Use of Investigational Tobacco Products

Guidance for Industry and Investigators

DRAFT GUIDANCE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For questions regarding this draft guidance, contact the Center for Tobacco Products at (Tel) 1-877-CTP-1373 (1-877-287-1373) Monday-Friday, 9 a.m. – 4 p.m. EDT.

Additional copies are available online at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm. You may send an e-mail request to SmallBiz.Tobacco@fda.hhs.gov to receive an electronic copy of this guidance. You may send a request for hard copies to U.S. Food and Drug Administration, Center for Tobacco Products, Attn: Office of Small Business Assistance, 10903 New Hampshire Ave., Silver Spring, MD 20993.

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

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Guidance for Industry and Investigators[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Section 910(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 387j(g)) gives FDA the authority to issue regulations to exempt tobacco products intended for investigational use from the requirements of Chapter IX of the FD&C Act, including premarket submission requirements. To date, FDA has not issued such regulations, and consequently investigational tobacco products are not exempt from FD&C Act requirements, including premarket submission requirements. This draft guidance describes FDA's current thinking regarding the definition of "investigational tobacco product" and discusses the kind of information FDA intends to consider in making enforcement decisions regarding the use of investigational tobacco products until regulations are issued and become effective or FDA provides written notice of its intent to change its enforcement policy. FDA has issued two other draft guidances that discuss investigational tobacco products: *Applications for Premarket Review of New Tobacco Products* (September 2011); and *Modified Risk Tobacco Product Applications* (March 2012). When finalized, this guidance will reflect FDA's most detailed recommendations on the use of investigational tobacco products.

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

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

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.

II. BACKGROUND

Section 910(g) of the FD&C Act states:

> The Secretary may exempt tobacco products intended for investigational use from the provisions of this chapter under such conditions as the Secretary may by regulation prescribe.

FDA intends to propose regulations establishing conditions for exempting investigational tobacco products from certain FD&C Act requirements. Until then, investigational tobacco products are *not* exempt from applicable FD&C Act requirements, including premarket submission requirements and tobacco product standards.

Section 910 of the FD&C Act requires premarket review of new tobacco products. A product is a "new tobacco product" within the meaning of section 910(a)(1) of the FD&C Act if:

- it was not commercially marketed in the United States as of February 15, 2007;[2] or
- it was commercially marketed in the United States as of February 15, 2007, but the product was modified and commercially marketed after February 15, 2007.

"Modification" under section 910(a)(1)(B) 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" of a tobacco product.

To introduce, or deliver for introduction into interstate commerce, a new tobacco product, there must be in effect a marketing authorization order issued by FDA for the tobacco product under section 910(c)(1)(A)(i) of the FD&C Act[3] unless:

- the manufacturer has submitted a substantial equivalence report for the tobacco product under section 905(j) of the FD&C Act (21 U.S.C. 387e(j)) and obtained

[2] FDA's Draft Guidance for Industry: *Establishing that a Tobacco Product was Commercially Marketed in the United States as of February 15, 2007* (http://www fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM334750.pdf) discusses determinations that a tobacco product was commercially marketed in the United States on February 15, 2007.

[3] FDA's Draft Guidance for Industry: *Applications for Premarket Review of New Tobacco Products* (http://www fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM273425.pdf) discusses the submission process for premarket tobacco product applications.

from FDA a substantial equivalence order under section 910(a)(2)(A)(i) of the FD&C Act; [4]

- the manufacturer has submitted under 21 CFR 1107.1 a request for an exemption of the tobacco product from the requirement to obtain a substantial equivalence order, FDA has granted the exemption request, and the manufacturer has made the required submission under section 905(j)(1)(A)(ii) of the FD&C Act and waited 90 days before introducing its product to the market;[5] or
- the manufacturer has submitted a substantial equivalence report in accordance with section 910(a)(2)(B) of the FD&C Act and there is no order finding that the tobacco product is not substantially equivalent.

Modified risk tobacco products also require premarket review by FDA. A *modified risk tobacco product* (MRTP) is "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"[6] (section 911(b)(1) of the FD&C Act). Specifically, to 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 and the applicant must satisfy any applicable premarket review requirements under section 910 of the FD&C Act.[7]

Any tobacco product, including a tobacco product intended for investigational use, is deemed adulterated if it is required by section 910(a) of the FD&C Act to have premarket review and it does not have an order in effect under section 910(c)(1)(A)(i). See sections 902(6)(A) and 910(a) of the FD&C Act (21 U.S.C. 387b(6)(A) and 387j(a)). Similarly, any tobacco product, including a tobacco product intended for investigational use, is deemed adulterated if it is a modified risk tobacco product and it does not have in effect an order under section 911(g) of the FD&C Act. See sections 902(8) and 911(a) of the FD&C Act (21 U.S.C. 387b(8) and 387k(a)).

Further, tobacco products must conform in all respects with any applicable tobacco product standards. See section 301(q)(1)(A) of the FD&C Act (21 U.S.C. 331(q)(1)(A)). Any tobacco product, including a tobacco product intended for investigational use, is

[4] 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) discuss the submission process for substantial equivalence reports.

[5] 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://edocket.access.gpo.gov/2011/pdf/2011-34.pdf), codified at 21 CFR 1107.1.

[6] A tobacco product is a modified risk tobacco product if, for example, the label, labeling, or advertising explicitly or implicitly represents the tobacco product presents lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products or the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance.

[7] FDA's Draft Guidance for Industry: *Modified Risk Tobacco Product Applications* (http://www fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf) discusses the submission process for modified risk tobacco product applications.

deemed adulterated if it is subject to a tobacco product standard established under section 907 of the FD&C Act and does not in all respects conform with such standard. See sections 902(5) and 907 of the FD&C Act (21 U.S.C. 387b(5) and 387g).

In order to file submissions with FDA to, among other things, demonstrate that new or modified risk tobacco products meet the criteria for marketing authorization, persons may need to conduct or sponsor studies involving tobacco products that do not have marketing authorization or that do not comply with an applicable tobacco product standard. Similarly, researchers may seek to study tobacco products that do not have marketing authorization or that do not comply with an applicable tobacco product standard. Until regulations governing the use of investigational tobacco products are issued and finalized, FDA intends to evaluate specific uses of investigational tobacco products according to potential public health concerns or other impacts on public health. In making enforcement decisions, FDA generally intends to consider:

- Whether there are controls on how and to whom the tobacco products intended for investigational use are distributed.
- Whether the protocol for the clinical investigation or the procedures used during the clinical investigation adequately provide for the protection of human subjects.
- Whether the study is designed to ensure the quality and integrity of the study data and permit other investigators to replicate the findings.
- Whether there are adequate procedures in place to ensure that investigational tobacco products are not commercialized.

As used in this guidance document:

An *investigational tobacco product* is a tobacco product that is:

(1) a new or modified risk tobacco product that is not legally marketed; or
(2) a tobacco product that is required to comply with a tobacco product standard and that does not conform in all respects to the applicable tobacco product standard,

and is intended for investigational use.

A new tobacco product "is not legally marketed" if it is not exempt from the requirement to obtain a substantial equivalence order and is not subject to section 910(a)(2)(B) of the FD&C Act, and there is no substantial equivalence order or order under section 910(c) of the FD&C Act in effect for the product.[8] A modified risk tobacco product "is not legally marketed" if there is no order under section 911(g) of the FD&C Act in effect for the product. A modified risk tobacco product may also be a new tobacco product for which there must be in effect an order under section 910(c) of the FD&C Act.

III. PURPOSE

[8] A new tobacco product that is on the market under an exercise of FDA's enforcement discretion is an investigational tobacco product if it is intended for investigational use.

This guidance describes FDA's current thinking regarding the definition of *investigational tobacco product* and discusses the kind of information FDA intends to consider in making enforcement decisions regarding the use of investigational tobacco products in the United States (U.S.) until regulations become effective or FDA provides written notice of its intent to change its enforcement policy. It is intended to provide guidance not only to persons who currently intend to submit study information to FDA, but also to all persons who conduct nonclinical laboratory studies and clinical investigations using investigational tobacco products. Such persons may include sponsors, investigators, sponsor-investigators, contract research organizations (CROs),[9] and committees or groups formally designated to oversee research involving human subjects (e.g., institutional review boards (IRBs)) involved in investigations using investigational tobacco products.

For purposes of this guidance, a *clinical investigation* means any experiment or study involving an investigational tobacco product and one or more human subjects, including research, development, testing, and evaluation. As used in this guidance document, *sponsor* means a person who takes responsibility for and initiates a nonclinical laboratory study or clinical investigation. In limited instances in which an individual both initiates and conducts an investigation, the individual is a sponsor-investigator. A sponsor of a study may be a tobacco manufacturer, a scientific institution, or any other person who takes responsibility for and initiates the scientific investigation of tobacco products. An *investigator* is the individual who actually conducts a nonclinical laboratory study or clinical investigation (e.g., under whose immediate direction the tobacco product is administered or dispensed to a subject). If a clinical investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

IV. FDA'S ENFORCEMENT POLICY FOR INVESTIGATIONAL TOBACCO PRODUCTS

A. Use of Investigational Tobacco Products in Nonclinical Laboratory Studies

FDA intends to consider the following information in making enforcement decisions regarding the use of investigational tobacco products in nonclinical laboratory studies:

- Whether there are controls on how and to whom the tobacco products for use in a nonclinical laboratory study are distributed. For example, whether investigational tobacco products are distributed only to qualified investigators[10] with labeling indicating that they are limited to investigational use in research animals or for tests in vitro.

[9] *Contract research organization* (CRO) as used in this guidance means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of the sponsor (e.g., design of a protocol).
[10] *Qualified investigators*, as used throughout this guidance, means experts qualified by scientific training and experience to evaluate tobacco products.

- Whether there are adequate procedures in place to ensure that investigational tobacco products are not commercialized.
- Whether the study is designed to ensure the quality and integrity of the study data and permit other investigators to replicate the findings.

For purposes of this guidance, the term *nonclinical laboratory study* means in vivo or in vitro experiments in which tobacco products are studied prospectively in test systems under laboratory conditions. Nonclinical laboratory studies should be conducted in laboratories accredited by a nationally or internationally recognized external accreditation organization.

FDA supports reducing the reliance on animal testing methods where adequate and scientifically valid non-animal alternatives can be substituted. FDA encourages sponsors to meet with CTP early in the development process to discuss what, if any, animal testing is appropriate and the suitability and acceptability of non-animal tests for their particular tobacco product. When animal-based nonclinical laboratory studies are conducted, investigators should 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, such as 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). Investigators should also adopt measures to ensure the reliability and validity of nonclinical laboratory studies. One approach to implementing such measures would be to follow good laboratory practices as specified in 21 CFR part 58. Sponsors with specific questions about good laboratory practice regulations are encouraged to contact CTP.

B. Use of Investigational Tobacco Products in Clinical Investigations

Clinical investigations are likely to raise concerns about human subject protection, public health, or both. FDA intends to consider the following factors in making enforcement decisions with respect to the use of an investigational tobacco product in a clinical investigation:

- Whether there are controls on how and to whom the tobacco products for use in a clinical investigation are distributed. For example, whether investigational tobacco products are distributed only to qualified investigators with labeling indicating that they are limited to investigational use only.
- Whether the protocol for the clinical investigation and procedures used during the clinical investigation adequately provide for the protection of human subjects.
- Whether the study is designed to ensure the quality and integrity of the study data and permit other investigators to replicate the findings.
- Whether there are adequate procedures in place to ensure that investigational tobacco products are not commercialized.

Adequate procedures for human subject protection ensure that the rights, safety, and welfare of human subjects are protected in accordance with ethical principles acceptable to the international community and that the data are scientifically valid. One approach to implementing such measures would be to conduct the study in accordance with the appropriate provisions found in 21 CFR part 50 (informed consent of human subjects) and ensure study oversight by a qualified IRB duly constituted and operating under 21 CFR part 56 (Institutional Review Boards). Additional information about informed consent and IRBs can be found in FDA's guidance documents. http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219433.htm. Sponsors with specific questions about human subject protection are encouraged to contact CTP.

For example, in evaluating the factors above, FDA would consider who the subjects of a clinical investigation are (e.g., whether the subjects are youth or women who are pregnant or nursing) and whether the protocol for the clinical investigation and procedures used during the investigation adequately provide for the protection of human subjects, as well as whether the study is conducted in a manner that ensures the quality and integrity of study data, and whether the sponsor labels the investigational tobacco product for investigational use and ensures the investigational tobacco product is distributed only to qualified investigators in accordance with study protocols.

V. INFORMATION REGARDING PROPOSED USE OF AN INVESTIGATIONAL TOBACCO PRODUCT IN A CLINICAL INVESTIGATION

This section of the guidance provides examples of the kinds of information relevant to FDA's consideration of the factors described above. FDA encourages sponsors to meet with CTP to discuss their specific proposed uses of investigational tobacco products. Information on how to request a meeting with FDA is found in section IX of this guidance.

A sponsor may also submit information regarding its proposed use of an investigational tobacco product to FDA for review prior to enrolling subjects in the planned investigation. We encourage this type of voluntary submission because it will allow FDA to work with sponsors to help ensure that the factors FDA considers in making enforcement decisions are appropriately accounted for – i.e., that there are controls on how and to whom the tobacco products for use in a clinical investigation are distributed; that clinical investigations provide adequate procedures for human subject protection, are designed to ensure the quality and integrity of the study data and permit other investigators to replicate the findings; and that there are adequate procedures in place to ensure that investigational tobacco products are not commercialized.

1. Recommendations on Information to Include in Voluntary Submissions

A sponsor may seek feedback from FDA by submitting information regarding its proposed use of an investigational tobacco product in a clinical investigation. Generally, FDA expects to review and respond to these submissions within 60 calendar days.

For example, sponsors may submit the following information (or where applicable, an explanation of why such information is unavailable or not relevant) to help FDA evaluate how the specific proposed use of an investigational tobacco product in a clinical investigation accounts for the factors FDA considers in making enforcement decisions:

- Administrative information that:
  - Identifies the submission as information regarding proposed use of an investigational tobacco product in a clinical investigation (or addition of information to an existing submission);
  - Contains the name, address (mailing and email), telephone number and facsimile number of the sponsor; name, title, address (mailing and email), telephone number and facsimile number of an individual who resides or maintains a place of business in the United States and is designated to act as the authorized representative for the sponsor; and the date of the submission;
  - Provides the name, including brand name/sub-brand name or product code, if available, of the investigational tobacco product;
  - Identifies the product, such as by category (e.g., cigarette, smokeless tobacco) and product subcategory (e.g., snus or dissolvables);
  - Lists, by FDA submission tracking number, cross references for all previous submissions referenced in the submission;
  - Contains the name(s) and title(s) of the person(s) responsible for monitoring the conduct and progress of the clinical investigation;
  - Contains the name(s) and title(s) of the person(s) responsible for review and evaluation of information relevant to the effects of the investigational tobacco product; and
  - If the sponsor has transferred any responsibilities for the conduct of any clinical investigation (or part of a clinical investigation) to a CRO, the information should also contain the name and address of each CRO, identify the clinical investigation it is involved in conducting, and describe the responsibilities transferred. If all responsibilities governing the conduct of an investigation have been transferred, a general statement that all responsibilities have been transferred is acceptable;
  - Contains the signature of the authorized representative.
- A table of contents;
- A description of the investigational tobacco product and any comparator or placebo to be used in the study (this information may be provided in a table format), including each product's composition, design, and manufacture, that includes:
  - A description of the product design with schematics of the complete product and product components, a description of the design features (e.g., location of ventilation holes, heat source, paper porosity, coatings, nicotine concentration gradient), and performance specifications;
  - A complete list of, or a reference to the manufacturer's complete list of, uniquely identified components, ingredients, and additives by quantity in

the tobacco product, including product chemistry and a table of any harmful or potentially harmful constituents (HPHCs), as well as the applicable specifications and a description of the intended function of each;[11]
  - The name and address of the manufacturer of the tobacco product;
  - A description of the methods, facilities, and controls used for the manufacture, processing, packing, and storage of the tobacco product; and
  - Data and information sufficient to demonstrate the tobacco product will be stable during the conduct of the study.

If this information can be found in a master file[12] or other submission by a third party to which the sponsor has a right of reference, the sponsor should provide FDA with a copy of the letter from the owner of the information authorizing the sponsor to reference it and authorizing FDA to access it on the sponsor's behalf.

- Use information:
  - For actual use studies, a description of the way in which a human subject will use the investigational tobacco product, including a description of how a human subject operates the product (e.g., whether a human subject places the tobacco product in the mouth or nose; whether a human subject ignites the tobacco product and, if so, by what means; whether the product is designed to be smoked, inhaled, swallowed, dissolved, sniffed, chewed);
- Any information about the investigational tobacco product, both favorable and unfavorable, known or reasonably obtainable by the sponsor, such as results of product testing, nonclinical laboratory studies, and clinical investigations, and information on marketed tobacco products similar to the investigational tobacco product;
- A study protocol;
- Identification of the study sites and a summary of qualifications for each clinical investigator who will be participating at each site in the study;
- Copies of all packaging and labeling to be provided to clinical investigators or study subjects;
- A copy of the Investigator's Brochure, if applicable;
- A copy of any information to be provided to the clinical investigator to ensure consistent implementation of a protocol across study sites;
- A copy of the case report forms;

[11] For the purposes of this guidance, components, ingredients, and 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.

[12] A master file is a submission of information to FDA by a person (the master file owner) who intends to incorporate the information by reference in a submission to FDA or intends to authorize other persons to rely on the information to support a submission to FDA without the master file owner having to disclose the information to the person.

- A copy of the study participant informed consent form, recruitment materials, and any other information to be provided to participants, such as a debriefing script, and a summary of the informed consent procedures to be followed;
- The name, and contact information for, the committee or group which has been formally designated to oversee the clinical investigation;
- Disclosure of the financial arrangements between the sponsor and the clinical investigators and any interest of the clinical investigators in the product under study or in the sponsor of the study; and
- A description of the sponsor's procedures for maintaining records regarding the receipt, use, and disposition of investigational tobacco products, and for updating clinical investigators on important new information that affects the clinical investigation.

2. Study Protocols

Regardless of whether you intend to consult with FDA in conducting research with an investigational tobacco product, we generally recommend that your study protocol include the following information, which may be considered should FDA assess the enforcement priority of a particular investigation:

- A statement of the study objective(s);
- The study hypothesis or hypotheses;
- Background information (e.g., a brief description of the investigational tobacco product, a critical review of the literature, the significance of the study to be conducted, a summary of information relevant to the health risks of the investigational tobacco product (e.g., available information on a marketed product that is similar to the investigational tobacco product));
- The general investigational plan;
- A description of the design and setting (e.g., clinical, community) for the study, including the type of control group, if any, to be used and a description of methods to be used to minimize bias and confounding;
- A description of the study population, including the methods used for recruitment, number of subjects to be enrolled, inclusion/exclusion criteria, and comparison group(s);
- A description of the primary and secondary endpoints with definitions and success criteria;
- A statistical analysis plan. The plan should include a description of the statistical method to be used and the reason for choosing this method and sample size, including calculations of the power of the study and the level of significance or confidence level to be used;
- A copy of data collection procedures and samples of data collection instruments;
- The timing for baseline and follow-up assessments and duration of follow-up;
- A risk assessment, including a description of clinical procedures, laboratory tests, criteria for stopping the study, or other measures to be taken to monitor the effects of the product in human subjects and to minimize risk;

- Samples of case report forms;
- Written procedures for monitoring the investigation and the name and address of each monitor;
- A description of the steps that will be taken to protect human subjects (including any plans to report adverse experiences and to debrief subjects, if appropriate) and a sample of the informed consent forms to be used for the study;
- The name, address, and statement of qualifications (curriculum vitae or other statement) of each clinical investigator;
- The name and address of any facility where specimens will be tested;
- The method for determining the level of product exposure for the individual subject, including the quantity of each administration and maximum planned exposure over the duration of the study; and
- Study milestone and timeline elements, including study initiation, enrollment goals, completion of enrollment, completion of follow-up, and submission of final report.

We also recommend that:

- Protocols employ standardized and validated methods of analysis;
- Sample sizes permit robust statistical analyses;
- Designs permit valid comparisons with appropriate controls for the testing of study hypotheses (selection of the controls should be based on the endpoint or effect to be evaluated);
- Procedures be employed to minimize bias on the part of observers, researchers, participants, 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.;
- Methods for assigning subjects to different comparator groups are appropriate for making comparisons between groups with respect to pertinent variables;
- Procedures for the selection of human subjects allow for generalizability of study results to the U.S. population, as appropriate;
- Procedures call for oversampling of populations that are particularly likely to be affected, positively or negatively, by the marketing of the product;
- Protocols 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;
- Study duration allows for adequate assessment of selected endpoint(s) and/or effects;
- Analyses adequately address the effects of the product on the study measures, endpoints or outcomes; and
- Protocols include procedures and timelines for clinical investigators to report adverse experiences to study sponsors.

3. Additional Recommendations Regarding Human Subject Protection

In order to ensure that studies are conducted in a manner that protects human subjects, FDA recommends that sponsors put procedures in place to keep the Agency and the committee or group formally designated to oversee research involving human subjects informed about any changes relating to the conduct of, and issues that arise during, the study. The sponsor should ensure that clinical investigators maintain complete and accurate records to account for receipt, use, and disposition of investigational tobacco products. The sponsor should keep clinical investigators and any committee or group formally designated to oversee research involving human subjects informed of new information on the product, particularly adverse experience information.

FDA recommends that sponsors consult with CTP's Office of Science and any committee or group formally designated to oversee research involving human subjects if there are changes to the current investigational use to ensure that the sponsor's use of an investigational tobacco product continues to appropriately account for the factors FDA intends to consider in determining enforcement priorities. FDA recommends that sponsors keep records of the following information, which is relevant to the factors FDA intends to consider in determining its enforcement priorities:

- Protocol amendments;
- Names and qualifications of new clinical investigators, including clinical investigators replaced for cause (e.g., due to fraud or other misconduct);
- A description of any changes made to the investigational tobacco product or its conditions of use; and
- Adverse experience reports. If you are notified a study subject has a serious and unexpected adverse experience associated with the use of the investigational tobacco product, we recommend that you inform FDA, all participating clinical investigators, and any committee or group formally designated to oversee the study within a few days after initial receipt of the notification, and that you supply FDA with a completed case report form for the adverse experience.[13] In addition, we recommend that you notify FDA, all participating clinical investigators and any committee or group formally designated to oversee the study of any serious or unexpected adverse experience associated with the tobacco product you are investigating within a few weeks after initial notification, and that you supply FDA with a completed case report form for the adverse experience.

If you choose to terminate a study (or withdraw or inactivate a protocol or want to withdraw all studies of a product) before completion, we recommend you notify FDA within a few weeks of such action and include in the notification the reason(s) for the action taken. This information is relevant for FDA to consider in making decisions relating to future investigations involving the tobacco product that was the subject of the terminated study. You should provide, as appropriate, plans for continued monitoring of subjects or others exposed to the tobacco product during the clinical investigation. If

[13] For the purposes of this guidance, an adverse experience would be unexpected if, for example, the nature, severity, or frequency of an effect of using an investigational tobacco product was not consistent with known or foreseeable risks associated with such product or the research procedures.

there is a reasonable possibility that exposure to the investigational tobacco product caused a serious and unexpected adverse experience, you should also inform any clinical investigators who participated in the discontinued investigation of the reason(s) for discontinuing the clinical investigation.

VI. STUDIES OF TOBACCO PRODUCTS CONDUCTED OUTSIDE THE UNITED STATES

For nonclinical laboratory studies of investigational tobacco products conducted outside of the United States, but intended for submission to FDA, investigators should take measures to ensure the reliability and validity of nonclinical laboratory studies. One approach to implementing such measures would be to follow good laboratory practices as specified in 21 CFR part 58. In addition, we encourage investigators to 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. As stated in section IV.A, FDA supports reducing reliance on animal testing methods where adequate and scientifically valid non-animal alternatives can be substituted.

For clinical investigations of tobacco products conducted outside the United States, but intended for submission to FDA, we recommend that clinical investigators conduct such studies so that the rights, safety, and welfare of human subjects have been protected in accordance with ethical principles acceptable to the international community (e.g., as reflected in International Conference on Harmonisation (ICH) guidelines such as Good Clinical Practice: Consolidated Guideline (ICH E6)) and that the data are scientifically valid and applicable to the U.S. population. The clinical 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.

If you intend to export a tobacco product, including for investigational use, you should refer to section 801(e) of the FD&C Act (21 U.S.C. 381(e)).

FDA recommends that sponsors prepare and maintain records and reports, as described in section VII of this guidance, for studies conducted outside of the United States but intended for submission to FDA to permit FDA to evaluate the conduct of a clinical investigation, including assessing the quality and integrity of the study data and protection of human subjects.

VII. PREPARATION AND MAINTENANCE OF STUDY RECORDS

FDA recommends that sponsors, CROs, sponsor-investigators, and clinical investigators maintain documentation to permit evaluation of the conduct of a clinical investigation, including assessing the quality and integrity of the study data and protection of human subjects. Records should be maintained for a period of at least 2 years after the date on which the investigation is terminated or completed or the date that the records are no

longer required for supporting marketing of a product or the later of the two dates if both apply. However, in no instance is a tobacco product manufacturer of a regulated tobacco product relieved of its obligation to comply with the requirements of section 904(b) of the FD&C Act (21 U.S.C. 387d(b)) or any other applicable recordkeeping or submission requirements.

To permit evaluation of the conduct of a clinical investigation, including assessing the quality and integrity of the study data and protection of human subjects, sponsors should prepare and maintain complete and accurate records relating to the use of investigational tobacco products, including, but not limited to:

- Records showing the receipt, shipment, or other disposition of the investigational tobacco product;
- All correspondence with another sponsor, a monitor, an clinical investigator, the committee or group formally designated to oversee research involving human subjects, or FDA;
- Signed investigator agreements including financial disclosure information; and
- Records concerning serious or unexpected adverse experiences.

In addition, sponsors should provide a copy of this guidance to clinical investigators and ensure that clinical investigators prepare and maintain complete and accurate records relating to the use of an investigational tobacco product, including, but not limited to:

- Records of the receipt, use, and disposition of the investigational tobacco product, including dates, quantity, and use by subjects;
- All correspondence with another investigator, the committee or group formally designated to oversee research involving human subjects, the sponsor, a monitor, or FDA;
- Signed consent forms;
- Records of each subject's case history and exposure to tobacco products used in the investigation. Case histories should include the case report forms, progress notes, and medical records;
- All relevant observations, including records concerning adverse experiences; and
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

VIII. HOW TO SUBMIT INFORMATION REGARDING PROPOSED USE OF AN INVESTIGATIONAL TOBACCO PRODUCT

For sponsors who would like FDA's feedback on a particular proposed use of an investigational tobacco product, there are three ways to submit information regarding proposed use of an investigational tobacco product:

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

FDA has created a form to assist you should you choose to submit information to FDA regarding the use of an investigational tobacco product. While use of the form is voluntary, it will help ensure that you are providing complete information for FDA's consideration and will facilitate processing and review by FDA. A copy of the form is attached as Appendix A to this guidance and is available on FDA's website.

FDA strongly encourages you to submit the information regarding your proposed use in an electronic format to facilitate efficiency and timeliness of data submission and processing. You can securely submit your information 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 www.fda.gov/ESG.

For submissions in paper, you should include the original signed cover letter, which prominently identifies the submission as a "Proposed Use of an Investigational Tobacco Product." A submission regarding proposed use of an investigational tobacco product submitted in paper or on electronic media should be sent to the address included on our website (www.fda.gov/tobaccoproducts).

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, "Proposed Use of an Investigational Tobacco Product – *name of the tobacco product under investigation*," submission date, and series number (e.g., "disc 1 of 2"). The files should include a signed cover letter prominently identified as a "Proposed Use of an Investigational Tobacco Product" 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.

Electronic Submission Formats

For clinical investigation information 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 without the use of additional plug-ins other than those provided by Adobe as part of Acrobat. For data files, we recommend that either Excel (.xls, .csv) or SAS transport (.xpt) files be used, and be accompanied by instructions for use and your statistical program code. Data contained in Excel files should be actual values and not calculated values from a cell formula. 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; and

- Create a submission table of contents and format it using bookmarks designed to help the reader navigate through the document efficiently.

IX. REQUESTING A MEETING WITH FDA

We recommend that persons who intend to study investigational tobacco products meet with FDA to discuss research plans.

Information about how to request meetings with CTP can be found in FDA's guidance: *Meetings with Industry and Investigators on the Research and Development of Tobacco Products* (http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM305282.pdf).

633 # Appendix A: Form: Proposed Use of an Investigational Tobacco
634 Product

Form Approval OMB Control No. 0910-3934
Expiration Date xx/xx/xxxx
See PRA Statement on page X

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
PROPOSED USE OF AN INVESTIGATIONAL TOBACCO PRODUCT

Sponsor Information		
1. Name of Sponsor Click here to enter text.		2. Date of Submission Click here to enter a date.
3. Sponsor Address and Contact		
Primary Address (Street Address, P.O. Box) Click here to enter text.	City Click here to enter text.	State/Province/Region Click here to enter text.
Address 2 (Apt, Suite, Unit, Bldg., Floor, etc.) Click here to enter text.	Country Click here to enter text.	ZIP or Postal Code Click here to enter text.
Telephone Click here to enter text.	Email Click here to enter text.	Fax
Authorized Representative Information (Individual residing or maintaining a place of business within the United States who is designated by the sponsor to receive communication from the FDA)		
4. Name of Authorized Representative Click here to enter text.		
5. Authorized Representative Address and Contact Information		
Primary Address (Street Address, P.O. Box) Click here to enter text.	City Click here to enter text.	State/Province/Region Click here to enter text.
Address 2 (Apt, Suite, Unit, Bldg., Floor, etc.) Click here to enter text.	Country Click here to enter text.	ZIP or Postal Code Click here to enter text.
Telephone	Email Click here to enter text.	FAX Click here to enter text.
Investigational Tobacco Product Information		
6. Name of Tobacco Product (Include Brand Name/Sub-Brand Name or Product code if available)		
7. Product Category Choose an item.	8. Product Sub-Category Choose an item.	
9. Is the tobacco product intended for investigational use a legally marketed product? (Select applicable) Yes, this product has grandfathered status. Please provide GF_#######if available. Yes, this product has a marketing order. Please provide STN (SE/EX/PM#######). Yes, this product has provisional status. Please provide STN (SE#######). No		

10. Will the clinical study involve actual use of the investigational tobacco product?

☐Yes ☐No

11. Related Submissions: List the FDA submission tracking numbers (STNs, IUXXXXXXX, etc.) for all of your previous requests for proposed use of this investigational tobacco product
Click here to enter text.

FDA Use Only	
CTP/DCC Receipt Stamp	STN #

Submission Information

12. This submission contains the following (Select all that apply)

☐ New Proposal, i.e., your first communication regarding the proposed investigational use of this product
☐ Additional Information IU####### (Check all that apply in the boxes below)

Protocol	**Administrative Amendments**
☐New Protocol, product not previously studied ☐New Protocol [Product previously studied, P#####] **Protocol amendments,** ☐Change in Protocol (include P#####) ☐New Investigator (include P#####) **Information Amendments** ☐Response to [DATE] FDA Request for Info ☐Composition, Design, & Manufacture of Product ☐Pharmacology/Toxicology ☐Clinical	☐Change in Sponsor ☐Change in Address ☐Notification to Withdraw Protocol [P#####] ☐Notification to Inactivate Protocol [P#####] ☐Notification to Withdraw all studies of Product [IU#######] **Report of Adverse Experience** ☐Initial Adverse Experience Report, Specify Protocol [P#####] ☐Follow-up Adverse Experience Report, Specify Protocol(s)[P#####]

Other Information
Other, Please attach the information *(Specify; e.g., updates on the status of studies, changes to investigational plan)*

13. Is any part of the clinical study to be conducted by (transferred to) a Contract Research Organization (CRO) ☐Yes ☐No
If yes, provide the name and address of the CRO, identification of the clinical study, and a description of the specific responsibilities being assumed by the CRO
Click here to enter text.

14. Are you referencing information in a Master File? ☐Yes ☐No If yes, please attach a copy of the letter of authorization from the master file owner that permits FDA to reference such file on your behalf.	
15. Name and title of the person responsible for monitoring the conduct and progress of the clinical investigations. Click here to enter text.	
16. Name(s) and title(s) of the person(s) responsible for review and evaluation of information relevant to the effects of the investigational tobacco product. Click here to enter text.	
Signature of Authorized Representative	Type Name, Title and Date

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A. Protocol Submission

If the submission is a NEW PROTOCOL, attach document(s) which include the following information

1. Table of Contents and Cover Letter
2. Background Information (include as applicable):
   a. summary of results of product testing and nonclinical studies that have been conducted previously on the specific investigational tobacco product
   b. summary of results of any clinical studies (both favorable and unfavorable)
   c. summary of information relevant to the health risks of the investigational tobacco product (e.g., available information on a marketed product that is similar to the investigational tobacco product)
   d. Study Protocol Name
3. General Investigational Plan
4. Name of Investigational Tobacco Product (include Brand Name/Sub-Brand Name or product code)
5. Description of Investigational Tobacco Product
6. Description of product design with schematics of the complete product and product components and a description of the design features (attach Product Chemistry, including HPHC table)
7. Complete list of uniquely identified components, ingredients, and additives by quantity in the investigational tobacco product, applicable specifications, and a description of intended function of each.
8. Name/Address of manufacturer of the investigational tobacco product
9. Description of methods, facilities, & controls used for manufacturing, processing, packing, and storing of the product(s)
10. Information demonstrating the stability of the product(s) during the conduct of the study

11. If comparator and/or placebo product(s) will be used, attach a table that contains the information in items #5 through 11 of this list for each product that will be used in the clinical study
12. A statement of the study objectives, hypotheses, and design
13. A summary of the informed consent procedures and provide a copy of Informed Consent forms and any other information provided to participants
14. Sample Case Report Form
15. Copies of packaging and labeling provided to investigators or subjects
16. Investigational Brochure (if more than one investigator)
17. The name and contact information for the committee or group formally designated to oversee research involving human subjects (e.g. Institutional Review Board or IRB).
18. Statistical Analysis Plan
19. List all of the study sites and for each site provide a summary of the qualifications for each clinical investigator who will be participating in the study at that site
20. Disclose financial arrangements between you and the investigator and any interest the investigator may have in the product under study or in the sponsor

B. **Protocol Amendment** If the submission is a PROTOCOL AMENDMENT, attach document(s) which include the following information

1. Table of Contents and Cover Letter
2. Revised protocol with the proposed changes clearly documented (i.e., track changes or red line)
3. 'Clean' version of revised protocol

C. **Information Amendment**

If the submission is an INFORMATION AMENDMENT, attach document(s) which include the following information

1. Table of Contents and Cover Letter
2. Additional information related to the amendment. Include all information from the list under "A: Protocol Submission" that is applicable to the amendment.

D. Administrative Amendment

If the submission is an ADMINISTRATIVE AMENDMENT, attach document(s) which include the following information

1. Cover Letter including details of the administrative change (e.g., change in sponsor or address)

E. Adverse Experience If the submission is reporting an ADVERSE EXPERIENCE, attach document(s) which include the following information
1. Table of Contents and Cover letter 2. Study Protocol Name 3. Name of Investigational Tobacco Product (Include Brand Name/Sub-Brand Name or product code) 4. Completed case report form 5. Any additional or follow-up information
F. Other Information If the submission is OTHER INFORMATION not described above, attach document(s) which include the following information
1. Table of Contents and Cover Letter 2. Additional detailed information

Appendix B: Frequently Asked Questions

What is an "investigational tobacco product"?

A: For purposes of the draft guidance on the use of investigational tobacco products, FDA has defined "investigational tobacco product" to mean a tobacco product that is: (1) a new or modified risk tobacco product that is not legally marketed; or (2) a tobacco product that is required to comply with a tobacco product standard and that does not conform in all respects to the applicable tobacco product standard, and is intended for investigational use.

A new tobacco product "is not legally marketed" if it is not exempt from the requirement to obtain a substantial equivalence order and is not subject to section 910(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and there is no substantial equivalence order or order under section 910(c) of the FD&C Act in effect for the product.* A modified risk tobacco product "is not legally marketed" if there is no order under section 911(g) of the FD&C Act in effect for the product. A modified risk tobacco product may also be a new tobacco product for which there must be in effect an order under section 910(c) of the FD&C Act.

> * A new tobacco product that is on the market under an exercise of FDA's enforcement discretion is an investigational tobacco product if it is intended for investigational use.

Under what authority can FDA permit the use of investigational tobacco products?

A: Section 910(g) of the FD&C Act gives FDA the authority to issue regulations to exempt tobacco products intended for investigational use from the requirements of Chapter IX of the FD&C Act. FDA intends to propose regulations establishing the conditions for exempting investigational tobacco products from certain FD&C Act requirements. Until then, investigational tobacco products are *not* exempt from applicable FD&C Act requirements, including premarket submission requirements and tobacco product standards. The draft guidance on use of investigational tobacco products describes FDA's current thinking regarding the definition of "investigational tobacco product" and discusses the kind of information FDA intends to consider in making enforcement decisions regarding the use of investigational tobacco products until regulations become effective or FDA provides written notice of its intent to change its enforcement policy.

What are the overarching factors FDA will consider in making enforcement decisions establishing conditions for the use of investigational tobacco products?

A: The factors FDA will consider generally in making enforcement decisions are potential public health concerns or other impacts on the public health.

What factors will FDA consider in making enforcement decisions regarding the use of investigational tobacco products in nonclinical laboratory studies?

A: As used in the draft guidance, the term "nonclinical laboratory study" means an in vivo or in vitro experiment in which tobacco products are studied prospectively in test systems under laboratory conditions.

In making enforcement decisions with respect to the use of an investigational tobacco product in nonclinical laboratory studies, FDA intends to consider whether there are controls on how and to whom investigational tobacco products are distributed, whether there are adequate procedures in place to assure that investigational tobacco products are not commercialized, and whether the study is designed to ensure the quality and integrity of the study data and permit other investigators to replicate the findings. One approach to ensure the quality and integrity of the study data would be to follow good laboratory practices as specified in 21 CFR part 58.

What factors will FDA consider in making enforcement decisions regarding the use of investigational tobacco products in clinical studies?

A: As used in the draft guidance, the term "clinical investigation" means any experiment or study involving an investigational tobacco product and one or more human subjects, including research, development, testing, and evaluation. Clinical studies are likely to raise concerns about human subject protection, public health, or both.

In making enforcement decisions with respect to the use of an investigational tobacco product in clinical investigations, FDA intends to consider the following:

- Whether there are controls on how and to whom the tobacco products are distributed;
- Whether the protocol for a clinical investigation and procedures used during the clinical investigation adequately provide for the protection of human subjects;
- Whether the investigation is designed to ensure the quality and integrity of the study data and permit other investigators to replicate the findings; and
- Whether there are adequate procedures in place to assure the investigational tobacco products are not commercialized. For example, investigational tobacco products should not be distributed for use except in accordance with a study protocol, and should not be promoted to consumers.

What kinds of information are relevant to FDA in making enforcement decisions with respect to a particular use of an investigational tobacco product in a clinical investigation?

A: Examples of information that may help FDA to evaluate specific proposed uses of investigational tobacco products include, but are not limited to:

- Information about the composition, design, and manufacture of the investigational tobacco product and any comparators or placebos;
- Information about the way in which a human subject will use the investigational tobacco product;
- Currently existing data and information regarding the investigational tobacco product, such as the results of product testing, nonclinical laboratory studies, results of favorable and unfavorable clinical investigations, and information available on marketed tobacco products similar to the investigational tobacco product;
- The study protocol;
- The packaging and labeling provided to investigators or study subjects;
- Recruitment materials and consent forms; and
- Information about any committee or group that has been formally designated to oversee the proposed clinical investigation.

How can I seek FDA's feedback regarding a proposed use of an investigational tobacco product?

A: FDA recommends that persons who intend to study investigational tobacco products meet with CTP to discuss research plans, including the conduct of nonclinical laboratory studies and clinical investigations. Information about how to request meetings with CTP can be found in FDA's guidance: *Meetings with Industry and Investigators on the Research and Development of Tobacco Products* (http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM305282.pdf).

For nonclinical laboratory studies, FDA encourages sponsors to meet with FDA to discuss, among other things, what, if any, animal testing is appropriate and the suitability and acceptability of non-animal tests for their particular tobacco product.

For clinical investigations, a sponsor may submit information regarding a proposed use of an investigational tobacco product to FDA for review prior to enrolling subjects. FDA encourages this type of voluntary submission because it will allow FDA to work with a sponsor to help ensure that the factors FDA considers in making enforcement decisions are appropriately accounted for – i.e., that there are controls on how and to whom the investigational tobacco products are distributed, that the protocol for the clinical investigation and procedures used during the clinical investigation adequately provide for human subject protection, that the clinical investigation is designed to ensure the quality and integrity of the study data and permit other investigators to replicate the findings, and that there are adequate procedures in place to assure that investigational tobacco products are not commercialized. The information FDA recommends you include in your submission is described in section V.1 of the draft guidance. FDA has created a form to assist you should you choose to submit information. While use of the form is voluntary, it will help ensure that you are providing complete information for FDA's consideration and will facilitate processing and review by FDA.

How do I submit information to FDA regarding a proposed use of an investigational tobacco product?

A: There are three ways to submit information regarding a proposed use of an investigational tobacco product:

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

If you elect to seek FDA's feedback, FDA strongly encourages you to submit the information in an electronic format to facilitate efficiency and timeliness of data submission and processing.

What information should be included in the protocol for a clinical study?

A: The information FDA recommends you include in your study protocol is described in section V.2 of the draft guidance.

Should I keep study records?

A: FDA recommends that sponsors, contract research organizations, sponsor-investigators, and clinical investigators maintain documentation to permit evaluation of the conduct of a clinical investigation, including assessing the quality and integrity of the study data and protection of human subjects. Section VII of the draft guidance describes some of the records FDA recommends maintaining. In no instance is a tobacco product manufacturer relieved of its obligation to comply with the requirements of section 904(b) of the FD&C Act or any other applicable recordkeeping or submission requirements.

When should I consult with FDA during the conduct of a clinical investigation?

A: FDA recommends that you consult with us and any committee or group formally designated to oversee research involving human subjects when certain events occur during the conduct of a clinical investigation, including when you:

- Amend your protocol;
- Add new investigators, including to replace investigators for cause; or
- Make changes to the investigational tobacco product or the way the product will actually be used by study subjects.

This will allow FDA to ensure that your use of an investigational tobacco product continues to appropriately account for the factors FDA intends to consider in making enforcement decisions.

If you are notified a study subject has a serious *and* unexpected adverse experience associated with the use of an investigational tobacco product, we recommend that that

you inform FDA, all participating clinical investigators, and any committee or group formally designated to oversee the study within a few days after initial receipt of the notification. In addition, we recommend that you notify FDA, all participating clinical investigators and any committee or group formally designated to oversee the study of any serious *or* unexpected adverse effect associated with the use of an investigational tobacco product within a few weeks after initial receipt of notification. If you submit information to FDA regarding any such adverse experience, you should submit such information through the safety reporting portal at https://www.safetyreporting.hhs.gov/fpsr/WorkflowLoginIO.aspx?metinstance=C1EB51816CC166C20BF09CF68EC9297B02BBD3A0.

What do I do if I have any questions regarding tobacco products intended for investigational use?

A: If you have submitted information regarding a proposed use of an investigational tobacco product, FDA will provide you with information regarding who to contact if you have related questions. Otherwise, you can direct questions to AskCTP@fda.hhs.gov or call 1-877-287-1373 (9am EST-4pm EST).