to labels and packaging (e.g., if modifications are made to comply with warning label requirements of the Tobacco Control Act).

(http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM273425.pdf).

C. Can I Introduce or Deliver for Introduction into Interstate Commerce an MRTP Without an Order Under Section 911(g) in Effect?

No. Such activity would violate section 911 of the FD&C Act, which provides that an MRTP may not be introduced or delivered for introduction into interstate commerce without an order under section 911(g) in effect with respect to such product. Section 911(a) of the FD&C Act.

Under section 301(pp) of the FD&C Act (21 U.S.C. 331(pp)), introduction or delivery for introduction into interstate commerce of a tobacco product in violation of section 911 is a prohibited act. In addition, under section 902(8) of the FD&C Act (21 U.S.C. 387b(8)), a tobacco product is deemed adulterated if it is in violation of section 911 of the FD&C Act, and the introduction or delivery for introduction into interstate commerce of any adulterated tobacco product is also a prohibited act. Section 301(a) of the FD&C Act (21 U.S.C. 331(a)). Violations of the FD&C Act are subject to regulatory and enforcement action by FDA, including, but not limited to, seizure and injunction. Note, however, that section 911 only applies to MRTPs; a responsible entity can introduce a new tobacco product *without* modified risk claims into interstate commerce so long as they satisfy the applicable premarket review requirements under section 910 of the FD&C Act.

V. Contents of an MRTPA

A. Contents of an MRTPA Required Under Section 911(d)

Under section 911(d) of the FD&C Act, you must provide the following information in your MRTPA:[5]

- A description of the proposed product and any proposed advertising and labeling;
- The conditions for using the product;
- The formulation of the product;
- Sample product labels and labeling;
- 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; and

[5] Under section 911(d)(7) of the FD&C Act, FDA has the authority to require the submission of additional information.

- Data and information on how consumers actually use the tobacco product.

This subsection (V.A) describes information that the Agency recommends you submit for each category of information required by section 911(d)(1)-(6) of FD&C Act. Section VI, in contrast, describes the information that you are required to submit, or that the Agency recommends you submit, to support the scientific demonstrations necessary for the issuance of an order under section 911(g) of the FD&C Act.

1. A Description of the Proposed Tobacco Product and Any Proposed Advertising and Labeling

You must include in your application a description of the product and any proposed advertising and labeling. Section 911(d)(1) of FD&C Act.

FDA recommends that your description of the proposed product include the following information:

- The brand name and, if applicable, subbrand name of the proposed modified risk tobacco product;
- A description of the product form (e.g., traditional cigarette, shredded tobacco, inhaler, liquid, gel, dissolvable strip, stick, or tablet);
- A description of the product dimensions and the overall construction of the product (using a diagram or schematic drawing that clearly depicts the finished product and its components with dimensions, operating parameters, and materials);
- Whether the product uses a heating source and, if so, a description of the heat source (e.g., burning coal or other substance, electric, chemical reaction, carbon tip);
- A description of all design features of the product[6] (e.g., location of ventilation holes, heat source, paper porosity, coatings, nicotine concentration gradient); and
- Any other information relevant to describing the tobacco product, such as whether the tobacco product requires special handling or storage.

FDA recommends that your description of proposed advertising and labeling include the following information, which is important in evaluating whether the product will benefit the health of the population as a whole (section 911(g)(1)(B) and (g)(2)(B)(iv) of the FD&C Act) and how consumers understand the risks posed by the product as the applicant proposes to label and market it (section 911(g)(2)(B)(iii) and (h)(1) of the FD&C Act):

- Copies of any draft promotional materials (e.g., advertising and labeling) developed by the time of filing that the applicant expects will be used in marketing the MRTP. FDA recognizes that some promotional materials may be

[6] Numerical levels should be supplied, where appropriate.

derivative of other materials submitted in the application, representing only minor differences in layout or format, or displaying a different health warning than material submitted in the application. Such derivative materials may be omitted; and,

- A description of how you intend to communicate the proposed modified risk claim(s) to consumers, including any actions directed to consumers that the tobacco product manufacturer or distributor of the tobacco product plans to take to communicate the proposed modified risk claim(s) to consumers (other than by means of the product label, labeling, or advertising).

2. The Conditions for Using the Tobacco Product

You must provide as part of your application "the conditions for using the product." Section 911(d)(2) of the FD&C Act. FDA recommends that you include the following information on conditions for using the product:

- A full narrative description of the way in which a consumer will use the tobacco product, including a description of how a consumer operates the product (e.g., whether a consumer places the tobacco product in the mouth or nose, whether a consumer ignites the tobacco product and by what means, whether the product is designed to be smoked, inhaled, swallowed, dissolved, sniffed, chewed, etc.);
- A description of the length of time it takes a consumer to consume a single unit of the product. The description should be quantitative in nature and include information about the pattern of use during that time (i.e., intermittent or continuous);
- Specific instructions on how to use and store the product to get the proposed reduction in risk or exposure; and
- Specific instructions on how to avoid using the product in a way that could reduce or eliminate the potential benefit or increase the risk of using the product.

3. The Formulation of the Tobacco Product

You must submit as part of your application, "the formulation of the product." Section 911(d)(3) of the FD&C Act. In submitting the formulation of your product, FDA recommends that you include the following:

- A complete list of uniquely identified components, ingredients, and additives by quantity in your tobacco product as well as the applicable specifications and a description of the intended function for each.[7] Components, ingredients, and

[7] For guidance on uniquely identifying components, ingredients, and additives and reporting their quantities, refer to FDA's Guidance for Industry *Listing of Ingredients in Tobacco Products* (http://www.fda.gov/downloads/TobaccoProduct/GuidanceComplianceRegulatoryInformation/UCM192053.pdf). If you have previously submitted this information under another section of the FD&C Act (e.g., a listing of ingredients or new tobacco product application), you can reference that submission in your MRTPA.

additives include anything that may reasonably be expected, directly or indirectly, to become part of, or affect the characteristics of, the finished tobacco product. This includes, but is not limited to tobacco, paper, glue, flavorings, burn-rate controllers, and pH modifiers;

- A description of tobacco blending, reconstitution, or manipulation;
- A description of manufacturing steps, including the sources of all components, and quality control measures in place. The applicant should provide sufficient detail to assure FDA that the product meets manufacturing specifications and that it may be manufactured in a consistent manner that minimizes the variability in levels of exposures and/or risk to users/nonusers across occasions of use;
- A description of how the design, materials, ingredients, and heating source (if applicable) combine to produce the final product;
- A quantitative description of the performance criteria for the tobacco product (e.g., burn rate, ventilation criteria, dissolution rate); and
- Data establishing the stability of the product through the stated shelf life.

FDA recommends that the list of components, ingredients, and additives contain all items used in the synthesis, extraction, and/or preparation of the product, regardless of whether the items are found in the final the product. You should list ingredients by component of the tobacco product, including:

- Chemical Abstract Service number, where applicable;
- Function and purpose;
- Unit of measure; and
- Level used in tobacco product.

4. Sample Product Labels and Labeling

You must include in your application "sample product labels and labeling." Section 911(d)(4) of the FD&C Act. You should include copies of each package label variation (including inserts and onserts) that is proposed to be used for the modified risk tobacco product, except that you may omit copies of package label variations for each health warning required by law.

5. All Documents Relating to Research Findings

You must include in your application all documents (including underlying scientific information) relating to research findings conducted, supported[8], or possessed[9], by the

[8] FDA considers a person to have supported a study if the person in any way provides assistance for the conduct of the study (e.g., by providing funding, personnel or other resources, protocols, product, etc.).
[9] FDA considers research findings possessed to include findings from studies not conducted or supported by the manufacturer, but which it has received, or has reviewed to inform the development of the modified risk tobacco product.

tobacco product manufacturer[10] 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. Section 911(d)(5) of the FD&C Act. The documents required to be submitted under section 911(d)(5) may include documents not in the possession of the tobacco product manufacturer. We request that you submit a description of the procedures you used to collect documents to comply with section 911(d)(5) as well as a list of the entities and individuals from whom you retrieved or attempted to retrieve documents.

You should submit documents relating to research findings from studies conducted both within and outside the United States. See section IX.C for further discussion on the use of studies conducted outside the United States in support of an MRPTA.

In general, for guidance on what constitutes a "document" and otherwise submitting "all documents . . . relating to research finding" refer to FDA's Guidance for Industry *Tobacco Health Document Submission* (http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM208916.pdf).

FDA expects that the applicant will include, among other things, as part of its submission of relevant documents:

- Study reports,
- Study protocols, and
- Raw data (in electronic format, where available, with instructions about its use).

If any of this information is not available, applicants should provide an explanation for the omission.

Additionally, if the applicant is aware of relevant research findings not conducted, supported, or possessed by the tobacco manufacturer, we ask that the applicant include copies of the research findings. Alternatively, if the research findings are found in published literature, applicants can submit a bibliography.

Further guidance regarding how to organize your scientific studies and analyses for submission to FDA is provided in section VIII.A.7.

6. Data and Information on How Consumers Actually Use the Tobacco Product

[10] You should include documents related to research findings conducted, supported, or possessed by entities that are the same, related, or affiliated with the tobacco product manufacturer, as well as any of the tobacco manufacturer's predecessors in interest.

You must include in your application data and information on how consumers actually use the tobacco product. Section 911(d)(6) of the FD&C Act. In providing this information, FDA recommends that you include data generated from consumer use in both controlled situations in which the subjects' use can be closely monitored, and natural environments in which the subjects may use the product as they would without the limitations inherent in a controlled setting. FDA recommends that the data and information provided address:

- Whether consumers can and are likely to comply with any instructions for product use;
- The number of units of the product consumed per day (e.g., cigarettes per day) and the way in which individuals consume each unit of the product (e.g., puffing profiles); and
- Concurrent use of multiple products containing nicotine or tobacco.

B. Other Information

FDA may request other information FDA finds it needs to determine whether a 911(g) order is appropriate.

For example, FDA may request:

- Additional product analyses to verify information provided about specific components, ingredients, additives, or constituents present in the final product
- Data to support comparative claims, i.e., data comparing the tobacco product to a commercially available tobacco product that is representative of that type of tobacco product on the market (see, e.g., section 911(h)(2) of the FD&C Act)
- Samples of the tobacco product
- For products that have been on the market prior to the MRTPA submission, a summary of information that the manufacturer possesses regarding the product, including, but not limited to, adverse events from use of the product, levels of product use in the market, and consumer feedback regarding the product
- For products that have not been on the market prior to the MRTPA submission, a summary of any market research and information that was used to inform the development of the new product and its label, labeling and marketing plan

If you become aware of any new information relating to the effect of the proposed product on tobacco-related diseases and health-related conditions (including adverse events) while your application is pending with FDA, you should promptly provide this information to FDA.

Further, each applicant granted an order under section 911(g) must conduct postmarket surveillance and studies and annually submit the results of the surveillance and studies so FDA can assess, among other things, the impact of an order on consumer perception, behavior, and health. See sections 911(g)(2)(C) and (i)(1) of the FD&C Act. FDA asks

the applicant to submit a plan for postmarket surveillance and studies. The plan should contain sufficient detail for FDA to evaluate whether the results from surveillance and studies will give FDA the information it needs to review the accuracy of the determinations on which it based the order. Section VII, "Postmarket Surveillance and Studies," below, provides information and recommendations.

C. Environmental Impact Considerations

FDA's regulation implementing the National Environmental Policy Act (NEPA) of 1969 requires that "[a]ll applications or petitions requesting agency action require the submission of an [environmental assessment] or a claim of categorical exclusion." 21 CFR 25.15(a).

Currently there are no categorical exclusions in place for tobacco products; therefore, you must submit an environmental assessment as part of your MRTPA. You should refer to 21 CFR Part 25 for additional information.

VI. Scientific Studies and Analyses in MRTPAs

This section sets forth recommendations regarding scientific studies and analyses that should be contained in an MRTPA so that FDA can determine whether the criteria for issuance of an order under section 911(g) of the FD&C Act have been satisfied. FDA encourages anyone who is considering development of, or preparing an application for, a modified risk tobacco product to meet with FDA to discuss what studies would be appropriate for your product, so that you can best use your resources to conduct studies that will support your application.

A. Key Areas of Investigation Regarding the Effect of an MRTP

In determining whether it can issue an order under section 911(g) of the FD&C Act for an MRTP, FDA must assess whether the applicant has demonstrated that the product will or is expected to benefit the health of individuals and the population as a whole. In order for an applicant to demonstrate that its product meets the criteria for issuance of an order under section 911(g) of the FD&C Act, the applicant's MRTPA should address the following key areas of investigation:

- 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.

1. Health Risks of the Tobacco Product

An MRTPA must provide scientific evidence regarding the effect of the product on the health of individuals so that FDA can determine whether the MRTP does, in fact, modify risk as claimed by the applicant and whether FDA can issue an order for such product under section 911(g) of the FD&C Act.

In the case of an application for a risk modification order, the MRTPA must provide scientific evidence to demonstrate that the product significantly reduces harm and the risk of tobacco-related disease to individual users. See section 911(g)(1)(A) of the FD&C Act. In the case of an application for an exposure modification order, the MRTPA must provide scientific evidence to demonstrate that:

- The magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial;
- Such substance or substances are harmful;
- Consumers actually use the product in a way that exposes them to the specified reduced level of the substance or substances;
- Consumers are not exposed to higher levels of other harmful substances, or if they are, those increases are minimal, such that the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in the overall morbidity and mortality among individual tobacco users; and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measureable and substantial reduction in morbidity or mortality is reasonably likely in subsequent studies.

See section 911(g)(2)(A)(iv) and (B)(i) & (ii) of the FD&C Act.

FDA must also assess whether the tobacco product will benefit (see section 911(g)(1)(B) of the FD&C Act) or is expected to benefit (see section 911(g)(2)(B)(iv)) the health of the population as a whole before an order can be issued under section 911(g) of the FD&C Act. To make this determination, FDA must consider, among other things, the risks and benefits to all persons who may potentially use or be exposed to the tobacco product that is the subject of the application, including as compared to the use of products for smoking cessation approved to treat nicotine dependence. Section 911(g)(4) of the FD&C Act.

In order to make the required demonstrations for issuance of an order, FDA recommends that applicants seeking either a risk modification order or an exposure modification order submit:

- Product analyses to validate information provided by the applicant regarding the formulation of the product as it relates to the risk or exposure modification;
- Product analyses to assess users' and non-users' potential exposure to harmful substances; and
- 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 as compared to using other commercially marketed tobacco products.

FDA also recommends that applicants seeking risk modification orders submit:

- 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.

FDA also recommends that applicants seeking exposure modification orders submit:

- Human studies that demonstrate that the level of exposure to harmful substances has been substantially reduced;
- Nonclinical and/or human studies that demonstrate that the substance(s) or exposure(s) that have been reduced are harmful; and
- 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 an endpoint that is reasonably likely, based on epidemiological, therapeutic, pathophysiologic, or other evidence, to predict an effect on reducing harm or disease.

Scientific studies submitted by the applicant regarding the risk of the product should enable FDA to fully assess – whether using clinical risk endpoints in the case of a risk modification order or exposure risk endpoints in the case of an exposure modification order - the health risks of the tobacco product as compared to other consumer behaviors, including:

- The health risks associated with use of the product as compared to using other tobacco products on the market, including tobacco products within the same class of products;
- The changes in health risks to users who switch from using another tobacco product to using the product, including tobacco products within the same class of products;
- The health risks associated with switching to the product as compared to quitting the use of tobacco products;
- The health risks associated with using the product in conjunction with other tobacco products;
- The health risks associated with switching to the product as compared to using an FDA-approved tobacco cessation medication; and

- The health risks associated with initiating use of the product as compared to never using tobacco products.

Where a tobacco product presents novel features that may cause risks to non-users, you should also submit information regarding the health risks posed to non-users of the product.

2. Effect on Tobacco Use Behavior among Current Tobacco Users

In order for FDA to assess the full effect that an MRTP and its marketing may have on population health under section 911(g)(1)(B) or 911(g)(2)(B)(iv) of the FD&C Act, an MRTPA should contain scientific evidence about the effect the product may have on tobacco use behavior among current tobacco users. This includes consideration of areas such as the expected rates of use of the tobacco product by current tobacco users, the use of the tobacco product in conjunction with other tobacco products, and the potential for abuse and misuse of the product. An application must provide evidence regarding whether the product and its marketing will increase or decrease the likelihood that existing users of tobacco products who would otherwise stop using such products would instead switch to the tobacco product that is the subject of the application. See section 911(g)(4)(B) of the FD&C Act.

To address the effect on behavior among current tobacco users, FDA recommends that applicants submit:

- Nonclinical and/or human studies to assess the abuse liability and the potential for misuse of the product as compared to other tobacco products on the market;[11] and
- Human studies regarding actual use of the product and consumer perception of the product, including its labeling, marketing and advertising.

The scientific studies submitted by the applicant should inform FDA's evaluation of the tobacco product's impact on tobacco use behavior, including:

- The likelihood that current tobacco product users will start using the product;
- The likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk;
- The likelihood that consumers will use the product in conjunction with other tobacco products;

[11] Abuse liability is the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product. Physical dependence is characterized by the development of tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping use of the tobacco product. Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently.

- The likelihood that users who may have otherwise quit using tobacco products will instead use the product; and
- The likelihood that consumers will use the product as intended or designed.

3. Effect on Tobacco Use Initiation among Non-Users

A critical population health consideration under section 911(g)(1)(B) and 911(g)(2)(B)(iv) of the FD&C Act is the effect that an MRTP and its marketing will have on tobacco use initiation among non-users (both never users and former users). An MRTPA must contain scientific evidence regarding the effect the product and its marketing will have on increasing the likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application. See section 911(g)(4)(C) of the FD&C Act.

To address the effect of the MRTP on tobacco use initiation, FDA recommends that applicants submit:

- Human studies that evaluate consumer perception of the product, including its labeling, marketing and advertising.

These studies should be designed to provide evidence regarding the likelihood of population benefit or harm from the proposed product, including:

- The likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product;
- The likelihood that non-users who adopt the tobacco product will switch to other tobacco products that present higher levels of individual health risk; and
- The likelihood that former users of tobacco products will re-initiate use with the tobacco product.

4. Effect of Marketing on Consumer Understanding and Perceptions

Another important consideration is the effect that an MRTP and its marketing will have on consumer understanding and perceptions. All MRTPAs must contain evidence to show that the advertising and labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products. See section 911(h)(1) of the FD&C Act.

For exposure modification orders, any aspect of the product's label, labeling, and advertising that would make it a modified risk tobacco product must be limited to an explicit or implicit representation that the product or its smoke does not contain or is free of a substance or contains or presents a reduced level of exposure to a substance. See section 911(g)(2)(A)(ii) of the FD&C Act. Applicants seeking an exposure modification

order must demonstrate through testing of actual consumer perception that the proposed labeling and marketing of the product does not mislead consumers into believing that the product is or has been demonstrated to be less harmful, or mislead consumers into believing that the product presents less of a risk of disease than one or more other commercially marketed tobacco products. See section 911(g)(2)(B)(iii) of the FD&C Act.

To address the effect of marketing on consumer understanding and perception, FDA recommends that applicants submit:

- Human studies regarding consumer understanding of the product, including its labeling, marketing and advertising.

The scientific studies submitted by the applicant should inform FDA's evaluation of the tobacco product's marketing on consumer perception and understanding, including:

- The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
- Consumers' beliefs about the health risks of using the product relative to other tobacco products, including those within the same class of products;
- Consumer beliefs about the health risks of using the product relative to cessation aids; and
- Consumer beliefs about the risks of using the product relative to quitting all tobacco use.

5. Effect on the Population as a Whole

All applicants must demonstrate that the marketing of the tobacco product will or is expected to "benefit the health of the population as a whole." See section 911(g)(1)(B) and 911(g)(2)(B)(iv) of the FD&C Act. Applicants seeking an exposure modification order must further demonstrate that issuance of an exposure modification order would be "appropriate to promote the public health." Section 911(g)(2)(A)(i) of the FD&C Act. Therefore, an MRTPA should contain an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality in the population as a whole.

To address the effect of an MRTP on the population as a whole, FDA recommends that applicants submit:

- Quantitative estimates of the effect the marketing of the product, as proposed, may have on the health of the population as a whole.

The estimates should integrate all of the information regarding the marketing of the product and its potential effects on health, tobacco use behavior and tobacco use initiation to provide an overall assessment of the potential effect that the product's introduction to

the market may have on overall tobacco-related morbidity and mortality. FDA recommends that the applicant estimate the attributable risk of all of the various health effects for various types of individuals in the U.S. population, as well as the total number of individuals of each type. As an illustration, consider a product that an applicant maintains poses one-tenth of the risk of death from lung cancer as compared to smoking cigarettes. FDA recommends that the applicant quantify the potential changes in mortality to the various types of affected individuals in the U.S. population (see bullets below). This would include, among other things, an estimate of the number of smokers who are likely to switch to the product and the subsequent reduction in the number of lives lost due to tobacco use, the number of smokers who may use the product in conjunction with other tobacco products or instead of quitting and the subsequent effect on the number of lives lost due to tobacco use, as well as the number of non-smokers who may initiate use of tobacco with the product and the subsequent increase in the number of lives lost to tobacco use. FDA recommends that a similar approach be used to assess the potential impact on mortality resulting from other diseases, as well as morbidity in the various types of affected individuals in the U.S. population. The types of individuals may include, but are not limited to, the following:

- Tobacco users who switch from other commercially marketed tobacco products to the proposed product;
- Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk;
- Tobacco users who opt to use the proposed product rather than cease tobacco use altogether;
- Tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication;
- Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users;
- Tobacco users who use the product in conjunction with other tobacco products; and
- Non-users who experience health risks from the product.

B. Detailed Considerations Regarding the Recommended Studies and Analyses

Given the breadth of evidence needed to support the issuance of an order under section 911(g) of the FD&C Act, it is unlikely that a single study will provide sufficient evidence to support FDA's issuance of an order. Furthermore, it is unlikely that a set of studies of one type will provide sufficient evidence to support the issuance of an order. Therefore, as described above in section VI.A, FDA recommends that applicants provide information from a number of studies of different types in order to address the full range of areas of investigation set forth in section 911 of the FD&C Act so that FDA can determine whether or not it can issue an order under section 911(g) for the MRTP. These

include product analyses, nonclinical studies, studies in adult human subjects, and secondary data analyses and modeling. Below is a more detailed description of the types of studies and analyses that FDA recommends an applicant use to address the key areas of investigation and recommendations for the conduct of these studies and analyses.

In general, studies should be quantitative in nature[12] and designed in accordance with the principles outlined in section VI.C. The information that follows identifies the various outcomes these studies should assess when evaluating the impact of the tobacco product.

1. Product Analyses

Product analyses regarding the chemistry and engineering of the product may be used to verify and validate the information submitted regarding the formulation of the product. In addition, product analyses will facilitate FDA's understanding of the product, the potential for exposure to harmful or potentially harmful constituents from use of the product, and provide context for evaluating other data submitted in an MRTPA.

For each product, FDA recommends that applicants conduct product analyses to determine levels of harmful and potentially harmful constituents (HPHC), including smoke constituents, as appropriate to the product.[13] Applicants should test for and report on the HPHC list as established by FDA under section 904(d) of the FD&C Act.[14]

In testing your product for HPHCs, you should adhere to any rules or guidance FDA has issued in connection with section 904(a)(3) of the FD&C Act or, as applicable, under section 915. Absent rules or guidance to the contrary, for cigarettes, applicants should determine quantitative levels in smoke using both the ISO and Canadian Intense smoking regimens.[15] For other smoked tobacco products, applicants should determine quantitative levels in smoke using smoking regimens to reflect a wide range of smoking intensities that would be appropriate for the product. Applicants should justify the use of any alternative testing methods.

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[12] The results of qualitative research, e.g., interviews and focus groups, may be submitted to provide insight about how consumers interact with the product or why consumers hold certain beliefs about a product. However, qualitative research alone is not sufficient and will not enable FDA to assess the effect that the product may have on the population.

[13] For a discussion of harmful and potentially harmful constituents, including smoke constituents, in tobacco products or tobacco smoke, see FDA's Guidance for Industry and FDA Staff *"Harmful and Potentially Harmful Constituents" in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act* (http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM241352.pdf).

[14] Further information about the list is available on the Internet (under the Regulatory Information heading) at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm.

[15] The ISO method is available at http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=28325&commid=52158. The Canadian method for measuring emissions from tobacco products is available in Part 3 of SOR 2000-273, available at http://laws-lois.justice.gc.ca/PDF/SOR-2000-273.pdf.

FDA recommends that applicants conduct product analyses on samples of the product manufactured on the same date and complete those analyses within a short timeframe. Where feasible, applicants should also provide data on multiple batches of product to provide evidence that product characteristics remain consistent across batches of production.

2. Nonclinical Studies

Nonclinical studies include *in vitro*, *in vivo*, and *ex vivo* studies. The results of these studies may offer useful information about the health risks and abuse liability of a tobacco product. These studies may also provide context for data obtained from other types of studies, such as product analyses and human studies.

FDA recommends that applicants conduct nonclinical studies to address the known clinical toxicities of tobacco products and evaluate a range of potential toxicities of the product as compared to other tobacco products on the market. Applicants should choose appropriate models for nonclinical studies that are sufficiently sensitive for the evaluation of the selected endpoint and be able to provide support for the model used, including an explanation of the sensitivity and probative value of the model chosen. For *in vivo* animal studies, researchers should administer the test product to animals by a route representative of human exposure, where feasible. Nonclinical toxicology studies should use methods that are sufficiently sensitive to assess the actual differences between use of the product and use of other tobacco products, or between use of the product and non-use of tobacco products.

With respect to abuse liability, nonclinical studies should address differences in the abuse liability of the product compared to other tobacco products currently on the market. An assessment of abuse liability may rely on a battery of studies that could include animal models of conditioned place preference, drug discrimination and self-administration.

3. Studies in Adult Human Subjects

Studies in human subjects (human studies) include clinical investigations, epidemiological studies, consumer perception studies, actual use studies and other studies that involve humans actually consuming or interacting with the product, its proposed labeling and/or marketing materials. Human studies provide FDA with information critical for determining what effect the product may have on the health of individuals and on the population as a whole if the product is commercially marketed as an MRTP.

Health Risks and Tobacco Use Behavior

The types of human studies that can be conducted to evaluate the impact of a tobacco product on health risks and tobacco use behavior include experimental studies (e.g.,

randomized clinical trials); observational epidemiological studies such as cross-sectional surveys, longitudinal surveys, case-controls studies, and cohort studies; and others.

FDA recommends that applicants conduct human studies to assess the full range of the human health risks related to the use of the tobacco product, including exposure to tobacco-related compounds (e.g., biomarkers of exposure) and health outcomes (e.g., disease incidence or mortality), as well as tobacco use behaviors, including initiation of use of the tobacco product among never users and former users, rates that current tobacco users switch to the tobacco product, and patterns of use of the tobacco product by current tobacco users.

When conducting human studies in controlled settings, it is important to adhere to principles of good clinical practices, including adequate human subject protection. Further information on FDA regulations and available guidance documents on this topic can be accessed at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

When conducting observational epidemiological studies, applicants should take measures to reduce or prevent the occurrence of bias and to control for confounding factors, either by using an appropriate study design or applicable statistical methods during data analysis. The applicant should present information on the reliability and validity of measures used to assess the various outcomes.

Actual use

Actual use studies should allow consumers to interact freely with the product in real-world conditions. FDA recommends that these studies assess:

- How the product is consumed in early stages of use;
- How the product is consumed during continued use;
- The frequency and intensity (e.g., depth of inhalation) of product use;
- The amount of the product typically used per occasion;
- The duration of use per occasion;
- The use of the product with other tobacco products (i.e., the use of multiple tobacco products);
- The possible ways that a user may consume the product; specifically those that may differ from that intended by the applicant;
- The likelihood that a user may consume the product in a manner that may differ from that intended by the applicant;
- The potential impact to individual and public health from the failure to use the product as intended; and
- The elements of the product's design and manufacture that may lend themselves to product misuse by users.

Human abuse liability

FDA recommends that applicants conduct human abuse liability studies to assess the impact of various features of the product on the speed and efficiency of nicotine delivery and the formation of unprotonated nicotine. These features may include:

- The presence of pharmacologically active constituents (e.g., nicotine, acetaldehyde, anabasine, and nornicotine);
- Other ingredients in the product (e.g., buffering agents); and
- Design features (e.g., tobacco cut size, use of reconstituted tobacco and/or filter ventilation).

Human abuse liability studies should also assess the threshold dose(s) of nicotine for producing reinforcing effects, discriminative stimulus effects, and physical dependence (e.g., symptoms of withdrawal), accounting for variability of this dose across individuals.

Consumer perception and understanding

In order to assess how consumers perceive the product and its associated labels, labeling, and/or marketing, FDA recommends that applicants conduct consumer perception studies. These studies should provide data regarding how consumers perceive the risks to health from using the product, and the likelihood of trying the product. Furthermore, the applicant should provide data regarding consumer understanding of the product's instructions for use and of the information concerning modified risk in the context of total health. Applicants are encouraged to use methods that assess the impact of repeated exposure to labels and advertising on consumer perceptions.

When designing consumer perception studies, applicants should take care that the studies themselves do not promote use of the product, particularly among vulnerable populations, such as youth, non-users of tobacco products, and pregnant women. FDA recommends that applicants meet with FDA to discuss research plans before embarking on research with vulnerable populations. Section IX.B of this guidance provides information on requesting a meeting with FDA.

Applicants seeking exposure modification orders must also demonstrate that testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful, or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products. See section 911(g)(2)(B)(iii) of the FD&C Act. FDA acknowledges that there may be challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products. As such, FDA recommends, when assessing consumer perception of the product, labeling and/or marketing, that the applicant consider testing several variations of the proposed claim(s) on labels and/or in advertisements. As

indicated previously, the applicant must provide FDA with the results of all studies, both favorable and unfavorable, related to the product. Section 911(d)(5) of the FD&C Act.

4. Secondary Data Analyses and Computational Modeling

FDA acknowledges the difficulties inherent in making premarket assessments of the effect that the introduction of a modified risk product would have on the population as a whole and the public health. FDA encourages the development and application of innovative analytical methods to make preliminary estimates of the potential effects of some change in the marketplace. Methods for making similar estimates are commonly used in the fields of economics, statistics, decision sciences, and demography, and include secondary data analyses and computational modeling. Applicants may opt to use currently available models in the scientific literature to forecast the harm to public health from tobacco use. At this time, FDA does not endorse the use of any particular model. Applicants may also opt to conduct secondary analyses of existing data to provide further insight on the potential effects of modified risk products.

When applying secondary data analyses and computational modeling techniques, applicants should select appropriate techniques, use data from scientific analyses and studies conducted in accordance with the general principles outlined below in section VI.C, and conduct analyses of various scenarios, including worst-case scenarios.

C. General Principles for Scientific Studies and Analyses

This subsection describes sound scientific principles relating to the design and conduct of studies to support submissions to FDA, including MRTPAs. Following these recommendations will help to ensure that researchers and analysts conduct adequate and well-designed studies.

Applicants should conduct well-designed studies and analyses and provide sufficient information about those studies and analyses to allow for critical evaluation and so that other investigators could conduct similar studies and analyses to replicate the applicant's findings. This will help provide adequate assurance that a finding in a study can be replicated to show that the finding is not the result of unanticipated, undetected, or systematic biases, study site or investigator-specific factors, or chance. It will also provide a safeguard against instances in which the results of a study are the product of fraudulent reporting of scientific studies because it allows for verification of study results.

Following these recommendations will also help FDA determine whether the results of an analysis or study can be generalized from the study population under the conditions tested to the population who will use the proposed modified risk tobacco product (e.g., broad segments of the U.S. population) under actual conditions of use.

FDA recommends that studies and analyses conducted to support an MRTPA have the following characteristics:

- Clearly articulated objectives and hypotheses;
- Protocols that employ standardized and validated methods of analysis;
- Sample sizes that permit for robust statistical analyses;
- Designs that permit valid comparisons with appropriate controls for the testing of study hypotheses (selection of the control group(s) should be based on the endpoint or effect to be evaluated[16]);
- Procedures to minimize bias on the part of observers and analysts of the data and prevent undue influences on the results and interpretation of the study data, such as blinding, masking, random assignment to condition, etc.;
- Procedures for the selection of human subjects to allow for generalizability of study results to the U.S. population;
- Methods for assigning subjects to different comparator groups that are appropriate for making comparisons between groups with respect to pertinent variables;
- Oversampling of populations that are particularly likely to be affected, positively or negatively, by the marketing of the product;
- Protocols that allow for conditions of use of the product that are reflective of how the product will actually be used by consumers when it is marketed;
- A study duration to allow for adequate assessment of selected endpoint(s) and/or effects;[17] and
- Analyses that adequately address the effects of the product on the study measures, endpoints or outcomes.

In order to assure the quality and integrity of the data from studies and analyses relied on or referenced in an MRTPA, the studies or analyses should, as applicable:

- Be conducted in laboratories accredited by a nationally or internationally recognized external accreditation organization;
- Use appropriate animal models and adhere to the best practices of refinement, reduction, and replacement of animals in research and to applicable laws, regulations, and policies governing animal testing, for example, the Animal Welfare Act (7 U.S.C. 2131 et seq.) and the Public Health Service Policy of Humane Care and Use of Laboratory Animals (available at http://grants.nih.gov/grants/olaw/references/phspol.htm);

[16] For example, in a study designed to assess the effect of a modified risk tobacco product on disease risk compared to a commercially marketed tobacco product, it would be appropriate to include multiple comparator groups of both the product and the commercially marketed tobacco product based on tobacco use levels (e.g., smokers of less than 10 cigarettes per day, smokers of 10 or more cigarettes per day). In a study designed to assess the impact of a product's labeling on consumer perception of risk, the study may include comparator groups that view product labels that bear alternate versions of the proposed claim(s) or do not bear modified risk claims at all.

[17] For example, a study of the product's effect on cessation from tobacco use would likely require greater duration than a study to assess the topography of product use or consumer perception of the product.

- Implement good laboratory practices, for example, as specified in 21 CFR Part 58;
- Be conducted by qualified and appropriately trained investigators;
- Accurately account for and document the receipt, use, and disposition of all investigational product(s);
- Ensure the protection of human subjects by, for example:
    - Implementing procedures for informed consent, such as those found in 21 CFR Part 50, and
    - Ensuring study oversight by an Institutional Review Board, governed by 21 CFR Part 56.
- Be conducted in accordance with study protocols and implementation procedures that ensure that all study subjects receiving tobacco products are current daily tobacco product users at least 21 years of age.

VII. Postmarket Surveillance and Studies

Each applicant who receives a risk modification or exposure modification order must conduct postmarket surveillance and studies. See section 911(g)(2)(C)(ii) and (i)(1) of the FD&C Act. For the purposes of implementing section 911 of the FD&C Act, postmarket surveillance involves the identification and collection of unanticipated and undesired events related to the tobacco product once it is introduced to the market; postmarket studies generally are prospective, have well-defined study objectives and require active recruitment compared to surveillance.[18]

These postmarket surveillance and studies allow for evaluation of the effect of issuance of an order on consumer perception, behavior, and health, and enable FDA to review the accuracy of the determinations upon which the order was based. *Id*. An applicant who receives a risk modification order must also conduct postmarket surveillance and studies that provide information that FDA determines is otherwise necessary regarding the use or health risks involving the tobacco product. See section 911(i)(1) of the FD&C Act.

Applicants granted a risk modification order must submit protocols for required postmarket surveillance for FDA concurrence within 30 days after receiving notice that they are required to conduct such surveillance. Within 60 days of receipt of the protocol, FDA must determine whether:

[18] We recognize that section 505(o) of the FD&C Act regarding postmarket review of new drugs and the related guidance document (see Guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf) make distinctions between the postmarket studies and postmarket clinical trials. No such distinctions are made in section 911 of the FD&C Act and we do not make such distinctions in this guidance.

- The principal investigator responsible for the surveillance has sufficient qualifications and experience to conduct such surveillance; and
- The protocol will result in collection of the data or other information FDA determines is necessary to protect the public health, including data and information that the MRTP continues to satisfy the requirements for the issuance of an order under section 911(g)(1).

Applicants who receive an exposure modification order must agree to conduct postmarket surveillance and studies in accordance with a protocol approved by FDA. See section 911(g)(2)(C)(ii) of the FD&C Act. FDA recommends that these applicants follow the same timelines that apply to the approval of protocols relating to risk modification orders.

All applicants must submit the results of postmarket surveillance and studies annually. See sections 911(g)(2)(C)(iii) and 911(i)(1). Failure to conduct or submit the required postmarket surveillance and studies is a basis for withdrawal of an applicant's order. See section 911(j)(4) of the FD&C Act. Furthermore, any applicant who fails to conduct or submit the required postmarket surveillance and studies would be liable for civil monetary penalties under section 303(f)(9)(B)(ii) of the FD&C Act (21 U.S.C. 333(f)(9)(B)(ii)), and may be subject to other regulatory and enforcement action by FDA.

In order to ensure that applicants are prepared to satisfy the post-market review requirements in section 911 of the FD&C Act, FDA encourages applicants to submit with their MRTPAs draft protocols and/or detailed outlines of the postmarket surveillance and studies they plan to conduct. FDA will review and comment on these materials and work with applicants in developing appropriate protocols during the MRTPA review process so that a final version of the protocols can be timely completed and approved if an order under section 911(g) is issued.

A. Postmarket Surveillance

In order to grant a risk modification or exposure modification order, the Agency must have sufficient evidence at the time of issuance of the order that marketing of the MRTP will or is expected to benefit the health of individuals and of the population as a whole, taking into account both users and non-users of tobacco products. See section 911(g)(1)(B) and (g)(2)(B)(iv) of the FD&C Act. The knowledge related to the effect of the MRTP on individuals and the population as a whole can change over time due to a variety of factors, including changes in tobacco use behavior, consumer perceptions, and changes in the tobacco product marketplace. During the postmarket period, the MRTP will be used in settings different from studies in human subjects conducted during the development of the MRTP, and a much larger population may be exposed to the product for a much longer term. Therefore, postmarket surveillance is a very important tool for monitoring the effects of the MRTP on individual and population health.

For the purposes of this draft guidance, we identify two types of postmarket surveillance:

- Passive surveillance, which relies on spontaneous reports submitted by tobacco product manufacturers, health care professionals, or consumers; and
- Active surveillance, which relies on an active collection of data. Data may be collected by local agencies (e.g., city, state, American Indian tribal) or through registries established by tobacco product manufacturers, published literature or other sources.

B. Postmarket Studies

The objective of conducting postmarket studies is to gather and assess information about the product after introduction into the marketplace, including but not limited to:

- Data on real world use of the MRTP in a general population of tobacco users;
- Tobacco-related adverse events;
- Longer-term assessment of exposure and health outcomes, including intermediate clinical outcomes and mortality; and
- Ongoing assessment of consumer perception and tobacco use behavior (e.g., initiation, cessation, frequency of use).

C. Outcomes Evaluated in Postmarket Surveillance and Studies

The outcomes evaluated in postmarket surveillance and studies should focus on the effect of the MRTP on consumer perception, behavior and health under real world conditions of use.

Postmarket surveillance and studies of consumer perception should provide data regarding how consumers perceive the risks to health from using the marketed product, and the likelihood they will try the product. These studies should also provide information concerning consumers' understanding of the marketed product's instructions for use and its modified risk claims.

Postmarket surveillance and studies of consumer behavior should provide data with respect to the effect the product's marketing has on whether current tobacco users switch to the product from their usual product, whether current tobacco users continue using the product, whether current tobacco users who would otherwise cease all tobacco use switch to the product instead, and whether non-users start using the product.

Postmarket surveillance and studies of consumer health should provide data with respect to the health risks of the MRTP, including the effect the product has on tobacco-related morbidity and mortality. Surveillance and studies should measure the health risks to individuals from using the product as compared to using other tobacco products or quitting use of tobacco products. Specific health outcomes to consider may include, but are not limited to:

- New diagnosis or worsening diagnosis by health care providers of particular disease risks that may be associated with the use of the MRTP, including the risk of development of cancers, stroke, cardiovascular diseases, non-malignant respiratory diseases, fetal toxicity, oral/dental diseases, etc.
- Occurrence of emergency room visits or hospitalizations for illnesses associated with the use of the MRTP (e.g., rate of hospitalization and the proportion of subjects with hospitalizations for tobacco-related illness).
- Physiologic or blood chemistry parameters of MRTP users such as HPHC levels, measures of biomarkers of exposure, measures of biomarkers of disease, ECG, and pulmonary function testing.

Adverse Events[19]

An important component of postmarket surveillance and studies is to collect information on adverse events that occur in relation to a product. For purposes of this draft guidance, an adverse event (AE) is any health-related event associated with the use of a tobacco product in humans that is adverse or unfavorable, whether or not it is considered tobacco-product related.[20] An AE can arise from any use of the product (including use in combination with other products and overdose).

Postmarket surveillance and studies should identify adverse events and provide data on their nature, frequency, and potential risk factors so that informed decisions on risk minimization can be made. A serious AE is an AE that results in any of the following:

- Death;
- A life-threatening condition or event;
- Persistent or substantial disability or incapacitation;
- Hospitalization or prolonged hospitalization; or
- A congenital anomaly or birth defect.

You should report all adverse events that occur during surveillance or while monitoring studies. Non-serious AEs should be reported as part of your annual submission of the results of postmarket studies and surveillance. FDA requests that serious AEs be reported to CTP's Office of Science within 15 business days after the report is received by the applicant.

D. Design of Postmarket Studies and Active Surveillance

Depending on the study objectives, the study design used for postmarket studies could include observational epidemiological studies, interventional studies, such as randomized

[19] Section 909(a) of the FD&C Act directs FDA to issue regulations requiring the reporting of adverse events for tobacco products. FDA has not yet issued such regulations.

[20] Your submission will not be construed by FDA as an admission that the tobacco product involved caused or contributed to the adverse event being reported. See section 756 of the FD&C Act (21 U.S.C. 379v).

clinical trials, or studies of other design. For all studies and active surveillance, the draft protocol or the outline submitted to FDA with your MRTPA should include the following elements:

- Objective(s);
- Hypotheses;
- Background information (e.g., a critical review of the literature, brief description of the new tobacco product and any regulatory history, the significance of the study to be conducted);
- Design and setting (e.g., clinic, community) of the study;
- Sample size and power calculation (please specify strata and clustering as appropriate);
- Relative standard errors for subgroups (if appropriate);
- Study population (selection of study population, number of subjects to be enrolled, inclusion/exclusion criteria, comparison group(s));
- Primary and secondary endpoints (definition and success criteria);
- Statistical analysis plan (description of the statistical methods to be employed, the reason for your choice of sample size, including calculations of the power of each study, and the level of significance and/or confidence level to be used);
- Data collection procedures and instruments;
- Baseline and follow-up assessments and duration of follow-up;
- Case report forms;
- Documentation describing steps to be taken to ensure the protection of human subjects, for example, proposed informed consent and IRB approval forms; and
- Study milestone and timeline elements, including study initiation, annual enrollment goals, completion of enrollment, completion of follow-up, and submission of final report.

VIII. Submission Information

A. Organizing Your MRTPA for Submission to FDA

You should organize your MRTPA into the following distinct sections:

1. Cover Letter

The cover letter should contain:

- The name and address of your company;
- An authorized contact's name, title, address, phone number, fax number, and email address;
- The brand name and, if applicable, subbrand name of the proposed modified risk tobacco product;

- The name of the manufacturer;
- A list of all previous submissions to CTP for the proposed MRTP product or any product that is the same except for the claims that are the subject of your application, e.g., a submission of listing of ingredients in tobacco products submitted pursuant to section 904 of the FD&C Act, a substantial equivalence report, a request for an exemption from substantial equivalence, or a premarket tobacco product application, or a previous MRTPA, and what action FDA took as a result of any such submission;
- A statement regarding how you have satisfied, or intend to satisfy, any applicable premarket review requirements under section 910 of the FD&C Act;
- A list of dates of any prior meetings with FDA about the tobacco product that is the subject of the MRTPA;
- A statement whether you are seeking a risk modification order or an exposure modification order; and
- A description or listing of the specific portions of the application you believe constitute trade secret or confidential commercial information that is exempt from disclosure. In the alternative, you may submit a second version of the application with transparent highlights of proposed redactions. (See section X, Confidentiality, for more information).

2. Table of Contents and Summary

A comprehensive table of contents should precede a summary of the application and all other sections of the application.

The application should contain a summary of the application in enough detail that the reader may gain a good general understanding of the data and information in the application, including the quantitative aspects of the data. The summary should discuss all aspects of the application, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific journals. To the extent possible, data in the summary should be presented in tabular and graphic forms. The summary should contain the following information:

- The proposed modified risk claims;
- A statement briefly describing the type of tobacco product and providing the scientific rationale for the potential benefits of the tobacco product;
- A summary of the information and scientific data submitted in the application; and
- A concluding discussion describing how you have met each of the relevant statutory requirements for the type of order you are seeking under section 911(g) of the FD&C Act.

3. Descriptive Information

The application should contain a section that includes the following descriptive subsections:

- A subsection describing the proposed product;
- A subsection describing the formulation of the product;
- A subsection describing the conditions for using the product; and
- A subsection describing how consumers actually use the product. [21]

See section V for guidance about the information that should be contained in each of these descriptive subsections.

4. Labels, Labeling and Advertising

The application should contain a section describing how the applicant intends to communicate the proposed modified risk claim(s) to the public and including copies of proposed advertising and labeling and sample product labels and labeling as described above in section V.A.1 and 4.

5. Environmental Impact

The application should contain an environmental assessment under 21 CFR Part 25.

6. Summary of All Research Findings

The application should contain a section summarizing all of the research findings related to the product, both favorable and unfavorable. FDA recommends that this portion of the application be organized according to the key areas described in section VI.A:

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

We also recommend that applicants include a tabulated index of all studies and analyses organized by the key areas above. This index should also be organized by study type (product analyses, nonclinical studies, studies in adult human subjects, secondary data analyses and modeling) and identify each study and analysis by name, section and page numbers. For electronic submissions, the index should also include a hypertext link to

[21] Findings from actual use studies should be submitted as part of your summary of all research findings.

each study and analysis. If any of the documents provided appear in peer-reviewed literature, please provide a citation.

7. Scientific Studies and Analyses

This section should include the documents relating to the research referenced elsewhere in the MRTPA as well as any other documents related to research findings conducted, supported, or possessed by the tobacco product manufacturer. See section V.A.5. To facilitate review, the documents relating to research findings should be complete and well-organized.

Applicants should organize studies by study type (i.e., product analyses, non-clinical studies, human studies, and secondary analyses and modeling) and follow the submission recommendations below for each study type.

Product Analyses

FDA recommends reporting HPHC information in a tabular format using separate columns, in the order listed below (from left to right) for each of the following:

- The constituent name;
- The constituent's common name(s);
- The corresponding Chemical Abstract Services (CAS) number;
- The unit of measure;
- The level measured for the proposed product (with 95% confidence intervals);
- The sample size; and
- The method of measuring and reference quotes.

FDA recommends separate tables for results generated using the ISO and Canadian Intense smoking regimens, when applicable. Documentation of laboratory accreditation should be included in the MRTPA.

FDA recommends reporting information related to other product features (e.g., total particulate matter, packaging, shelf life, etc.) as follows:

- Mean level measured for the product (with 95% confidence intervals);
- Unit of measure;
- Sample size;
- Test method, linked to method defined within design specifications;
- Test date and location; and
- Product lot number or the date of manufacture.

Nonclinical and Human Studies

For individual study reports, the applicant should submit descriptions of:

- The study objective;
- The hypotheses tested;
- The study design;
- The study population, animals, bacteria strain, or cell line; including sample size, and comparator groups;
- The methods of data collection and analysis; and
- The findings, key limitations, and conclusions.

In addition, the following information should be included, where applicable:

- The original study protocol(s) used;
- Any amendments (which should be dated) to the study protocol;
- The final study protocol;
- A justification for the method selected, i.e. appropriateness for the evaluation of the selected endpoint;
- All raw data and data files used to generate the results;
- The questionnaires used;
- Any transcripts or recordings of interviews and focus groups, where applicable;
- Case report forms;
- For nonclinical studies, documentation describing the actions taken to ensure reliability and validity of the study (for example, documentation of good laboratory practices as specified in 21 CFR Part 58);
- Documentation describing the actions taken to ensure the protection of human subjects (for example, documentation of study oversight by a qualified Institutional Review Board duly constituted and operating under 21 CFR Part 56, and documentation of informed consent procedures such as those described in 21 CFR Part 50);
- A detailed description of the statistical analyses employed, including all variables, confounders, and subgroup analyses, and a full report of the findings;
- Information on Data Monitoring Committee members;
- Information on any contract research organization if obligations were transferred for the conduct of any study; and
- Investigator expertise and credentials.

For each study, the report should also identify whether the study was conducted by or on the applicant's behalf.

Secondary Data Analyses and Modeling

For other analyses and modeling, the applicant should provide:

- Explanations and justification of the technique used;
- Assumptions used in the development of any models and parameters;
- A listing of the parameters used in the analyses and/or models;
- Data used to derive parameters or estimates and a rationale for the applicability of the data for the given parameter; and
- The results of various scenarios, including worst-case scenarios.

Applicants should also address the inherent uncertainty in these approaches as they discuss the results derived from available secondary data and use of computational models.

B. Single Application

Section 911(l)(4) of the FD&C Act requires FDA to permit the filing of a single application for any tobacco product that is a new tobacco product under section 910 of the FD&C Act and which the applicant seeks to commercially market with modified risk claims. Accordingly, if the tobacco product for which you are seeking an order under section 911(g) of the FD&C Act is a new tobacco product for which you must also satisfy applicable premarket review requirements under section 910 of the FD&C Act, you may file a single application. The single application must include the information required for the applicable premarket review (i.e., a substantial equivalence report, request for exemption from substantial equivalence requirements, or the information required for premarket review under section 910(b) of the FD&C Act), as well as the information required to support issuance of an order under section 911(g) of the FD&C Act.

If you file a single application, it should be organized as follows:

- Cover letter. The cover letter should include:
  - Identification of the submission as a single application permitted under section 911(l)(4) of the FD&C Act;
  - The name and address of your company;
  - An authorized contact's name, title, address, phone number, fax number, and email address;
  - The brand name and, if applicable, subbrand name of the tobacco product;
  - The name of the manufacturer;
  - A list of all previous submissions to CTP for the proposed MRTP product or any product that is the same except for the claims that are the subject of your application, e.g., a submission of listing of ingredients in tobacco products submitted pursuant to section 904 of the FD&C Act or a previous MRTPA, and what action FDA took as a result of any such submission;

- A statement regarding what type of premarket review you are seeking (a substantial equivalence determination, an exemption from substantial equivalence requirements, or a marketing authorization order under section 910(c)(1)((A)(i));
- A list of dates of any prior meetings with FDA about the tobacco product that is the subject of the MRTPA;
- A statement whether you are seeking a risk modification order or an exposure modification order; and
- A description or listing of the specific portions of the application you believe constitute trade secret or confidential commercial information that is exempt from disclosure. In the alternative, you may submit a second version of the application with transparent highlights of proposed redactions. (See section X, Confidentiality, for more information).

- Premarket review information. Your application must contain all the information required for a substantial equivalence report, request for exemption from substantial equivalence requirements, or for premarket review under section 910(b) of the FD&C Act. For details on how to submit a substantial equivalence report under section 905(j) (21 U.S.C. 387e(j)), see FDA's Guidance for Industry *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products* and FDA's Draft Guidance for Industry *Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions*. For details on how to request exemptions from the substantial evidence requirements, see FDA's final rule – *Exemptions from Substantial Equivalence Requirements for Tobacco Products* (76 FR 38961; July 5, 2011). For details on how to submit a Premarket Tobacco Product Application (PMTA) under section 910(b) (21 U.S.C. 387j(b)), see FDA's Draft Guidance for Industry *Applications for Premarket Review of New Tobacco Products*.
- Modified risk information. Your application must also contain all the information required for issuance of a modified risk order under section 911(g) of the FD&C Act. To the extent data or information contained in the premarket review portion of the application is also relevant to or required for the modified risk determination, you may cross-reference that data or information rather than duplicating it in the modified risk portion of the application.

C. How and Where Should I Submit My MRTPA?

In order to ensure the accessibility of documents and facilitate more effective and efficient communication between you and FDA regarding your submission, FDA recommends that you do the following:

- Uniquely number all pages of your submission using continuous pagination;
- Provide English translations for any foreign language documents. Applicants should also provide the original foreign language document and certification that the translation into English is accurate; and

- Create and submit a glossary or explanation of any abbreviations, acronyms, or industry-specific terminology or codes.

There are three ways to submit your MRTPA:

- Electronic format submitted via the FDA Electronic Submission Gateway;
- Electronic format submitted on physical media (e.g., CD or DVD); or
- Paper format.

FDA strongly encourages you to submit your MRTPA in an electronic format to facilitate efficiency and timeliness of data submission and processing. You can securely submit your application via the FDA Electronic Submissions Gateway (ESG). To prepare for this capability, please refer to the ESG website instructions for setting up a WebTrader account at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm114831.htm.

MRTPAs submitted in paper or on electronic media should be sent to:

Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Physical Electronic Media

Files submitted on electronic media should be stored on a CD/DVD or flash drive media. Electronic media should be labeled with your company name, a contact phone number, "Modified Risk Tobacco Product Application - *name of proposed modified risk tobacco product*," submission date, and series number (e.g., "disc 1 of 2"). The files should include a signed cover letter prominently identified as a "Modified Risk Tobacco Product Application," and should also identify the software (name, version, and company) that you used to confirm the submission is free of viruses or other malware. In case we have difficulty accessing the digital media, we recommend that you also include a paper copy of the cover letter that prominently identifies the submission as a "Modified Risk Tobacco Product Application – *name of proposed modified risk tobacco product*" and includes the manufacturer's name, address and phone number.

Electronic Submission Formats

For MRTPAs submitted in electronic format, we recommend that all content (including the cover letter), except raw data, be in Portable Document Format (PDF) files compatible with Adobe Acrobat 6.0 or higher. Files should not be password protected or encrypted. In preparing your submission in PDF format, we recommend that you:

- Create PDF files directly from an electronic source such as a word processing file or excel;
- Avoid image-only based PDF files whenever possible because scanned images are more difficult to read and search. If you scan a document to create a PDF file, we recommend that you capture text by optical character recognition (OCR) software so that the text of the resulting electronic documents is reasonably accessible and searchable;
- Create a submission table of contents and format it using bookmarks designed to help the reader navigate through the document efficiently.

Any raw data submitted with an MRTPA should be submitted in an electronic source file format such as Microsoft Excel or SAS transport file.

D. What Happens After You Submit an MRTPA?

FDA will first conduct an administrative review of your MRTPA for completeness. Applicants should prepare complete, high quality submissions that facilitate FDA's complete and timely review. If FDA finds that your MRTPA does not contain information required by section 911 of the FD&C Act for a risk modification order or exposure modification order,[22] FDA may refuse to file your application.

FDA may request additional information to clarify issues, ask questions that arise during the review process, and ask for updates on ongoing studies.

As required by section 911(f) of the FD&C Act, FDA will refer your application to the Tobacco Products Scientific Advisory Committee (TPSAC) and ask TPSAC to report its recommendations on the application to FDA within 60 days. FDA will also make the application available to the public (except for matters in the application that are trade secrets or otherwise confidential commercial information) and request comments pursuant to section 911(e) of the FD&C Act. FDA intends to make the application available to the public through FDA's Center for Tobacco Products' website: http://www.fda.gov/TobaccoProducts/default.htm.

E. Can I Withdraw My Pending MRTPA?

You may withdraw your pending MRTPA at any time. You should promptly notify FDA in writing of your decision to withdraw your application. Withdrawal of an MRTPA does not prevent you from submitting a subsequent MRTPA for the same tobacco product in the future. However, any subsequent MRTPA should be complete without referencing data or any other information in the original MRTPA. FDA intends to act upon any subsequent MRTPA no later than 360 days after its receipt.

[22] For example, FDA may refuse to file your application if you do not provide sample product labels and labeling required by section 911(d)(4), or for an exposure modification order, you do not provide results from testing of actual consumer perception required by section 911(g)(2)(b)(iii).

F. What is FDA's Timeframe for Review of an MRTPA?

FDA intends to act upon your MRTPA no later than 360 days after the receipt of an application that contains the information required by section 911 of the FD&C Act.[23]

Similarly, if you choose to file a single application seeking authorization to market your new tobacco product under section 910 of the FD&C Act and an order under section 911(g) of the FD&C Act, FDA intends to act upon your single application no later than 360 days after its receipt.

G. What Happens After an Order Under Section 911(g) of the FD&C Act is Issued?

An applicant granted an order under section 911(g) of the FD&C Act may commercially market the tobacco product as described in the order issued by FDA. Note that an order under section 911(g) is issued for specific modified risk claims. Introducing or delivering for introduction into interstate commerce a tobacco product the label, labeling, or advertising of which makes modified risk claims other than those described in the product's order is a violation of section 911 of the FD&C Act.

Furthermore, the 911(g) order is issued for the product that is the subject of the MRTPA. Introducing or delivering for introduction into interstate commerce a tobacco product other than that described in an order issued under section 911(g) of the FD&C Act may cause the tobacco product to be in violation of section 911 of the FD&C Act. If an applicant makes changes to the product that would trigger the premarket requirements of section 905(j) or 910 of the FD&C Act,[24] the applicant must (in addition to satisfying any applicable premarket review requirements under section 910 of the FD&C Act) submit an MRTPA and FDA must issue an order under section 911(g) of the FD&C Act for the new tobacco product. Note that FDA's Guidances for Industry *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Product* and *Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions* describe changes that can be made to tobacco products for which FDA does not intend to enforce the premarket review requirements of section 905(j) and 910 of the FD&C Act. In such situations, FDA also does not intend to enforce the premarket review requirements of section 911.

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[23] For additional information regarding timing of FDA's review of MRTPAs refer to FDA's Draft Guidance for Industry, *Preliminary Timetable for the Review of Applications for Modified Risk Tobacco Products under the Federal Food, Drug, and Cosmetic Act* (http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM191915.pdf).

[24] FDA's Guidance for Industry *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products* and FDA's Draft Guidance for Industry *Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions* provide further guidance on the changes to a tobacco product that make it a "new tobacco product."

H. Can FDA Withdraw an Order Issued Under Section 911(g)?

Yes. The grounds for withdrawal of an order issued under section 911(g) are set forth in section 911(j) of the FD&C Act.

I. Can I Renew an Order Issued Under Section 911(g)?

An exposure modification order issued under section 911(g)(2) of the FD&C Act will be effective for a term of not more than 5 years. FDA may renew an exposure modification order if the applicant files a new application and FDA finds that the requirements for such order under section 911(g)(2) continue to be satisfied. Section 911(g)(2)(C)(i) of the FD&C Act.

A risk modification order issued under section 911(g)(1) of FD&C Act will be effective for the period of time specified in the order issued by FDA. Section 911(h)(4) of the FD&C Act. FDA may renew a risk modification order if the applicant files a new application and FDA finds that the requirements for such order under section 911(g)(1) continue to be satisfied.

When submitting an application for renewal of an order issued under section 911(g), you should ensure that you have complied with applicable requirements to provide results from the required postmarket surveillance and studies conducted pursuant to your order. Section 911(g)(2)(C)(iii) and 911(i)(1) of the FD&C Act. You should also submit with your application any updated study results from and all data collected in the required postmarket surveillance and studies. See section 911(l)(1)(E) and 911(d)(5) of the FD&C Act.

IX. Investigational Use of Tobacco Products

A. Exemptions for Investigational Use of Tobacco Products

You must file an MRTPA and obtain an order from FDA under section 911(g) of the FD&C Act before you can introduce or deliver for introduction into interstate commerce a modified risk tobacco product. Section 911(a) of the FD&C Act. FDA plans to issue regulations pursuant to section 910(g) of the FD&C Act (21 U.S.C. 387j(g)) providing conditions under which modified risk tobacco products may be exempted from the requirements of section 911 of the FD&C Act when used for investigational purposes. Until these regulations are issued, FDA will consider exercising discretion in enforcing the requirements of section 911 of the FD&C Act, in some circumstances, for the purposes of allowing investigational use of proposed modified risk tobacco products.

Specifically, at this time, FDA does not intend to enforce the requirements of section 911 of the FD&C Act with respect to the use of proposed modified risk tobacco products in studies that follow the specifications listed below that will help ensure that the studies are

well-controlled, data derived from such studies are reliable, and study subjects are adequately protected.

For all studies (both human and nonclinical), you should:

- Limit direct distribution of the proposed modified risk tobacco product to qualified and appropriately trained investigators;
- Not promote for commercial distribution or test market the proposed modified risk tobacco product;
- Account for receipt, use, and disposition of all investigational product(s), and
- Label the product "for investigational use only."

For human studies, you should:

- Take measures to ensure the reliability and validity of the study, for example, through sound study design and adherence to study protocol. In addition, you should ensure that all studies are conducted such that the rights, safety, and welfare of human subjects have been protected in accordance with ethical principles acceptable to the world community and that the data are scientifically valid. One approach to implementing such measures would be to conduct the study in accordance with appropriate provisions found in 21 CFR Part 50 (informed consent of human subjects) and ensure that the IRB oversight is governed by 21 CFR Part 56 (IRB review and approval of clinical investigations). Additional information about informed consent and IRBs can be found in FDA's guidance documents. Applicants with specific questions about human subject protections are encouraged to contact the Center for Tobacco Products.
- Ensure that all study subjects receiving product be current daily tobacco product users at least 21 years of age.

For nonclinical studies, you should:

- Take measures to ensure the reliability and validity of the study. One approach to implementing such measures would be to follow good laboratory practices as specified in 21 CFR Part 58. Additional information about good laboratory practice regulations can be found in FDA's guidance documents. Applicants with specific questions about good laboratory practice regulations are encouraged to contact the Center for Tobacco Products.

Applicants who would like to conduct research using their modified risk tobacco products should contact the Office of Science at the Center for Tobacco Products to discuss the submission of a study protocol and/or study endpoints for investigations intended to support an MRTPA.

B. Requesting a Meeting with FDA

You should send your request for a meeting in writing to the Director of CTP's Office of Science at the following address:

Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The meeting request should include adequate information for FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss the proposed agenda items, including the following:

- A brief statement of the purpose of the meeting, including the name of your new tobacco product, a brief description of the product, and the role of your planned study(s) in overall product development plans;
- A list of your specific questions grouped by discipline;
- A proposed agenda, including objectives and outcomes expected from the meeting;
- A list of all individuals (including titles) expected to attend the meeting on your behalf; and
- An investigational plan to support the demonstrations required for issuance of an order under section 911(g) of the FD&C Act.

We recommend that the summary of your proposed study protocol(s) include the following information:

- Study objective(s);
- Study hypotheses;
- Background information (a brief description of the modified risk tobacco product and any regulatory history);
- Study design;
- Study population (number of subjects to be enrolled, inclusion/exclusion criteria, comparison group(s));
- Human subject protection information, including IRB information;
- Primary and secondary endpoints (definition and success criteria);
- Statistical analysis plan (description of the statistical methods to be employed, the reason for your choice of sample size, including calculations of the power of each study and the level of significance and/or confidence level to be used);
- Data collection procedures; and
- Baseline and follow-up assessments and duration of follow-up.

Pre-meeting preparation is critical for achieving a productive discussion or exchange of information. After FDA schedules a meeting, we request that you submit a fully paginated meeting package, organized according to the final agenda, containing a detailed description of your product, the status of product development, an investigational plan for evaluating whether the product meets the criteria for issuance of an order under section 911(g) of the FD&C Act (including a summary of your proposed study protocols), the specific questions to be discussed, and background information relevant to those questions.

FDA's receipt of a complete meeting package, including clearly articulated questions for FDA, well in advance of a meeting will enable FDA staff to review the information adequately and is therefore important to achieving a productive meeting.

C. Studies Conducted Outside of the United States

You may submit studies of your product conducted outside the United States as part of your MRTPA. You should follow the general principles for scientific studies and analyses described in section VI.C. All human studies conducted outside the United States should be conducted to ensure that the rights, safety, and welfare of human subjects have been protected in accordance with ethical principles acceptable to the world community and that the data are scientifically valid and applicable to the U.S. population. The investigator should conduct these studies in conformance with international standards for good clinical practices or obey the laws and regulations of the country in which the research is conducted, whichever affords the greater protection of human subjects. These patient protection and data integrity measures ensure that data from studies conducted outside the United States are from adequate and well-designed studies and provide reliable information to FDA.

X. Confidentiality

Information submitted under section 911 of the FD&C Act may include, but is not limited to, a company's non-public, trade secret, or confidential commercial information.

Several laws govern the confidentiality of tobacco product information submitted under section 911 of the FD&C Act, including sections 301(j) and 906(c) of the FD&C Act (21 U.S.C. 331(j) and 387f(c)), the Trade Secrets Act (18 U.S.C. 1905), and the Freedom of Information Act (FOIA) (5 U.S.C. 552) as well as FDA's implementing regulations.

FDA's general regulations concerning the public availability of FDA records are contained in 21 CFR Part 20.

Section 911(e) of the FD&C Act requires FDA to make an MRTPA publicly available except matters in the application, which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable

portions of your MRTPA under section 911(e) for public comment, FDA recommends that you identify the portions of the application you believe constitute trade secret or confidential commercial information that is exempt from disclosure by either:

- Including in your cover letter a description or listing of such information; or
- Submitting two versions of your application – a complete, unredacted version and a second version with transparent highlights of the information you believe is exempt from disclosure.

FDA will make the final evaluation regarding what information can be made publicly available under section 911(e) of the FD&C Act.