Frequently Asked Questions
Responsiveness to FDA's Center for Tobacco Products Regulatory Authority
June 13, 2022

The FAQs detailed in this document are not specific to any funding opportunity announcement (FOA), but rather attempt to clarify research that is and is not within scope of the FDA's Center for Tobacco Products (CTP) regulatory authority.

For FAQs specific to currently active Tobacco Regulatory Science (TRS) FOAs, please use the links below:

- CASEL U54 RFA-OD-22-003 FAQs
- TCORS U54 RFA-OD-22-004 FAQs
- Secondary Analyses R21 RFA-OD-21-003 FAQs
- Biospecimen Collections R21 RFA-OD-21-004 FAQs
- TRS R01 RFA-OD-21-002 FAQs
- TRS K01 (Clinical Trial Not Allowed) RFA-OD-20-008 FAQs
- TRS K99/R00 (Clinical Trial Not Allowed) RFA-OD-20-009 FAQs
- TRS K99/R00 (Clinical Trial Required) RFA-OD-20-010 FAQs
- TRS K01 (Clinical Trial Required) RFA-OD-20-011 FAQs

Potential applicants to CTP-supported FOAs are *strongly encouraged* to consult with NIH scientific contacts listed in FOAs to confirm that their research ideas are responsive to the research priorities outlined in the FOA and to FDA CTP's regulatory authority. Only research that is within the regulatory authority of the FDA CTP will be considered for funding.

Questions and examples provided in this document are for illustrative purposes only and should not be viewed as definitive or comprehensive.

1. General Information

How do I know if my application is responsive to a given FOA?

This is a critical question, as each of the specific aims in the application must meet the following criteria to be considered responsive. The project must:

- Address the research focus of the FOA, and
- Fall within the scope of the FDA CTP's regulatory authority.

As such, applicants are strongly encouraged to contact the scientific research contacts listed in FOAs for feedback about responsiveness prior to submitting an application. Sharing your research ideas and specific aims and submitting a letter of intent (LOI) prior to applying will allow NIH staff to provide responsiveness feedback.

If your application is deemed responsive, it will undergo scientific peer review by experts convened specifically for that purpose (by the NIH Center for Scientific Review). If your application is deemed non-responsive, it will be withdrawn prior to evaluation of its scientific merit, i.e., peer review. Program officials will let you know if the application must be withdrawn from peer review.

2. Letter of Intent (LOI)

Am I required to submit a letter of intent (LOI)?

An LOI is not required, and it is not part of the peer review process. However, it allows NIH staff to estimate the potential review workload and plan the review. We suggest sending the LOI 60 days before the application due date. Investigators are encouraged to send their specific aims with their LOI so that NIH scientific research contacts can review their research ideas and specific aims prior to submitting applications, as all proposed research-specific aims must be within the regulatory authority of the FDA CTP in order to be deemed responsive. Applications that are non-responsive will not be reviewed.

Suggested content of LOI:

- Descriptive title of proposed activity
- Name(s), address(es), and telephone number(s) of the Program Director(s) (PD(s))/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity
- Specific aims

Where do I send the LOI?

The letter may be sent by email to: TRSP@mail.nih.gov
Or by regular mail to:
Tobacco Regulatory Science Program
Office of Disease Prevention
6100 Executive Boulevard
Room 3B01, MSC 7530
Bethesda, MD 20892-7530 (Use Rockville, MD 20852 for Express Mail)
Tel: 301-451-7464
Fax: 301-480-2230

3. FDA-CTP's regulatory authorities

The FDA CTP has regulatory authority over the manufacture, marketing, and distribution of tobacco products. What are some examples of these authorities?

The Family Smoking Prevention and Tobacco Control Act gave the FDA responsibility and authority to, among other things:

- Restrict the sale and distribution of tobacco products, including advertising and promotion, as appropriate to protect public health.
- Review modified risk tobacco product applications, such as those marketed for use to reduce harm, prior to their introduction to the market.
- Adjust warning labels for cigarettes and smokeless tobacco products in order to promote greater public understanding of the risks of tobacco use.
- Establish standards for tobacco products (for example, setting limits on harmful and potentially harmful constituents and nicotine levels) as appropriate to protect the public health.
- Review new tobacco products prior to their introduction to the market.

For more information, see "Family Smoking Prevention and Tobacco Control Act - An Overview"

In general, what areas of research are within the FDA CTP's regulatory authority?

Research is encouraged in the following scientific domains:

- Chemistry and Engineering
- Toxicity
- Addiction
- Health effects
- Behavior
- Communications
- Marketing influences
- Impact analysis

In general, what areas of research are not within the FDA CTP's regulatory authority?

The Family Smoking Prevention and Tobacco Control Act gives the FDA the authority to regulate the manufacture, marketing, and distribution of tobacco products to protect public health and to reduce tobacco use by youth. In general, the FDA CTP's regulatory authorities do NOT extend to the following:

- Setting tax rates for tobacco products
- Regulating therapeutic products, such as those marketed to treat tobacco dependence (regulated by other parts of FDA)
- Setting clean indoor air policies
- Regulating tobacco growing
- Requiring the reduction of nicotine yields to zero
- Providing cessation services
- Banning all cigarettes, smokeless tobacco products, little cigars, other cigars, pipe tobacco, or roll-your-own tobacco products
- Changing the minimum age to purchase tobacco products
- Mechanistic studies (i.e., basic science of disease development) unless biomarkers of harm with predictive value for disease development associated with tobacco product use is an outcome

4. COVID-19 related research

Is research on COVID-19 and tobacco use responsive to FDA CTP's regulatory authority?

It depends on the proposed research question. A study designed to investigate how COVID-19 impacts tobacco perceptions, use, and product access could be responsive to FDA CTP regulatory authorities. For example, a study designed to provide context to ongoing tobacco surveillance, evaluation research and/or characterize the public health burden of tobacco use is responsive to CTP regulatory authorities. Research designed to investigate the impact of tobacco use on COVID-19 infection, severity and disease outcome **primarily to inform** diagnosis and treatment of COVID-19 is not responsive to FDA CTP regulatory authorities.

5. Research related to disease risk, incidence, or progression

Is an application in which the primary outcome identifies differential effects of various tobacco products on disease risk, incidence, or progression of disease considered responsive?

Yes. An application identifying differential effects of various tobacco products on disease would be responsive. Examples might include:

- Pulmonary function-testing outcomes following use of various combustible tobacco products
- Oral manifestations following use of various tobacco products, especially new and emerging tobacco products

6. Toxicity, Addiction and Health Effects

Within the scientific domains of "toxicity" or "health effects," is an application which investigates the mechanisms and/or etiology of tobacco-related disease responsive?

It depends. Mechanistic and/or etiologic research is largely relevant to disease prevention or treatment, neither of which is within the FDA CTP's regulatory authority, so would not be considered responsive. These types of research may in some cases be responsive, but only if the outcomes of the research inform the mandate of the FDA CTP. For example, research that identifies which constituents and/or flavors in a particular tobacco product contribute to disease outcomes may be considered responsive.

Within the scientific domains of "addiction," toxicity," or "health effects," is a treatment intervention study designed to compare the effectiveness of various tobacco products on tobacco cessation considered responsive?

No. The FDA CTP's regulatory authority does not extend to regulating therapeutic uses of tobacco products as this authority rests with other Centers within the FDA. However, examples of research projects that would be considered responsive include: (1) an observational study to examine the natural history of whether participants quit smoking cigarettes while using a different tobacco product, and (2) assessing if communications regarding the health consequences of using tobacco products have an impact on usage rates. In many of its key regulatory areas, the FDA CTP is charged with assessing the impact of tobacco products on the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products—as well as the increased or decreased likelihood that existing users of tobacco products will stop using such products, and the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Within the scientific domains of "toxicity" or "health effects," is research in which the primary outcome informs treatment of disease considered responsive?

No. The FDA CTP does not regulate products or support development of clinical interventions intended for the treatment of disease. For example, pharmacotherapy for treatment of cancer or emphysema, screening, physical activity, or dietary interventions for heart disease would all be considered non-responsive.

Are studies of second-hand or third-hand smoke responsive?

It depends. As FDA CTP cannot set clean indoor air policies, research investigating second- or third-hand smoke that is designed to evaluate or support these policies would not be responsive. Studies examining the health effects of these exposures and could inform potential regulation of tobacco products may be responsive. For example, examination of the health impact of second- and/or third-hand exposures due to e-cigarette constituents or device parameters may be responsive.

7. Cannabis or marijuana research

Is a research proposal with primary aims designed to investigate cannabis or marijuana perceptions, addiction, and use when used in e-cigarettes considered responsive?

No. A study with marijuana as the primary outcomes is not responsive because FDA CTP does not regulate marijuana under its tobacco product authorities. However, research designed to evaluate the extent to which e-cigarettes users are using marijuana in their tobacco products as a means to more accurately characterize or assess tobacco product use behavior is responsive to FDA CTP authorities.

8. Research related to nicotine and/or nicotinic receptors

What types of research on nicotine and/or nicotinic receptors are appropriate for consideration of funding by the FDA CTP?

If the research provides information on outcomes such as motor activity, memory, or neuronal responses to particular ligands, the research is likely not responsive. Research to rapidly screen tobacco constituents for activity at the nicotinic receptor to determine their dependence potential would be considered responsive.

9. Biomarker research

What types of biomarker research may be appropriate for FDA CTP funding?

Applications identifying biomarkers of specific tobacco product exposure and/or disease and those with the potential to differentiate exposure of differing tobacco products could be considered responsive. Examples include:

- Biomarkers to measure exposure to new and emerging tobacco products.
- Biomarkers of disease (e.g., cancer, cardiovascular disease, pulmonary disease, and reproductive and developmental effects) that can be associated with specific measures of tobacco exposure.
- Development of a non-clinical biomarker of disease coupled with traditional toxicology and/or pharmacology studies to provide a relevant framework for the regulatory application.
- Studies linking biomarkers of disease in non-clinical models that translate to biomarkers that are measurable in the clinical setting.
- Magnitude of changes in biomarkers that translates into clinically meaningful impacts on human health outcomes.

Biomarker research may fall within the scope of one or more of FDA CTP interest areas, depending on the intended use of the biomarker. However, some biomarker research will remain outside of FDA CTP authorities, such as biomarker research with a primary focus to inform treatment.

10. Communications

Is the FDA CTP interested in graphic health warning research?

Yes, CTP is interested in graphic health warnings research. Please refer to specific funding opportunity announcements for priority research.

11. Marketing influences

Are studies examining the impact of restrictions on selling tobacco products in pharmacies or other types of retail establishments responsive?

Studies examining the impact of pharmacies or other types of stores ceasing the sale of tobacco products are not responsive, as the FDA cannot ban face-to-face sales in a particular category of retail outlets. However, a study proposing to understand how minors can access (use behavior) tobacco products in these establishments may be of interest to FDA CTP.

Is research regarding vape shops responsive to FDA CTP tobacco regulatory authorities?

It depends. If a vape shop is a retail establishment that sells tobacco products for personal consumption, FDA CTP has the authority to regulate the following research pertaining to the following retailer requirements:

- Checking ID to assure appropriate age for sales
- Not selling tobacco products to persons under the age of 21
- Not selling tobacco products via vending machines unless in an adult-only facility
- Not breaking open packages to sell smaller amounts
- Not giving away free samples to consumers (exception is free samples of smokeless tobacco can be provided in limited quantities in "qualified adult-only facilities")
- Only selling tobacco products and displaying advertisements that contain proper health warning statement(s)

See https://www.fda.gov/tobacco-products/retail-sales-tobacco-products/selling-tobacco-products-retail-stores for a list of retailer requirements.

Given FDA CTP's authority as it relates to vape shops as described above, an example of responsive research is understanding knowledge, attitudes, and behaviors of vape shop customers and retailers to inform communications about the health effects of ENDS. An example of research that would not be responsive are studies that assess whether retail locations are opened or closed, as FDA CTP does not regulate the number, type, location, proximity, or density of retail establishments.

Are products marketed as "tobacco free nicotine," i.e., synthetic nicotine, responsive?

Yes. Although the definition of a tobacco product is any product made or derived from tobacco and intended for human consumption, including any component, part, or accessory of a tobacco product, it is not clear whether products marketed as using synthetic nicotine are tobacco free. As such, examples of research that would be considered responsive include marketing and subsequent behaviors and developing analytical methods to assess whether nicotine is not derived from tobacco.

12. Impact analysis

What topics are considered responsive within the scientific domain of "impact analysis"?

The following types of analyses are examples of topics that would be considered responsive under "impact analysis":

- Computational/mathematical modeling and simulation and/or statistical modeling of the public health impact of potential FDA CTP action.
- Health and economic impact of tobacco use and/or tobacco regulatory policies on vulnerable populations.
- Economic burden (e.g., healthcare cost, productivity loss) of tobacco-related diseases on users and non-users (e.g., secondhand and thirdhand exposure).
- Studies evaluating the impact of tobacco regulatory actions (e.g., mandated changes in product characteristics) on consumer behavior or behavioral intentions.

Is research related to tobacco product prices as a result of taxes responsive?

No. As FDA CTP does not have the authority to set tobacco product prices or set tobacco taxes, research meant to inform pricing would not be responsive.

Are studies on the impact of state and local tobacco control policies responsive?

It depends upon the specific policies being examined and whether they fall under the purview of the FDA CTP. Studies evaluating the impact of a tobacco tax increase are not responsive, as the FDA CTP does not have regulatory authority regarding tax rates on tobacco products. Similarly, the FDA CTP does not have authority over the sale of tobacco cessation medications. For example, a study evaluating the effectiveness for tobacco cessation of providing free nicotine replacement therapy would not be considered responsive. Studies evaluating the impact of a tobacco advertising restriction, a ban on the sale of flavored tobacco products, restrictions on price promotions such as coupons and discounts, or restrictions on the sale of single serving products, however, may be considered responsive.

Are public opinion polls about tobacco regulations responsive to FDA CTP regulatory authorities?

No. Unlike state or local policymaking, where public support can be an important factor in the adoption and implementation of policies, public opinions about potential or proposed tobacco regulatory actions cannot be used to support federal regulations. However, research examining

understanding of regulations, or social norms or perceptions of tobacco products may be responsive.

13. Research including foreign populations or products

Will applications that propose to study products not yet available in the United States be considered responsive?

Potentially, yes. If the product(s) meets the statutory definition of a "tobacco product" under the Tobacco Control Act (i.e., any product made or derived from tobacco and intended for human consumption, including any component, part, or accessory of a tobacco product), then studies examining these products could be considered responsive. However, the application must demonstrate that the proposed research can directly contribute to the FDA CTP's regulatory authority over the manufacture, marketing, and distribution of tobacco products within the United States.

May researchers include foreign populations in their proposed research?

Foreign populations may be included. However, results from foreign populations research must be relevant to the U.S. population and U.S. regulation of tobacco products. For example, studies assessing biomarkers of exposure, biomarkers of potential harm, and health effects would be relevant to the extent that the findings could be generalized to the U.S. Studies assessing the impact of policies that FDA could replicate in the U.S. would be relevant. Studies assessing general knowledge or attitudes about tobacco products among foreign populations would not likely be relevant.

14. Products included in PMTAs and MRTPs

Would an application that proposed to study a heated tobacco product that is already included in a pre-market tobacco application (PMTA) or a modified-risk tobacco product (MRTP) application be considered responsive?

Potentially, yes. While a heated product is a tobacco product as defined in the Tobacco Control Act and would fall under the regulatory authority of the FDA CTP as a result of the deeming rule, both the responsiveness of a study investigating this product and its relevance to the FDA CTP priorities would depend upon the type of research being proposed.

15. Research related in vulnerable populations

Are studies addressing specific vulnerable populations responsive?

Yes, studies in vulnerable populations are responsive to CTP regulatory authorities. However, the population needs to be appropriate to the research question. The FDA CTP recommends research studies to include, where appropriate to the research question, populations of special relevance, including (but not limited to):youth and young adults, those with lower

socioeconomic status, certain races or ethnicities, sexual or gender minorities, underserved rural populations, those pregnant or trying to become pregnant, those in the military or veterans, and those with mental health conditions or substance use disorders.

For additional information on the NIH-FDA Tobacco Regulatory Science Program visit our website: http://prevention.nih.gov/tobacco/