# Use of Investigational Tobacco Products

## Guidance for Industry and Investigators

## *DRAFT GUIDANCE*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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# Use of Investigational Tobacco Products

## 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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; consequently, investigational tobacco products are not exempt from FD&C Act requirements, including premarket submission requirements. This draft guidance supersedes the draft guidance of the same title dated September 2015 and, when final, will describe FDA's current thinking regarding the definition of *investigational tobacco product* and discuss 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'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 (CTP) at FDA.

## 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.

Tobacco products intended for investigational use would be considered "new tobacco products" if they meet the definition in section 910(a)(1) (21 U.S.C. 387j(a)(1)). The term *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;[2] 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.

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

[2] FDA's guidance for industry *Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007*, dated September 2014, provides information on how a manufacturer may establish that a tobacco product was commercially marketed in the United States as of February 15, 2007. For the most recent version of a guidance, check the CTP guidance Web page at https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

[3] FDA's draft guidance for industry *Applications for Premarket Review of New Tobacco Products*, dated September 2011, discusses the general procedure for submitting a premarket tobacco product application (PMTA), including who can submit a PMTA and when and how PMTAs can be submitted. When finalized, this guidance will represent FDA's current thinking on this topic.

[4] FDA's guidance for industry *Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products,* dated January 2011, and FDA's guidance for industry *Demonstrating the Substantial*

- 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; 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 (NSE).[5]

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 (21 U.S.C. 387k(b)(1)). 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.

Further, tobacco products must conform in all respects with any applicable tobacco product standards issued under section 907 of the FD&C Act (21 U.S.C. 387g). 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 deemed adulterated if it is

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*Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions (Edition 3)*, dated December 2016, discuss the submission process for substantial equivalence reports.

[5] New tobacco products that are the subjects of "provisional" substantial equivalence applications may be legally sold and distributed, unless FDA finds the product is NSE to a predicate product. A provisional substantial equivalence application is one that was submitted before March 23, 2011, for a new tobacco product that was first commercially marketed between February 15, 2007, and March 22, 2011.

[6] A tobacco product is a modified risk tobacco product if, for example, the label, labeling, or advertising explicitly or implicitly represents that the tobacco product presents a 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*, dated April 2012, provides information about submitting applications for modified risk tobacco products. When finalized, this guidance will represent FDA's current thinking on this topic.

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.

This guidance document is intended to help researchers who 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 on a case-by-case basis according to potential human subject protection concerns or other impacts on public health.

In making enforcement decisions, FDA generally intends to consider, among other things:

- Whether there are controls on how and to whom investigational tobacco products 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; and
- Whether there are adequate procedures in place to ensure that investigational tobacco products are not commercialized.[8]

FDA recognizes that it may be difficult to assess a difference in risk between the use of an investigational product and the participants' use of their usual tobacco product. Nonetheless, when designing the conditions of use in a study, investigators should carefully consider the risk implications for study participants and any nonusers (for example, friends, family, and colleagues) who may be exposed to the investigational tobacco product.

As used in this guidance document:

> An *investigational tobacco product* means a tobacco product that is intended for investigational use and is:
>
> (1) a new tobacco product; 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.

[8] With respect to the investigational use of deemed, finished tobacco products that were on the U.S. market on August 8, 2016, we refer you to FDA's guidance for industry *Investigational Use of Deemed, Finished Tobacco Products That Were on the U.S. Market on August 8, 2016, During the Deeming Compliance Periods*, dated October 2016. Note that the compliance timelines related to the deeming rule have been updated; see FDA's guidance for industry *Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule* dated November 2018 (Revised).

## III. PURPOSE

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 until regulations become effective or FDA provides written notice of its intent to change its enforcement policy. It is intended to assist persons who currently intend to submit study information on tobacco products to FDA and persons who conduct investigations using investigational tobacco products.[9] Such persons may include sponsors, investigators, sponsor-investigators, and contract research organizations (CROs).[10] This guidance also is intended to assist committees or groups formally designated to oversee human subject research (e.g., institutional review boards (IRBs)) involving investigational tobacco products.

For purposes of this guidance, a *clinical investigation* means an experiment or study in which an investigational tobacco product is administered to, dispensed to, or used by one or more human subjects.

As used in this guidance document, an *investigator* is the individual who conducts the investigation (e.g., under whose immediate direction the tobacco product is administered or dispensed to a subject). If an investigation is conducted by a team of individuals, the leader of the team is the *lead investigator* and is responsible for directing the investigation. A *sponsor* means a person who takes responsibility for or initiates an investigation (e.g., a tobacco product manufacturer or an academic institution). In those instances, in which an individual both initiates and conducts an investigation, the individual is a *sponsor-investigator*.

[9] To provide clarity regarding our interpretation of the drug and device definitions in the FD&C Act with respect to products made or derived from tobacco, FDA issued a final rule entitled *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"* (82 FR 2193, Jan. 9, 2017). FDA notes that the portions of the final rule that describe the circumstances in which a product made or derived from tobacco that is intended for human consumption will be subject to regulation as a drug, device, or combination product under the FD&C Act are in effect. The effective date, however, of the amendments to the existing medical product "intended use" regulations is delayed indefinitely. (83 FR 11639, March 16, 2018).

[10] The term *contract research organization* (CRO), as used in this guidance document, means a person who assumes, as an independent contractor with the sponsor, one or more of the obligations of the sponsor (e.g., design of a protocol).

# IV. FDA'S ENFORCEMENT POLICY FOR INVESTIGATIONAL TOBACCO PRODUCTS

## A. 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, among others, 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 investigational tobacco products for use in a clinical investigation are distributed. For example, whether investigational tobacco products are distributed with labeling indicating that they are limited to investigational use only and are only distributed to qualified investigators.[11]
- Whether the protocol for a clinical investigation and procedures used during the clinical investigation adequately provide for the protection of human subjects. For example, FDA intends to consider the proposed study population of a clinical investigation (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 the population to be enrolled in the study.
    - While we consider each protocol on its own merits, some of the issues we would consider include assessing whether the trial participants currently are nicotine-using subjects and what is the risk to them in light of the route of administration of the investigational product. We also would consider the adequacy of the study settings, including monitoring and stopping criteria.
- Whether a 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 research and health care communities and that the data are scientifically valid. One approach to implementing such procedures would be to conduct the study in accordance with the appropriate provisions found in 21 CFR part 50 (Protection of Human Subjects) and ensure study oversight by a qualified IRB duly constituted and operating in accordance with 21 CFR part 56 (Institutional Review Boards).[12] Sponsors with specific

[11] The term *qualified investigators*, as used throughout this guidance, means experts qualified by scientific training and experience to evaluate tobacco products.

[12] For additional, general information on clinical trials and human subject protection, go to: https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.

questions about human subject protection are encouraged to contact FDA at AskCTP@fda.hhs.gov.

### B. Use of Investigational Tobacco Products in Nonclinical Laboratory Studies

For purposes of this guidance, *nonclinical laboratory study* means in vivo or in vitro experiments in which investigational tobacco products are studied prospectively in test systems under laboratory conditions. We note that, for tobacco products, the data generated from nonclinical laboratory studies may provide important information regarding the relative toxicities of new or modified risk tobacco products.

Generally, FDA does not recommend that investigators correspond with us about the use of investigational tobacco products in nonclinical studies. However, sponsors of nonclinical studies may elect to meet with FDA early in the development process to discuss what, if any, animal testing is appropriate and the suitability and acceptability of non-animal tests for a particular tobacco product. FDA supports reducing the reliance on animal testing where adequate and scientifically valid non-animal alternatives can be substituted.

When animal-based nonclinical laboratory studies are conducted, 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, such as the Animal Welfare Act (7 U.S.C. 2131 et seq.) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (available at https://grants.nih.gov/grants/olaw/references/phspol.htm).

FDA encourages investigators to 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 (Good Laboratory Practice for Nonclinical Laboratory Studies).[13]

## 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 that is likely to be relevant to FDA's consideration of the factors described above. We encourage sponsors to meet with FDA to discuss their specific proposed uses of investigational

[13] In the *Federal Register* of August 24, 2016, FDA published a proposed rule entitled *Good Laboratory Practice for Nonclinical Laboratory Studies* to amend the regulations for good laboratory practices for nonclinical studies (81 FR 58342). Among other proposed modifications, FDA proposed to expand the scope of these regulations to include tobacco products as appropriate under the FD&C Act.

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 the proposed use of an investigational tobacco product to FDA for review prior to enrolling subjects in the planned investigation. We encourage this voluntary type of submission because it will help FDA in determining whether to exercise enforcement discretion based on the sponsor's investigational plan, including helping FDA assess the factors described above: e.g., that there are controls on how and to whom the investigational tobacco products for use in a clinical investigation are distributed; that clinical investigations provide adequate procedures for human subject protection and 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.

### A. 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. The amount of information that will assist FDA with providing the most informative feedback generally depends on the scope of the investigation. For example, for studies involving the use of legally marketed products that are subsequently modified, the information provided may be limited to the modification(s). Generally, FDA expects to consider and respond to these submissions within 60 calendar days.

The following information (or where applicable, an explanation of why such information is unavailable or not relevant) would generally help FDA evaluate the specific proposed use of an investigational tobacco product in a clinical investigation:

- Administrative information that:
  - Identifies the submission as information regarding the proposed use of an investigational tobacco product in a clinical investigation (or the addition of information to an existing submission);
  - Contains the name, address (physical and mailing address (if these addresses are different) along with an email address), telephone number and facsimile number of the sponsor; name, title, physical address, mailing address, 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;
  - 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., unfiltered cigarette or portioned snus);
  - Lists cross-references by FDA submission tracking number for 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;
- 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; and
- Contains the signature of the sponsor or the authorized representative.

- A description of the investigational tobacco product. For studies involving the use of legally marketed products that are subsequently modified, it would be helpful to receive only that information that relates to the modification.
  - It also will facilitate our review if we receive product information in a table format.
  - Alternatively, if appropriate, your reference to a tobacco product master file could help facilitate FDA review.[14]
- FDA recommends that the description of the investigational tobacco product include, as appropriate:
  - 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, components or parts,[15] ingredients, and additives[16] by quantity in the tobacco product, including product chemistry and a table of any harmful

[14] For more information on the use of master files, please see the guidance *Tobacco Product Master Files*, dated May 2016. This guidance is available on the CTP guidance Web page at https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

[15] In 21 CFR 1100.3, *component* or *part* is defined as any software or assembly of materials intended or reasonably expected (1) to alter or affect the tobacco product's performance, composition, constituents, or characteristics; or (2) to be used with or for the human consumption of a tobacco product. The term does not include anything that is an accessory of a tobacco product.

[16] In section 900(1) of the FD&C Act, *additive* is defined as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substances intended for use as a flavoring or coloring or in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding), except that such term does not include tobacco or a pesticide chemical residue in or on raw tobacco or a pesticide chemical (section 900(1) of the FD&C Act (21 U.S.C. 387(1))).

or potentially harmful constituents,[17] as well as the applicable specifications and a description of the intended function of each;
  - The name and address of the manufacturer(s) of the tobacco product and components or parts;
  - A description of the methods, facilities, and controls used for the manufacture, processing, packing, and storage of the investigational tobacco product; and
  - Data and information sufficient to demonstrate the investigational tobacco product will be stable during the conduct of the study.
- Any known or reasonably known information, both favorable and unfavorable, about the investigational tobacco product, such as results of product testing, nonclinical laboratory studies, and clinical investigations, and information on marketed tobacco products similar to the investigational tobacco product (if available);
- A study protocol;
- Identification of the study sites;
- Identification of the lead investigator(s) and a statement of his/her qualifications;
- 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 the informed consent form and a summary of the informed consent procedures to be followed;
- A copy of recruitment materials and any other information to be provided to participants, such as a debriefing script; and
- Information about the oversight committee or group (e.g., IRB) that has been formally designated to oversee the clinical investigation.

**Study Protocols**

Generally, FDA recommends that your study protocol include the following information, which may be considered should FDA assess the enforcement priority of a particular investigation:

- Protocol title;

[17] See FDA's guidance *"Harmful and Potentially Harmful Constituents" in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act*, dated August 2016 *(Revised)*, for information on our current thinking on the meaning of "harmful and potentially harmful constituent." This guidance is available on the CTP guidance Web page at https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

- A statement of the study objective(s), hypotheses, study endpoints, definitions, and success criteria;
- Background information, such as a brief description of the investigational tobacco product, a summary of relevant literature, the significance of the study to be conducted, and a summary of information relevant to the health risks of the investigational tobacco product. Such a summary could consist of available information on a marketed product that is similar to the investigational tobacco product;
- 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 dosing/exposure plan that describes the manner, quantity, and frequency for administration of the investigational tobacco product(s), including the principles of operation for the investigational tobacco product(s) (e.g., whether the tobacco product is administered via the mouth or nose and whether the tobacco product is ignited and, if so, by what means). In addition, the description should explain how the product is designed to be smoked, inhaled, swallowed, dissolved, sniffed, chewed, or otherwise ingested or absorbed into the body.
- A copy of data collection procedures and samples of data collection instruments;
- The timing for baseline and follow-up assessments, including assessment of adverse experiences, and duration of follow-up;
- A risk assessment, including a description of clinical procedures, laboratory tests, criteria for stopping the study, criteria for withdrawing a study participant, or other measures to be taken to monitor the effects of the product in human subjects and to minimize risk;
- A sample case report form;
- 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
- The name and address of any facility where laboratory testing will be performed.

We also recommend that the protocol include a statistical analysis plan that includes:

- A description of the statistical method(s) to be used and the reason for choosing this method(s);
- A discussion of sample size, including calculations of the power of the study and the level of significance or confidence level to be used;
- A description of the study design with appropriate controls for the testing of study hypotheses (selection of the controls should be based on the endpoint or effect to be evaluated). The study duration should allow for adequate assessment of selected endpoint(s) and/or effects; and
- The procedures that will 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. Procedures for the selection of human subjects should allow for generalizability of study results to the U.S. population, as appropriate.

### B. Additional Recommendations Regarding Human Subject Protection

To help ensure that studies are conducted in a manner that protects human subjects, FDA recommends that sponsors have procedures to keep the Agency and the sponsor's oversight 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 (e.g., changes to current investigational use or adverse experiences). Relatedly, ensuring that clinical investigators maintain complete and accurate records to account for receipt, use, and disposition of investigational tobacco products generally also helps to protect human subjects.

Furthermore, FDA recommends that sponsors keep records of the following information, which FDA will generally consider in determining its enforcement priorities:

- Protocol amendments;
- Names of the clinical investigators, including any clinical investigators who have been 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[18] adverse experience (for example, burns resulting from an exploding battery in an

[18] For 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.

electronic nicotine delivery system (ENDS)), 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.

- 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.

We encourage the reporting of adverse experiences associated with a clinical investigation of an investigational tobacco product to FDA through the FDA CTP Safety Reporting Portal for Researchers.[19]

If you choose to terminate a study, withdraw or inactivate a protocol, or want to withdraw 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 discontinuation. 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 there is a reasonable possibility that exposure to the investigational tobacco product is directly related to a serious and unexpected adverse experience, you should inform any clinical investigators who participated in the investigation of the reason(s) for discontinuing the clinical investigation.

## VI. STUDIES OF TOBACCO PRODUCTS CONDUCTED OUTSIDE THE UNITED STATES

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 Council for Harmonisation (ICH) guidelines such as Guideline for Good Clinical Practice (ICH E6(R2))) 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. For nonclinical laboratory studies of

[19] The researcher pathway for the FDA CTP safety reporting portal may be accessed at https://www.safetyreporting.hhs.gov.

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investigational tobacco products conducted outside of the United States, investigators should take measures to help ensure the reliability and validity of the studies as discussed in section IV.B of this guidance.

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 the 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 the protection of human subjects. FDA may seek to review records, and thus recommends that records be maintained and available to FDA for a period of at least 4 years after the date on which the investigation is terminated or completed or the date that the records are no longer considered necessary 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.

FDA believes that records that would permit the evaluation described above include:

- Records showing the receipt, shipment, or other disposition of the investigational tobacco product;
- Correspondence with another sponsor, a monitor,[20] a clinical investigator, the committee or group formally designated to oversee research involving human subjects, or FDA;
- Signed investigator agreements, including financial disclosure information;[21] and
- Adverse experience reports.

[20] For purposes of this guidance, the term *monitor* means a qualified individual designated by a sponsor or CRO to oversee the progress of an investigation.

[21] One approach to determine what type of financial disclosure information to gather would be to consider the appropriate provisions found in 21 CFR part 54 (Financial Disclosure by Clinical Investigators).

In addition, FDA recommends that sponsors provide a copy of this guidance to clinical investigators to assist them in preparing and maintaining records. Generally, records that would assist FDA's evaluation include:

- Records of the receipt, use, and disposition of the investigational tobacco product, including dates, quantity, and use by subjects;
- Correspondence with another investigator, the oversight 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, protocol amendments, and 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 four ways to submit information regarding a proposed use of an investigational tobacco product:

- Electronic format submitted via the CTP Portal;[22]
- Electronic format submitted via the FDA Electronic Submissions Gateway;[23]
- Electronic format submitted on physical media (e.g., CD, DVD); or
- Paper format.[24]

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. For the same reason, we also encourage you to provide us with a table of contents as to your submission.

Files submitted on physical media should be stored on a CD/DVD or flash drive. Physical 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. We recommend that you also include a paper copy of the cover letter in case we have difficulty accessing the physical media.

Should you choose to submit information to FDA regarding the use of an investigational tobacco product, FDA has created a form to assist you. Although use of the form is voluntary, it will help ensure that you are providing useful information for FDA's consideration and will facilitate processing and review by FDA. A copy of the form is attached to this guidance (Appendix A) and, when this guidance is final, will be available on FDA's Web site. For ease of processing, FDA suggests that you use this form whenever you submit information to FDA regarding a clinical investigation, for example, in response to an FDA request for information regarding your investigation or to submit a

[22] For information, go to: https://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/Manufacturing/ucm515047.htm.

[23] For information, go to: https://www.fda.gov/forindustry/electronicsubmissionsgateway/default.htm.

[24] Physical media and paper submissions may be sent via U.S. Mail or courier using the address on our Web site: https://www.fda.gov/tobaccoproducts/default.htm.

revised protocol. The form is not intended for use in submitting adverse experience reports.

### *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 Microsoft 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 of PDF files, we recommend that you:

- Create PDF files directly from an electronic source such as a word processing file or Excel file;
- Avoid image-based PDF files whenever possible because scanned images are more difficult to read and search. If you scan a paper 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 document 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

If a sponsor or investigator wishes to discuss the study of an investigational tobacco product with FDA, you may request a meeting with FDA as discussed in FDA's guidance *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*, dated July 2016 (Revised).[25]

[25] This guidance is available on the CTP guidance Web page at https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

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## 594 Appendix A: Form - Proposed Use of an Investigational Tobacco Product

Form Approval OMB Control No. XXXX-XXXX
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**

**Note:** FDA recommends submitting information only if this investigation involves an experiment or study in which an investigational tobacco product is administered to, dispensed to, or used by one or more human subjects. The time it takes to complete the form may vary – depending on the information you wish (or are able) to provide. For more information, please see the guidance *Use of Investigational Tobacco Products* on our website.

| Sponsor Information | | |
|---|---|---|
| 1. Name of Sponsor<br>Click here to enter text | | 2. Date of Submission<br>Click here to enter text |
| 3. Sponsor Address and Contact Information | | |
| Physical Address<br>Click here to enter text | City<br>Click here to enter text | State/Province/Region<br>Click here to enter text |
| Mailing Address (if different)<br>Click here to enter text | City<br>Click here to enter text | State/Province/Region<br>Click here to enter text |
| Telephone Number<br>Click here to enter text | Country<br>Click here to enter text | ZIP or Postal Code<br>Click here to enter text |
| Email Address<br>Click here to enter text | Facsimile Number<br>Click here to enter text | |
| 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<br>Click here to enter text | | |
| 5. Authorized Representative Address and Contact Information | | |
| Physical Address<br>Click here to enter text | City<br>Click here to enter text | State/Province/Region<br>Click here to enter text |
| Mailing Address (if different)<br>Click here to enter text | City<br>Click here to enter text | State/Province/Region<br>Click here to enter text |
| Telephone Number<br>Click here to enter text | Country<br>Click here to enter text | ZIP or Postal Code<br>Click here to enter text |
| Email Address<br>Click here to enter text | Facsimile Number<br>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)<br>Click here to enter text | | |
| 7. Product Category<br>Choose an item | 8. Product Sub-Category<br>Choose an item | |
| FDA Use Only | | |
| CTP/DCC Receipt Stamp | STN # | |

9. Is the tobacco product intended for investigational use a tobacco product that is a modification of a legally marketed tobacco product? (select applicable)

☐ Yes, and the legally marketed tobacco product that was modified has grandfathered status.
Please provide GF#######, if available.

☐ Yes, and the legally marketed tobacco product that was modified has a marketing order.
Please provide STN (SE/EX/PM#######).

☐ Yes, and the legally marketed tobacco product that was modified has provisional status.
Please provide STN (SE#######).

☐ No

10. Related Submissions: Please list the FDA submission tracking numbers (STNs, IUXXXXXXX, etc.) for previous submissions to CTP in connection with this investigational tobacco product.
Click here to enter text

Submission Information

11. This submission contains the following

☐ New Proposal (i.e., your first communication regarding the proposed investigational use of this product)
**or**
☐ Additional Information IU#######; IU#######; IU####### (list all applicable IUs)

| **Protocol** | **Information Amendments** |
|---|---|
| ☐New Protocol<br><br>**Protocol Amendments (check all that apply)**<br>☐Change in Protocol (include P#####)<br>☐Response to [DATE] FDA Request for Information<br>☐New Investigator (include P#####)<br>☐Other | ☐Additional Product Information<br>☐Other (e.g., final study report)<br><br>**Administrative Amendments**<br>☐Change in Sponsor or POC<br>☐Change in Address<br>☐Notification to Withdraw Protocol [P#####]<br>☐Notification to Inactivate Protocol [P#####]<br>☐Notification to Withdraw All Studies of Product(s) [IU#######] |

12. Is any part of the clinical study to be conducted by (transferred to) a contract research organization (CRO)?
☐Yes ☐No
If yes, please 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

13. Are you referencing information in a tobacco product 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.

14. Name and title of the person responsible for monitoring the conduct and progress of the clinical investigations (i.e., study monitor).
Click here to enter text

15. 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 (e.g., investigator, lead investigator, sponsor-investigator)
Click here to enter text

| Signature of Sponsor/Authorized Representative | Type Name, Title, and Date |
|---|---|
| | |

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**A. Recommended Administrative Information for Submission of New Protocols, Amended Protocols, and Information Amendments for Investigational Tobacco Product(s) (unless previously provided in a related submission and the information is still accurate)**

1. Identifying information that describes contents of the submission (i.e., cover letter)
2. Table of Contents
3. Description of the investigational tobacco product and any comparator or placebo to be used in the study
4. A description of the way the investigational tobacco product will be used by study participants
5. Any known or reasonably known information, both favorable and unfavorable, about the investigational tobacco product or similar marketed tobacco products
6. A new or amended study protocol
7. Identification of the study sites
8. Identification of the lead investigator(s) and a statement of his/her qualifications
9. Copies of all packaging and labeling to be provided to clinical investigators or study participants
10. A copy of the Investigator's Brochure, if applicable
11. A summary of the informed consent procedures to be followed and a copy of the informed consent form
12. A copy of recruitment materials and any other information to be provided to study participants (e.g., debriefing script)
13. Information about the oversight committee or group (e.g., IRB) formally designated to oversee the clinical investigation

**B.** In addition to items listed in section A, for a **New Protocol**, please also include the following:

1. Protocol title
2. Background information (include as applicable):
    a. summary of known or reasonably known results of any product testing and nonclinical studies that have been conducted previously on the specific investigational tobacco product
    b. summary of known or reasonably known 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)
3. A statement of the study objectives, hypotheses, endpoints, definitions, and success criteria
4. A description of the study design, including duration and extent of tobacco product exposure
5. A description of the study setting (e.g., clinical, community) and study population, including recruitment methods, inclusion/exclusion criteria, number of planned participants, and any planned comparator and/or control groups
6. A copy of data collection procedures and samples of data collection instruments
7. The timing for baseline and follow-up assessments and duration of follow-up
8. A risk assessment, including a description of clinical procedures, laboratory tests, and criteria for stopping the study or withdrawing a study participant
9. A sample case report form
10. A description of the plan to solicit and report adverse experiences and debrief subjects
11. The name and address of any test facility(ies)

**C.** In addition to items listed in section A, for a **Protocol Amendment**, please also include the following:

1. Revised protocol with the proposed changes clearly documented (i.e., track changes or red line). Include all information from the list under section B of this form that is applicable to the amendment.
2. "Clean" version of revised protocol

**D.** In addition to items listed in section A, for an **Information Amendment**, please also include the following:

1. Additional information related to the amendment. Include the information from the list under section B of this form directly above that is applicable to the amendment.

| | |
|---|---|
| **E.** | For an **Administrative Amendment**, please attach a cover letter including details of the administrative change (e.g., change in sponsor or address) |
| **F.** | For any **Other Information**, please attach document(s) that include the additional detailed information |

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