

The following slides were presented to attendees at the Society for Research on Nicotine & Tobacco's Annual Meeting, held February 21, 2018 in Baltimore, Maryland. The slides accompanied oral remarks by representatives from FDA's Center for Drug Evaluation and Research and Center for Tobacco Products. The slides include examples of FDA's approach with respect to the use of particular investigational products in the context of particular studies. Determining how any particular nicotine-containing product for investigational use will be regulated is a fact-specific inquiry made on a case-by-case basis.

TOBACCO PRODUCT OR MEDICAL PRODUCT?

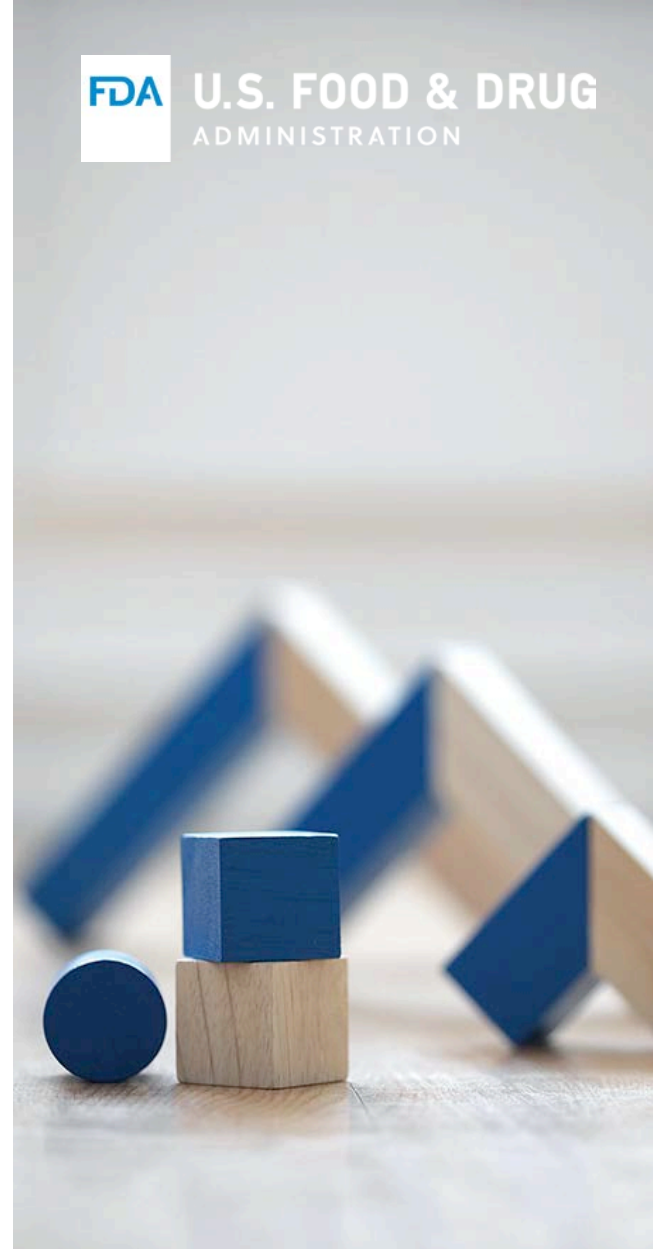
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FDA

U.S. FOOD & DRUG
ADMINISTRATION



- JURISDICTION RULE
- TOBACCO PRODUCT DEFINITIONS
- INVESTIGATIONAL TOBACCO PRODUCTS (ITPs)
- DRUG PRODUCT DEFINITIONS
- INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs)
- ITP OR IND?
- CONCLUSIONS



- The Tobacco Control Act defines tobacco product: any product made or derived from tobacco that is intended for human consumption
 - Definition excludes any article that is a drug, device, or combination product under the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Confusion arose as to when a product made from tobacco is considered a drug/device/combination product vs. a tobacco product.
- The Jurisdiction Rule* provides clarity about when products made or derived from tobacco will be regulated as tobacco products or as drugs, devices, or combination products.

*Docket Number: FDA-2015-N-2002; Published 01/09/2017

The Jurisdiction Rule describes two 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 a combination product under the FD&C Act.

- The product is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, including use in the cure or treatment of nicotine addiction (e.g., smoking cessation), relapse prevention, or relief of nicotine withdrawal symptoms.
- The product is intended to affect the structure or any function of the body in any way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000.

JURISDICTION RULE: MODIFIED RISK VS. MEDICAL PRODUCT



- Modified Risk Product: tobacco products that are sold or distributed for use to **reduce harm or the risk of tobacco-related disease**
 - May have the effect of lowering disease risk
 - May present **relatively less risk of disease or be less harmful** but do not affirmatively act to mitigate, prevent, or otherwise treat disease
 - Are still a tobacco product; users are still exposed to inherent (although reduced) risks
- Medical Product: **intended for disease mitigation or prevention**
 - Must be determined to be both **safe and effective** for the treatment of a specific condition(s)
 - Act affirmatively to combat a disease or health condition

TOBACCO PRODUCT DEFINITIONS

A tobacco product is a “new tobacco product” within the meaning of section 910(a)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) if:

- It was not commercially marketed in the United States as of February 15, 2007
- **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

INVESTIGATIONAL TOBACCO PRODUCT (ITP)



The September 2015 Draft Guidance* on Use of Investigational Tobacco Products describes an ITP as:

- a new or modified risk tobacco product that is not legally marketed, or
- 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

*Use of Investigational Tobacco Products Draft Guidance; published September, 2015; available for comment

MODIFICATION



Modification under 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.

When a marketed tobacco product is modified, the modified product becomes a new tobacco product.

INVESTIGATIONAL TOBACCO PRODUCTS

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, including premarket submission requirements.

The September 2015 Draft Guidance on Use of Investigational Tobacco Products states:

“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.”

Upon finalization of the deeming rule* in August, 2016:

- Newly deemed products that remain available on the market due to enforcement discretion (e.g., e-cigarettes) are not legally marketed – meaning these are ITPs if they are used for investigational purposes.
- The Draft Guidance on Use of Investigational Tobacco Products (available for comment) states that investigators should have “adequate procedures in place to ensure that investigational tobacco products are not commercialized.”

*Docket Number: FDA-2014-N-0189; Published 05/10/2016

On October 12, 2016, FDA published a guidance “Investigational Use of Deemed, Finished Products That Were on the U.S. Market on August 8, 2016, During the Deeming Compliance Periods.”

This guidance clarifies that FDA does not intend to enforce the premarket authorization requirements for newly deemed, finished tobacco products that were on the U.S. market on August 8, 2016. FDA is clarifying that the compliance policy described in the preamble to the deeming final rule applies to such products even if they are used in a scientific investigation.

To Clarify:

- If the tobacco product was on the market August 8, 2016 and will be used in an investigation without modification, FDA does not intend to enforce the premarket requirements during the compliance periods even if the tobacco product is being used in a scientific investigation as well as being marketed to consumers.
- If the tobacco product is modified, it becomes a new tobacco product and we recommend the study be submitted to FDA.

THE ITP PROCESS – GENERAL APPROACH*



1. Submit a “Request to Use an ITP” to CTP
2. CTP assesses administrative properties of the submission
 - a. Ensure the study involves investigational tobacco products under CTP jurisdiction
 - b. Ensure the submission can be assessed (e.g., in English, can be opened and read, product(s) identified, protocol included)
3. CTP conducts a multidisciplinary scientific assessment of use of the ITP in the context of the proposed protocol
4. Sponsor is notified of CTP’s assessment

*Described in the Draft Guidance on Use of Investigational Tobacco Products

SCIENTIFIC ASSESSMENT OF REQUESTS TO USE AN ITP



The primary focus of CTP assessment is whether use of the product(s), as proposed to be studied, raises concerns for human subject protection

CTP also assesses proposals for studies using investigational products to determine if:

- Sponsors can ensure that studies are well-controlled
- Data derived from studies will be reliable

Note: CTP does not review protocols that do not involve actual product use by humans (e.g., animal studies, perception studies)

DRUG PRODUCT DEFINITIONS

Drug is defined in § 201(g) of the FD&C Act as:

- (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary; and
- (B) articles **intended for use** in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles **intended for use** as a component of any articles specified in (A), (B), or (C).
- (D) articles (other than food) **intended to affect** the structure or any function of the body of man or other animals; and

A clinical investigation is defined in FDA's regulations as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects ... except for the use of a marketed drug in the course of medical practice"
(21 CFR 312.3)

INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs)

Section 505(a) of the FD&C Act requires that a new drug be the subject of an approved marketing application before it is transported or distributed across state lines

FDA has the authority under § 505(i) to exempt drugs intended solely for investigational use from this requirement

- The Investigational New Drug Application (IND) is the means through which sponsors of clinical investigations technically obtain an exemption from § 505(a)
- An IND allows sponsors to ship investigational drugs in interstate commerce for the purposes of conducting clinical investigations of the drug

WHEN IS AN IND REQUIRED?



When conducting a “clinical investigation” of a drug subject to § 505 of the FD&C Act or a biological product subject to the licensing provisions of the PHS Act

INDs are **NOT** limited to clinical investigations conducted in support of a marketing application!

Under FDA's regulations, a clinical investigation of **a drug that is lawfully marketed in the U.S.** is exempt from the requirement for an IND if:

- The study is not intended to be reported to FDA to support a new indication or a significant change in drug labeling or prescription drug advertising;
- The study does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with use of the drug;
- The study is conducted in compliance with requirements for IRB review and informed consent and is not intended to promote or commercialize the drug

FDA regulations contain other limited exemptions for specific clinical investigations of:

- In vitro diagnostic biological products
- Drugs intended solely for testing in vitro or in laboratory research animals
- Placebos
- Bioavailability studies

- Ensure the safety and rights of individuals who will participate in the clinical studies
- Ensure that clinical studies are planned and conducted by qualified investigators
- Help ensure the scientific quality and adequacy of clinical studies intended to evaluate a drug's safety and effectiveness

- Cover sheet
- Introductory statement and general investigative plan
- Investigator's Brochure
- Protocols (for each planned study)
- Chemistry, manufacturing, & control (CMC) information
- Pharmacology/toxicology information
- Previous human experience
- Additional information

THE IND PROCESS – BASIC STEPS



1. IND should be accompanied by Forms **FDA 1571** (cover sheet), **FDA 1572** (investigator's statement), and **FDA 3674** (certification of compliance with § 402(j) of the Public Health Service Act)
2. Submit an original and two copies of the IND to CDER's Central Document Room
3. Upon receipt of the IND, FDA will:
 - Assign an IND number
 - Forward IND to the appropriate reviewing division
 - Send the IND applicant a letter acknowledging receipt
4. CDER conducts a multidisciplinary scientific assessment of the IND in the context of the proposed protocol

THE IND PROCESS – FDA REVIEW



A clinical investigation must not begin unless it is subject to an IND that is “in effect” and the sponsor is in compliance with the requirements for IRB review and informed consent. An IND goes into effect **30 days** after FDA receives the IND, **unless**:

- FDA provides earlier notification; or
- FDA issues a clinical hold

A clinical hold means:

- A proposed study may not start
- An ongoing study must halt enrollment, and patients already in the study should be taken off therapy unless specifically permitted by FDA in the interest of patient safety

THE IND PROCESS – CLINICAL HOLDS



Grounds for putting a phase 1 study on clinical hold:

- Would expose persons to unreasonable and significant risk of illness or injury
- Clinical investigator(s) not qualified to conduct study
- Investigator brochure is misleading, erroneous, or materially incomplete
- Insufficient information to assess risks to subjects
- For study of a life-threatening disease, exclusion of 1 gender due to potential reproductive toxicity

Grounds for putting a phase 2 or 3 study on clinical hold:

- Any reason that applies to phase 1 studies; or
- Study plan or protocol is clearly deficient in design to meet its stated objectives

ITP OR IND?

- Sometimes it is not obvious. You can ask FDA for assistance. There is a cross-center FDA task force that is responsible for determining whether a study should be evaluated by CTP or one of the medical product centers at FDA.
- Generally, the default for an investigational product "made or derived from tobacco" is ITP unless the intended uses of the product bring it within the definitions of drug, device, or combination product, as described in the jurisdiction rule.
- FDA acknowledges that over time, some types of products may be evaluated by both CTP and CDER.
- For the protocol under review, FDA considers the purpose of the study, including the study hypotheses and objectives.

- What are the study's stated objectives? Does the study-design support the stated objectives?
 - Therapeutic endpoint?
 - Primary objectives vs. secondary objectives
- What is the nature of the product(s) being studied?
 - Made or derived from tobacco?
 - Using a product that is potentially exempt from the requirement for an IND?
- Is the study part of a drug development plan?

EXAMPLES

EXAMPLE 1: LOW NICOTINE CIGARETTES AND NICOTINE PATCH



Study Objective:

Evaluate impact of low nicotine research cigarette with and without NRT patch on nicotine exposure, smoking behavior, dependence/withdrawal, quitting intention, perceived risk and cardiovascular function'

ITP: Low nicotine research cigarette (not a marketed product)

Why this is an ITP:

- Objective is evaluating the use patterns of smokers with no intent to quit when they are provided low nicotine cigarettes \pm the nicotine patch
- Withdrawal symptom measures, puff topography, and use patterns are measures for evaluation but the study is not designed to evaluate the low nicotine cigarette as a smoking cessation treatment

EXAMPLE 1: LOW NICOTINE CIGARETTES AND NICOTINE PATCH



Why an IND **is not** required:

- The use of nicotine patch—a lawfully marketed drug product—by study subjects is **exempt** from the IND requirements under FDA’s regulations
- The low nicotine research cigarette is not intended to be used in the study in a way that would make it a drug, device, or combination product (as described in the jurisdictional rule)
 - Nicotine exposure, smoking behavior, quitting intention, perceived risk, and cardiovascular function ≠ therapeutic endpoints
 - Although examining dependence/withdrawal could suggest a drug use in certain contexts (e.g., when evaluating efficacy of a product for quitting smoking), that is not the case in this study
 - The study is examining well-known effects related to nicotine use
- Study is not part of a drug development plan

EXAMPLE 2: LOW NICOTINE CIGARETTES AND E-CIGARETTES



Study Objective:

‘Examine the effects of dual use of low nicotine cigarettes and e-cigarettes on nicotine compensation, toxicant exposure, product liking and reinforcement, and patterns of use in daily and intermittent smokers’

ITP: Low nicotine research cigarette (not a marketed product)

Why this is an ITP:

- The e-cigarette device and liquids were marketed prior to August, 2016 and are not being modified for the investigation – meaning these products are covered by the Oct 2016 Guidance
- Study focusing on abuse liability and consumer behavior when the ‘only cigarette’ is a low nicotine cigarette and e-cigarettes are an alternative nicotine source
- Measures include withdrawal symptoms, craving, and satisfaction but focus is dual use, not cessation therapy

EXAMPLE 2: LOW NICOTINE CIGARETTES AND E-CIGARETTES



Why an IND **is not** required:

- The low nicotine cigarettes and e-cigarettes are not intended to be used in the study in a way that would make them a drug, device, or combination product (as described in the jurisdictional rule)
 - In the context of this study, withdrawal symptoms, craving, and satisfaction are not therapeutic endpoints
 - Although examining dependence/withdrawal could suggest a drug use in certain contexts (e.g., when evaluating efficacy of a product for quitting smoking), that is not the case in this study
 - The study is examining well-known effects related to nicotine use
- Study is not part of a drug development plan

EXAMPLE 3: A HEATED TOBACCO PRODUCT AND CIGARETTES



Study Objective:

- Determine selected clinical risk endpoints in smokers who switch to a heated tobacco product compared to those who continue to use cigarettes

ITP: Heated tobacco product (not marketed in U.S.)

Why this is an ITP:

- Sponsor clearly indicates an intent to pursue a tobacco product marketing application in the future
- The study focuses on the product as a smoking alternative not a cessation therapy

EXAMPLE 3: A HEATED TOBACCO PRODUCT AND CIGARETTES



Why an IND **is not** required:

- The heated tobacco product is not intended to be used in the study in a way that would make them a drug, device, or combination product (as described in the jurisdictional rule)
 - The study is not designed to evaluate whether the heated tobacco product is effective as a smoking cessation aid or for any other therapeutic purpose
 - The study is examining well-known effects related to nicotine use
- Study is not part of a drug development plan

EXAMPLE 4: TRADITIONAL AND ELECTRONIC WATER PIPE USE

Study Objectives:

- Evaluate smoking behaviors and acute physiological exposure and responses (e.g., blood pressure) between traditional water pipe and electronic water pipe use
- Determine subjective ratings of use and likelihood of future use from traditional water pipe and electronic water pipe smokers

ITP: Traditional and Electronic Water Pipes

Why this is an ITP:

- Study involves administration of tobacco products and measures of smoking behaviors and physiological changes.
- The study focuses on the potential for water pipe use as a smoking alternative not a cessation therapy.

EXAMPLE 4: TRADITIONAL AND ELECTRONIC WATER PIPE USE



Why an IND **is not** required:

- The water pipes are not intended to be used in the study in a way that would make them a drug, device, or combination product (as described in the jurisdictional rule)
 - Physiological data being recorded to provide insight into how the water pipe products affect health, not to evaluate a therapeutic endpoint
 - The study is examining well-known effects related to nicotine use
- Study is not part of a drug development plan

EXAMPLE 5: HOOKAH SMOKING, CO GAS, AND CORONARY ENDOTHELIAL FUNCTION



Study Objective:

- Examine the acute effect of inhaled 0.3% CO gas on coronary endothelial function in young adult hookah smokers

Why this is not an ITP:

- Study involves use of hookah (which is a tobacco product). However, the hookah products were marketed prior to August, 2016 and are not being modified for the investigation – meaning these products are covered by the Oct 2016 Guidance.
- The investigational product is CO which is not a tobacco product.

EXAMPLE 5: HOOKAH SMOKING, CO GAS, AND CORONARY ENDOTHELIAL FUNCTION



Why an IND **is** required:

- The need for an IND triggered by how CO gas used in the study
 - Although hookah is smoked during study sessions, the hookah is not intended to be used in the study in a way that would make them a drug, device, or combination product (as described in the jurisdictional rule)
 - CO gas is being used to affect a structure/function of the body = drug use
 - CO gas is not made or derived from tobacco, therefore it is not a tobacco product
- The use of CO gas in the study does not qualify for any of the IND exemptions in FDA's regulations

NIDA Standardized Research E-Cigarette (SREC) to Support Clinical Studies

- Extensively characterized device with associated Tobacco Product Master File.
- Nicotine plasma C_{max} and T_{max} in experienced vapers / smokers similar to other e-cigs and cigarettes.
- Current clinical studies focus on harm reduction (FDA-CTP). Future plans include nicotine cessation studies (FDA-CDER).
- Cessation studies using this new device would require animal toxicology data (per FDA-CDER).
- For more information and characterization data:
<https://www.drugabuse.gov/funding/supplemental-information-nida-e-cig>



- The determination of whether an ITP or IND product often requires careful analysis.
- FDA has a task force and can assist sponsors and facilitate communication with the correct FDA center contact.
- The study objectives/hypotheses and the study's stated purpose are a key part of the differentiation between ITP and IND.
- Smoking cessation, withdrawal symptoms, and craving are frequently used measures in studies involving the use of tobacco products. It can be acceptable to assess these in the context of an ITP study, although typically as secondary outcome measures.

Questions?

SELECTED RESOURCES



- Federal Register Notice for the Jurisdiction Rule ([Link](#))
- FDA.gov section on INDs ([Link](#))
- CDER's list of contacts for pre-IND consultations ([Link](#))
- Guidance: Investigational Use of Deemed, Finished Tobacco Products That Were on the U.S. Market on August 8, 2016, During the Deeming Compliance Periods (2016) ([Link](#))
- Draft Guidance: IND Applications Prepared and Submitted by Sponsor-Investigators (2015) ([Link](#))
- Draft Guidance: Use of Investigational Tobacco Products (2015) ([Link](#))