Guidance for Industry

Applications for Premarket Review of New Tobacco Products

DRAFT GUIDANCE

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

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

September 2011

Table of Contents

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance is intended to assist persons submitting applications for new tobacco products under section 910 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act; 21 U.S.C. 301 et seq.), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31). This draft guidance explains, among other things:

- Who may submit a new tobacco product application under section 910 of the FD&C Act (21 U.S.C. 387j);
- When to submit a new tobacco product application;
- How to submit a new tobacco product application;
- What information the FD&C Act requires you to submit in a new tobacco product application; and
- What information FDA recommends you submit in a new 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.

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

II. Background

When you create a new tobacco product or modify a tobacco product in any way, you must obtain an order from FDA authorizing the marketing of the product before the product may be introduced or delivered for introduction into interstate commerce (section 910(a)(2); 21 U.S.C. 387j(a)(2)). This includes "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" (section 910(a)(1)(B)).

Where a new tobacco product is not substantially equivalent to a tobacco product commercially marketed in the United States as of February 15, 2007 (see section 910(a)(2)(A)(i)) or exempt from the requirement to obtain a substantial equivalence determination pursuant to regulation (see section 910(a)(2)(A)(ii)), you must submit a premarket tobacco product application (PMTA) under section 910(b) of the FD&C Act and receive a marketing authorization order under section 910(c)(1)(A)(i) prior to marketing the product.

Section 910(c)(1)(A)(ii) of the FD&C Act requires that FDA deny a PMTA and issue an order that the product may not be introduced or delivered for introduction into interstate commerce where FDA finds that:

- You have not shown that the product is appropriate for the protection of the public health;
- The manufacturing methods, facilities, or controls do not conform to manufacturing regulations issued under section 906(e) (21 U.S.C. 387f(e));
- The proposed labeling is false or misleading; or
- You have not shown that the product complies with any tobacco product standard in effect under section 907 (21 U.S.C. 387g). (Section 910(c)(2); 21 U.S.C. 387j(c)(2))

Section 910(c)(1) of the FD&C Act requires that FDA issue an order stating whether the product may be introduced into interstate commerce "[a]s promptly as possible, but in no event later than 180 days after the receipt of an application."

Under section 902(6)(A) of the FD&C Act (21 U.S.C. 387b(6)(A)), a tobacco product is deemed adulterated if it is a new tobacco product and it "does not have an order in effect under section 910(c)(1)(A)(i)" as necessary under section 910(a) of the FD&C Act. Under section 301(a) of the FD&C Act (21 U.S.C. 331(a)), the introduction or delivery for introduction into interstate commerce of any adulterated tobacco product is a prohibited act. Violations of section 910 are subject to regulatory and enforcement action by FDA, including but not limited to, seizure and injunction.

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) of the FD&C Act; 21 U.S.C. 321(rr)). 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

A 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).

IV. Discussion

A. Who Submits a PMTA?

Persons seeking a marketing authorization order under section 910(c)(1)(A)(i) must submit a PMTA to FDA.

The term "new tobacco product" is defined in section 910(a)(1) of the FD&C Act and includes any regulated tobacco products, including their components, parts, or accessories, whether sold for further manufacturing or for consumer use.

At this time, FDA intends to limit its enforcement of the requirements of section 910 to finished, regulated tobacco products. These finished, regulated tobacco products include the products named in section 901(b) (i.e., cigarettes, cigarette tobacco, smokeless tobacco and roll-your-own tobacco) and tobacco products that may be deemed by

regulation to be subject to the FD&C Act, as well as the component parts of regulated tobacco products sold or distributed for consumer use (e.g., cigarette rolling papers, filters, or filter tubes sold separately to consumers or as part of kits). To avoid the submission of duplicative information, FDA does not intend at this time to enforce the requirements of section 910 for components of regulated tobacco products that are sold or distributed solely for further manufacturing into finished tobacco products. We anticipate receiving relevant information regarding such new tobacco products in the PMTA submission for the finished regulated tobacco product. Where there is a change to a component or ingredient of a finished tobacco product, that change constitutes a modification of the tobacco product and you must obtain the appropriate marketing authorization order for the finished tobacco product that contains the changed ingredient or component prior to marketing the finished tobacco product.

B. When Should You Submit a PMTA?

Except as described below, you must submit a PMTA and obtain a marketing authorization order under section 910(c)(1)(A)(i) of the FD&C Act prior to the introduction or delivery for introduction of a new tobacco product into interstate commerce. As defined in section 910(a)(1) of the FD&C Act, a new tobacco product is any tobacco product that was not commercially marketed in the United States as of February 15, 2007 or any product that was commercially marketed as of February 15, 2007 but which was subsequently modified.

1. Relationship of the PMTA process to section 905(j) substantial equivalence reports

Section 910 of the FD&C Act provides that manufacturers of new tobacco products may submit a substantial equivalence report under section 905(j) (21 U.S.C. 387e(j)) and obtain a substantial equivalence order under section 910(a)(2)(A)(i) as an alternative to submitting a PMTA and obtaining a marketing authorization order under section 910(c)(1)(A)(i). To obtain a substantial equivalence order, the 905(j) report must demonstrate that the product is substantially equivalent to a predicate product and otherwise in compliance with the FD&C Act (section 910(a)(2); 21 U.S.C. 387j(a)(2)) (for details on obtaining a substantial equivalence order see FDA's Guidance for Industry and FDA Staff *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products*). Furthermore, a new tobacco product may be exempted from the requirement to obtain a substantial equivalence order or a marketing authorization order if the product is exempt from the requirements of section 905(j) pursuant to a regulation issued under section 905(j)(3).[2]

For new tobacco products that are not exempt from premarket review pursuant to a regulation issued under section 905(j)(3), the following table details when you must

[2] See *Tobacco Products, Exemptions from Substantial Equivalence Requirements* (76 FR 38961, July 5, 2011).

obtain a marketing authorization order prior to introducing your product into interstate commerce:

If your new tobacco product . . .	**Then . . .**
Is marketed before March 22, 2011 and you submit a 905(j) report for the product by March 22, 2011	You may market your product unless and until FDA issues an order stating that the product is not substantially equivalent or not in compliance with the FD&C Act. If FDA issues such an order, you must cease marketing the product and cannot market the product again without first obtaining a marketing authorization order from FDA under either section 910(c)(1)(A)(i) or 910(a)(2)(A)(i) of the FD&C Act.
Is marketed before March 22, 2011 and you did not submit a 905(j) report for the product by March 22, 2011	You must cease marketing the product as of March 22, 2011 and cannot market the product again without first obtaining a marketing authorization order from FDA under either section 910(c)(1)(A)(i) or 910(a)(2)(A)(i) of the FD&C Act.
Will be marketed on or after March 22, 2011	You may not market the product without first obtaining a marketing authorization order from FDA under either section 910(c)(1)(A)(i) or 910(a)(2)(A)(i) of the FD&C Act.

2. Relationship of the PMTA process to section 911 modified risk tobacco product applications

Section 911(d) describes the statutory requirements for filing an application for a modified risk tobacco product (21 U.S.C. 387k(d)). A modified risk tobacco product is defined, in part, as "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). Under section 911(l)(1), FDA is required to issue regulations or guidance, or any combination thereof, on the scientific evidence required for the assessment and ongoing review of modified risk tobacco products.

Sections 910(b) and 911(d) of the FD&C Act describe separate applications for new tobacco products and modified risk tobacco products. Under section 911(l)(4) of the FD&C Act (21 U.S.C. 387k(l)(4)), FDA is required to issue regulations or guidance that

will permit you to submit a single application for any tobacco product that is a new tobacco product under section 910 and that you seek to commercially market as a modified risk tobacco product. Until that time, however, if you intend to market a new tobacco product as a modified risk tobacco product you must submit two separate applications — one to satisfy the requirements of section 910 and another to satisfy the requirements of section 911.

3. Relationship of the PMTA process to section 904 submission of listing of ingredients

Section 904(c)(1) of the FD&C Act (21 U.S.C. 387d(c)(1)) requires that no later than 90 days prior to introducing a new brand or subbrand into the market, "the manufacturer of such product shall provide [to FDA] the information required under subsection [904](a)." This information includes, but is not limited to, a listing of all ingredients of the tobacco product (section 904(a)(1)). Section 904(c)(2) of the FD&C Act requires that "the manufacturer . . . advise [FDA] in writing . . . at least 90 days prior to" the addition of or increase to an additive that has not been designated by FDA as an additive that is not a human or animal carcinogen. Section 904(c)(3) of the FD&C Act requires that the manufacturer notify FDA within 60 days of decreasing or eliminating any additive, or adding or increasing an additive that FDA has designated is not a human or animal carcinogen. FDA encourages you to submit the information required under sections 904(c)(1), (2), or (3) prior to, or concurrent with, your PMTA and that you reference those submissions in your PMTA (for information on ingredient listing, see FDA's Guidance for Industry *Listing of Ingredients in Tobacco Products*).

Please note that if you have submitted a PMTA and FDA issues an order authorizing marketing of the product under section 910(c)(1)(A)(i) of the FD&C Act within 90 days of receipt of a complete submission under section 904(c)(1) or (2), the product may not be delivered for introduction into interstate commerce until the conclusion of the 90 day period following the section 904(c)(1) or (2) submission.[3]

C. How Should You Submit a PMTA?

FDA recommends that an application for premarket review of a new tobacco product include the following:

- A cover letter (including the name and address of your company; an authorized contact's name, title, address, phone number, e-mail address, and fax number; the

[3] As discussed above, some new tobacco products may not be subject to the PMTA requirements, either because FDA has issued an order that the new tobacco product is substantially equivalent and in compliance with the requirements of the FD&C Act (see section 910(a)(2)(A)(i)), or because the product is exempt from the substantial equivalence requirements pursuant to a regulation issued under 905(j)(3) of the FD&C Act (see section 910(a)(2)(A)(ii)). Such products must still comply with section 904(c) of the FD&C Act and, consequently, may not be introduced into interstate commerce until 90 days after FDA has received the necessary submission under section 904(c)(1) or (2) of the FD&C Act.

name of your new tobacco product; any previous regulatory history, e.g., any prior section 905(j) decision); dates of any prior meetings with FDA about your tobacco product; and any request for review of your application by the Tobacco Products Scientific Advisory Committee (TPSAC)); and

- An executive summary (including an overview of your application; a description of your tobacco product; a summary of nonclinical and clinical studies and major findings; and why you believe allowing marketing of your new tobacco product is appropriate for the protection of the public health).

As set forth in section 910(b)(1) of the FD&C Act, and discussed in greater detail in section V of this guidance, your application must include:

- Full reports of all investigations of health risks (including studies submitted to support your showing that the tobacco product is appropriate for the protection of the public health as discussed in Section VI below);
- A full statement of all components, ingredients, additives, and properties, and of the principle or principles of operation of such tobacco product;
- A full description of methods of manufacturing and processing (which includes a listing of all manufacturing, packaging, and control sites for the product, including the facility name, address, and telephone number, and a contact name for each facility including the contact's telephone number and e-mail address);
- An explanation of how your product complies with any applicable tobacco product standards;
- Samples of the product and its components; and
- Specimens of proposed labeling.

Furthermore, FDA's regulations implementing the National Environmental Policy Act of 1969 require that "[a]ll applications... 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 PMTA. You should refer to 21 CFR Part 25 for additional information.

If you do not submit information on any of the above items, please include a statement that the information is not being submitted and an explanation of why the information is not being submitted.

As discussed later in this guidance, section 910(b)(1)(E) requires that you submit "samples of such tobacco product and of components thereof" as FDA may reasonably require. Samples of your new tobacco product and components should be sent to:

Southeast Regional Laboratory
U.S. Food and Drug Administration
60 8th Street
Atlanta, GA 30309

You should submit these samples to FDA on the same date as your PMTA. Each sample submission should be accompanied by a cover letter with information sufficient to link the sample(s) and/or component(s) to your premarket application, including your company's name and address, an authorized contact's name, title, address, phone number, e-mail address, and fax number, the name of your new tobacco product, and any other identifying information. You should also provide the shipping conditions used to submit the samples to FDA, the recommended storage conditions, the date of manufacture of the samples, and the dating period (shelf life). You should include a copy of this cover letter with your PMTA.

While electronic submission of your application is not required at this time, FDA is strongly encouraging electronic submission to facilitate efficiency and timeliness of data submission and processing. FDA intends to provide and update information on its website on how you may provide an electronic submission to FDA (e.g., information on media and methods of transmission).

Your application should be clearly labeled as a PMTA and sent to:

Center for Tobacco Products
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

D. How Will We Review a PMTA?

FDA will review your PMTA consistent with the requirements of section 910(c) of the FD&C Act. Under this section, FDA is required to review a PMTA "as promptly as possible, but in no event later than 180 days after the receipt of an application" (section 910(c)(1)(A)). After initial receipt of your application, FDA may request additional information about your PMTA as necessary.

Under section 910(b)(2) of the FD&C Act, FDA may, upon your request or on its own initiative, refer your PMTA to TPSAC. Please include any request that FDA refer your PMTA to TPSAC in the cover letter to your initial PMTA submission. Note that FDA has discretion in deciding whether to refer your PMTA to TPSAC.

At any time, you may withdraw your PMTA. You should notify FDA in writing of a decision to withdraw your application. This notification should be clearly labeled as a PMTA withdrawal and sent to the address previously listed for receiving PMTAs.

V. Contents of a PMTA

Your PMTA must include the information discussed below that is required by section 910(b)(1) of the FD&C Act.

A. Full Reports of Investigations of Health Risks

Section 910(b)(1)(A) of the FD&C Act requires that a PMTA contain "full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products." FDA interprets the information required under this provision to include, not only investigations that support the application, but also any investigations that do not support, or are adverse to, the application. Information on both nonclinical and clinical investigations should be provided, including, but not limited to, any studies assessing constituents of tobacco or tobacco smoke, toxicology, consumer exposure, and consumer use profiles. Further, information on investigations concerning products with novel components, ingredients, additives or design features that are similar or related to those of the new tobacco product and investigations concerning products that share novel components, ingredients, additives or design features with the new tobacco product should also be provided so that FDA may adequately assess the health risks of the product. To the extent the information is available, you should indicate the source of funding for all studies provided.

FDA interprets "full reports of all information, published or known to, or which should reasonably be known to, the applicant" to include all information from investigations conducted both within and outside the United States.[4] While all clinical investigations (both within and outside the United States) submitted to support your application should be conducted to ensure that the rights, safety, and welfare of human subjects have been protected, you must submit full reports of all information concerning relevant clinical investigations even if the study did not protect the rights, safety, and welfare of human subjects.

For published studies concerning investigations which have been made to show the health risks of your tobacco product, you should provide a bibliography of the studies and an abstract for each study. You should also provide an explanation of the scope of the literature review you conducted to discover the relevant published studies, including how you identified, collected, and reviewed the studies.

As discussed in section VI of this guidance, the data and information you submit in your PMTA must be sufficient to show that the marketing of your new tobacco product is "appropriate for the protection of the public health" (section 910(c)(4) of the FD&C Act). Your application should include a summary of the results of each study you submit to support your showing. The summary should include, where available or reasonably obtainable:

[4] As discussed in section VII of this guidance, well-controlled investigations conducted outside the United States may be submitted to FDA in support of a PMTA. If you submit a study or studies conducted outside the United States in support of your application, you should provide an explanation of how the rights, safety, and welfare of human subjects were protected or if you do not know and are unable to provide this information (e.g., because you were not the sponsor of those studies), you should explain why.

- A description of the study objective,
- A description of the study design (or hypothesis tested),
- A description of any statistical analysis plan, including how data were collected and analyzed, and
- A brief description of the findings and conclusions (positive, negative, or inconclusive).

In addition, for each study showing the health risks of your product, you should include, to the extent available or reasonably obtainable:

- Documentation of all actions taken to ensure the reliability of the study and the protection of human subjects – for example, documentation of study oversight by an Investigational Review Board (IRB) duly constituted and operating under 21 CFR Part 56, documentation of informed consent procedures such as appropriate procedures found in 21 CFR Part 50, and documentation of appropriate good laboratory practices such as those found in 21 CFR Part 58 (see additional details provided in section VII of this guidance);
- The original study protocol(s) and any amendments;
- If investigator instructions were produced in addition to the protocol, copies of all such instructions;
- The statistical analysis plan including a detailed description of the statistical analyses used, including all variables, confounders, and subgroup analyses, the reason for your choice of sample size (including calculations of the power of each study and the level of significance and/or confidence interval used), and any amendments;
- All raw data (To facilitate our review, we request data in SAS-transport file format, created by a procedure that allows the files to be readily read by the JMP software. We also request that you provide data definition files that include the names of the variables, codes, and formats used in each dataset, and copies of SAS programs and any necessary macro programs used to create derived datasets and the results reported in the study reports.);
- All versions of questionnaires used;
- All versions of case report forms used;
- All informed consent forms; and
- A full report of the findings.

B. Full Statement of All Components, Ingredients, Additives, and Properties, and of the Principle or Principles of Operation of the New Tobacco Product

As required in section 910(b)(1)(B) of the FD&C Act, your application must contain a "full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation" of your new tobacco product.

1. Components, ingredients, and additives

Section 910(b)(1)(B) of the FD&C Act requires you to submit a full statement of the components, ingredients, and additives of your tobacco product as part of your PMTA. FDA interprets this requirement to mean that you must provide a complete list of uniquely identified components, ingredients, and additives by quantity in your new tobacco product as well as the applicable specifications and a description of the intended function for each. Components, ingredients, and additives include anything that may reasonably be expected to result directly or indirectly in becoming part of, or affecting the characteristics of, the finished new tobacco product. This includes, but is not limited to, for example, tobacco (including type(s)), paper, glue, additives, burn-rate controllers, and pH modifiers.

For guidance on uniquely identifying components, ingredients, and additives and reporting their quantities, please refer to FDA's Guidance for Industry *Listing of Ingredients in Tobacco Products*.

2. Properties

Section 910(b)(1)(B) of the FD&C Act requires you to submit as part of your PMTA a full statement of the properties of the tobacco product. FDA interprets "a full statement of the properties" of the new tobacco product to mean a full narrative description of the tobacco product, including:

- A description of the form of the product (e.g., liquid, gel, dissolvable, combustible, chewable, dip, strip, stick, orb);
- 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);
- A description of all design features of the product (e.g., location of ventilation holes, heat source, paper porosity, coatings, nicotine concentration gradient); the description should specify nominal values or the explicit range of values as well as the design tolerance, where appropriate;
- A description of tobacco blending, reconstitution, or manipulation;
- A quantitative description of the performance criteria (e.g., burn rate, ventilation criteria, dissolution rate);
- A description of how the product differs from similar, currently marketed tobacco products;
- Summaries of the results of tests performed on the lot(s) represented by the submitted samples; and
- Established shelf life of the product (you should include data establishing the stability of the product through the stated shelf life).

3. Principles of operation

Section 910(b)(1)(B) of the FD&C Act requires you to submit as part of your PMTA a full statement of the "principle or principles of operation" of the tobacco product. FDA interprets "a full statement of the . . . principle or principles of operation" to mean:

- A full narrative description of the way in which a consumer will use the new 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, or chewed);
- How long it takes for a consumer to consume a single unit of the product; and
- Whether the product uses a heating source and, if so, a description of the heat source (e.g., burning coal or other substance, electric or butane, chemical reaction, carbon tip).

C. Full Description of Methods of Manufacturing and Processing

As required in section 910(b)(1)(C) of the FD&C Act, you must provide a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, where relevant, packing and installation of the new tobacco product.[5]

You should provide a listing of all manufacturing, packaging, and control sites for the product, including the facility name and address, and a contact name and telephone number for each facility. Moreover, you should provide a narrative description, accompanied by a list and summary of all standard operating procedures (SOPs) and examples of relevant forms and records for the following categories of information:

- Manufacturing and production activities, including a description of facilities and all production steps;
- Managerial oversight and employee training;
- Manufacturing processes and controls for product design and changes in products, including a hazard analysis that details the correlation of the product design attributes with public health risk, as well as any mitigations implemented;
- Activities related to identifying and monitoring suppliers and the products supplied (including, for example, purchase controls and product acceptance activities);
- Validation and verification activities used to ensure that the tobacco product matches specifications;
- Testing procedures carried out before the product is released to market; and

[5] The requirement to provide a full description of methods of manufacturing and processing is separate and distinct from good manufacturing practice requirements, for which FDA will promulgate regulations pursuant to section 906(e) of the FD&C Act. When such regulations have been promulgated, they will contain specific information applicants should address in this section of an application.

- Handling of complaints, nonconforming products and processes, and corrective and preventative actions.

FDA may request that you submit copies of selected SOPs if needed to enable FDA to more fully understand the methods used in, and the facilities and controls used for, the manufacturing and processing of the tobacco product.

D. Compliance with Tobacco Product Standards

As required in section 910(b)(1)(D) of the FD&C Act, you must identify any tobacco product standard under section 907 of the FD&C Act that would be applicable to your new tobacco product, and provide adequate information that either shows that your new tobacco product fully meets the tobacco product standard or justifies any deviation from such standard.

E. Samples and Components

You must provide with your PMTA samples of your new tobacco product and of components of your new tobacco product as FDA may reasonably require (section 910(b)(1)(E)). FDA may conduct its own testing and analyses of your new tobacco product and its components. Consequently, your PMTA should include a sufficient number of samples for FDA to conduct any testing and analyses.

For the categories of new tobacco products described below, FDA recommends that you provide the following number of samples necessary for FDA to conduct testing and analyses of your new tobacco product. If you believe a different number of samples is appropriate, you should explain why.

Type of New Tobacco Product	**Recommended Number of Samples**
Cigarette and cigarette-like tobacco products	4,000 pieces (approximately 20 cartons)
Roll-your-own tobacco	4,000 grams
Smokeless tobacco in pre-measured units of use (e.g., moist or dry snuff in sachets)	200 pieces
Loose smokeless tobacco (e.g., chewing tobacco, moist snuff)	200 grams
Finished component tobacco products sold separately to consumers (e.g. cigarette rolling paper)	200 pieces

In addition to samples of your finished tobacco product, the FD&C Act requires that you provide samples of the components (e.g., tobacco filler, filter(s), and/or paper(s)) of your new tobacco product as FDA may reasonably require. FDA will request samples of component parts of your new tobacco product if needed. In addition, as part of your PMTA you should provide summaries of the results of any tests you performed on the lot(s) represented by the submitted samples.

F. Proposed Labeling

As required in section 910(b)(1)(F) of the FD&C Act, the PMTA must include specimens of all proposed labeling for your new tobacco product. Labeling is defined in section 201(m) of the FD&C Act as, "all labels and other written, printed, or graphic matter (1) upon any article or any or its containers or wrappers, or (2) accompanying such article," and includes labels, inserts/onserts, instructions, and other accompanying information or materials (21 U.S.C. 321(m)).

VI. Information to support a showing that the new tobacco product is appropriate for the protection of public health

The information provided in the application described in section V.A of this guidance should present data and information sufficient to enable FDA to make a finding that the marketing of a new tobacco product is "appropriate for the protection of the public health" (section 910(c)(4) of the FD&C Act). The statute provides that the basis for this finding shall be determined:

> with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account —
>
> (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
>
> (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny applications where "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health."[6]

Under section 910(c)(5)(A) of the FD&C Act, whether a new tobacco product is appropriate for the protection of public health shall be determined "when appropriate... on the basis of well-controlled investigations."[7] Therefore, FDA recommends that you provide data from the studies described below.

FDA also recommends you provide a detailed explanation of how the data and information provided in the application support a finding that introducing your new tobacco product to the market is appropriate for the protection of the public health. FDA recommends that your explanation include a comparison of the new tobacco product to tobacco products currently on the market.

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[6] In addition, the statute provides that FDA shall deny applications under section 910(c)(2) where:

> (B) the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of such tobacco product do not conform to the requirements of section 906(e);
> (C) based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular; or
> (D) such tobacco product is not shown to conform in all respects to a tobacco product standard in effect under section 907, and there is a lack of adequate information to justify the deviation from such standard.

[7] In addition, section 910(c)(5)(B) provides that if the Secretary determines that there exists valid scientific evidence sufficient to evaluate the tobacco product, the Secretary may authorize that the determination whether the new tobacco product meets the public health standard be made on the basis of such evidence.

FDA requests comment on how best to evaluate whether an applicant has demonstrated that a new tobacco product is appropriate for the protection of the public health. We request comment on what product chemistry, nonclinical, and adult human subject studies could be used to demonstrate that the marketing of the product is appropriate for the protection of the public health. We also request comment on establishing a baseline for determining whether a new product affects the likelihood that tobacco users will quit or the likelihood that non-users will start using such products.

A. General Principles for Scientific Studies

Under section 910(c)(4) of the FD&C Act, your new tobacco product will be evaluated to determine whether the product is appropriate for the protection of the public health considering the risks and benefits, including the health risks of the product and the likelihood of changes in initiation and cessation rates. These considerations will allow for an evaluation of the impact of the new tobacco product on morbidity and mortality for the population as a whole. In demonstrating the public health impacts of the product, data from your well-controlled scientific investigations should address, among other things, the following questions:

(1) How do the health risks associated with your product compare to the health risks of other products on the market? How do the health risks of switching from another tobacco product to your product compare to the health risks associated with quitting the use of tobacco products? How do the health risks associated with your product compare to never using tobacco products? Accordingly, your scientific studies regarding health risks of your new tobacco product should allow for a comparison of the health risks of your tobacco product to the risks associated with quitting, using other tobacco products, and never using tobacco products.

(2) How will your new tobacco product affect the likelihood that current tobacco users will cease using tobacco products? In making this evaluation, you should address the attractiveness of your product and product labeling to current tobacco users (especially to those users interested in quitting smoking), the addictiveness and abuse liability of your product, and cessation rates associated with users who switch to your new tobacco product. Additionally, you should provide evidence regarding the likelihood that your new product will be used concurrently with other tobacco products currently on the market. Your evaluation of the impact of the introduction of your new tobacco product on cessation rates should provide data on the attractiveness, addictiveness, and cessation rates of your new tobacco product as compared to other tobacco products currently on the market.

(3) How will your new tobacco product affect the likelihood that never-users and former-users of tobacco products will use your new tobacco product? In making this evaluation, you should address the attractiveness of your product and product labeling to never-users and former-users of tobacco products (especially to those segments of the population that may be particularly likely to initiate or reinitiate tobacco use), as well as the addictiveness and abuse liability of your product. To provide a full

evaluation of the impact of your product on the market and on the population as a whole, your scientific evaluations should provide data on how the attractiveness and addictiveness of your product compares to that of products currently on the market. You should specify what product features may enhance the attractiveness/appeal of your product to children and adolescents and what product features may minimize the attractiveness/appeal of your product to children and adolescents.

All of your scientific evaluations should use control groups of comparator products and use various tobacco use levels sufficient to address the questions and considerations above. For example, in evaluating the health risks of your product, clinical studies should provide data on biomarkers for users of other tobacco products as well as biomarkers for quitters and never-users. Similarly, product chemistry evaluations should compare your new product's chemistry to other tobacco products currently on the market.

In addition, your studies should follow a pre-specified statistical analysis plan for data analysis to ensure the validity of your conclusions.

FDA encourages persons who would like to study their new tobacco product to meet with the Office of Science at the Center for Tobacco Products to discuss their investigational plan prior to distributing the product for investigational purposes (see section VII, below).

B. Product Chemistry

Product chemistry, while not determinative of issues related to the public health impact of your new tobacco product, is relevant to our evaluation of the health risks and addictiveness of your product and provides context for evaluating other nonclinical and clinical data submitted in support of your PMTA.

For each new tobacco product, you should report the levels of harmful and potentially harmful constituents (HPHC), including smoke constituents, as appropriate to the product.[8] For new tobacco products that are smoked (e.g., cigarettes), quantitative levels should be determined in smoke generated using both the ISO and Canadian Intense smoking regimens. If an alternative to these testing methods is used, you should provide the basis for your selection of the alternative method.

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),

[8] 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.*

- The corresponding Chemical Abstract Services number,
- The unit of measure,
- The level measured for the submitted 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. Documentation should be provided showing that the laboratories used to produce measurements have accreditation by a nationally or internationally recognized external accreditation organization. Documentation of such accreditation should be included in your application.

C. Nonclinical Studies

Nonclinical studies provide important probative information regarding the health risks and addictiveness of tobacco products. While nonclinical studies alone generally are not sufficient to support a determination that the product is appropriate for the protection of the public health, the information from these studies provides insight into the mechanisms of disease incidence caused by a tobacco product and more generally provides context for the data regarding health risks and addictiveness obtained from human studies.

Your nonclinical investigation should evaluate the toxicity, abuse liability, and carcinogenicity of your new tobacco product as compared to other tobacco products on the market.

You should generate data to evaluate these product properties using some combination of *in vitro*, *in vivo*, and/or *ex vivo* studies. The study designs should include adequate sample sizes (test samples or animal numbers) for robust statistical analyses and a range of biologically relevant concentrations. The models used in your studies should be sufficiently sensitive to the endpoint being evaluated. You should provide evidence and an explanation of the sensitivity and probative value of the nonclinical model chosen. For example, if you choose an Ames mutagenicity assay as part of an evaluation of the carcinogenicity of your tobacco product, you should explain:

- Why the assay is appropriate for evaluating your tobacco product,
- How the Ames assay has been used historically,
- What scientific evidence there is that the assay is useful in evaluating carcinogenicity and mutagenicity,
- The choice of strain of test bacteria,
- The choice of method of product administration, and
- What scientific evidence there is that the assay is sensitive enough to demonstrate a dose-response relationship and distinguish between tobacco products.

For *in vivo* studies, the test product should be administered through the route representative of human exposure, where feasible.

D. Studies in Adult Human Subjects

The primary goal of investigations in adult human subjects is to evaluate the health risks of a new tobacco product by assessing the effects of the new tobacco product on human health and behavior (i.e., pattern of use and tobacco use topography, toxicant exposure and biological effect, abuse potential, and consumer perception). These studies will provide FDA with important information to enable it to determine whether the product is appropriate for the protection of the public health.

Study protocols should specify the study design, conduct, and statistical analysis plan for analyzing the data collected to ensure the validity of the results. The extent to which the procedures in the protocol are followed and data analysis methods used are pre-specified will contribute to the degree of confidence in the final results and conclusions of your study. The interpretation of statistical measures of uncertainty of the effects of tobacco products and tobacco products comparisons should involve consideration of the potential contribution of bias to the p-value, confidence interval, or other inferences.

Your studies in adult human subjects should provide the following evaluations of your tobacco product:

- Tobacco user exposure to tobacco-related compounds;
- Tobacco user health risk and disease incidence;
- Tobacco product use patterns (e.g., smoking topography, frequency of use, and/or use by different age groups), including evaluation of consumers' use of the new tobacco product concurrently with other products already on the market;
- Abuse liability and addictiveness;
- Consumer perceptions including risk perceptions based on the product itself, as well as on the packaging and labeling of the new tobacco product; and
- Cessation rates for users of the new tobacco product.

You should conduct studies so as to ensure that the study findings are generalizable to the population of U.S. tobacco users and non-users as a whole. This requires careful consideration of study size, subject selection, and study duration. You should design subject selection to ensure sampling of a population that reflects the diversity of the U.S. adult tobacco user population. In addition, you should consider oversampling of populations particularly likely to be affected, whether positively or negatively, by the entry of a new tobacco product onto the market.

Based upon the endpoint(s) to be evaluated in a particular clinical investigation, you should identify the control group to be used. For example, in a study designed to assess the effect of a new tobacco product on disease risk, the study might include multiple

comparator groups based on tobacco use levels (e.g., smokers of less than 10 cigarettes per day, smokers of 10 or more cigarettes per day, and former users).

The duration of the study should be sufficient to ensure that the endpoint(s) studied can be adequately assessed to provide clinically meaningful and statistically valid and robust findings. For example, a study of the product's effect on cessation from tobacco use may take longer than an assessment of the tobacco product's use topography.

VII. Investigational Use of New Tobacco Products

A. Exemptions for Investigational Use of New Tobacco Products

FDA plans to issue regulations pursuant to section 910(g) (21 U.S.C. 387j(g)) providing conditions under which tobacco products may be exempted from the requirements of section 910 when used for investigational purposes. Until these regulations are issued, FDA will consider exercising discretion in enforcing the premarket review requirements of Chapter IX of the FD&C Act, in some circumstances, for the purposes of investigational use of new tobacco products. Applicants who would like to study their new tobacco products should contact the Office of Science at the Center for Tobacco Products to discuss submission of a study protocol and/or study endpoints for investigations intended to support a PMTA.

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

Center for Tobacco Products
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

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 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 for evaluating whether your product is appropriate for the protection of the public health, including a summary of your proposed study protocol(s).

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 new 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
- Duration of follow-up and baseline and follow-up assessments.

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 new tobacco product, the status of product development, an investigational plan for evaluating whether the product is appropriate for protection of the public health (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.

While the design of studies will be discussed on a case-by-case basis, at this time FDA does not intend to enforce the premarket review requirements in Chapter IX of the FD&C Act with respect to the use of 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 clinical and nonclinical) you should:

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

For clinical studies, you should:

- Take measures to ensure the reliability and validity of the study, for example through sound study design and adherence to the 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 may 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 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 may 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.

B. Studies Conducted Outside of the United States

You may submit studies of new tobacco products conducted outside the United States as part of your PMTA. All studies conducted outside the U.S. 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 help ensure that data from studies conducted outside the United States constitute "well-controlled investigations" (see section 910(c)(5)(A) of the FD&C Act) that provide reliable data to FDA.

VIII. Confidentiality

Information submitted under section 910 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 new tobacco product information submitted under section 910, 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.