Center for the Study of Tobacco Products
Pilot Research Program

Tobacco Regulatory Science: Research on New and Emerging Tobacco Products

Request for Applications

February 19, 2015
TOBACCO REGULATORY SCIENCE: RESEARCH ON NEW AND EMERGING TOBACCO PRODUCTS

RELEASE DATE: February 16, 2015

Center for the Study of Tobacco Products (CSTP), Department of Psychology, Virginia Commonwealth University (VCU)

APPLICATION RECEIPT DATE: May 1, 2015

PURPOSE OF THIS RFA

The passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) in June 2009, gave the Food and Drug Administration (FDA) the authority to regulate the manufacture, marketing, and distribution of tobacco products in order to protect public health. Under Section 901 of the FSPTCA, the FDA has authority to regulate tobacco products, defined as “any product made or derived from tobacco that is intended for human consumption, including any component, part or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory or a tobacco product)”.

Given this new regulatory authority and the fast pace of change in the U.S. tobacco marketplace, the FDA is acutely aware of the need to expand tobacco product research, and has dramatically increased the availability of funding in this area. A centerpiece of this effort is the establishment of a nationwide network of Tobacco Centers of Regulatory Science (TCORS) funded by the FDA via the NIH P50 mechanism. Because VCU has a strong history in regulatory science and tobacco product research, it has been successful in attracting a P50 research and training grant that started in September, 2013.

The overarching goal of the Center for the Study of Tobacco Products (CSTP) is to demonstrate an integrated, iterative evaluation model for Modified Risk Tobacco Products (MRTP) that uses analytic lab, human lab, RCT, and quantitative and qualitative methods to inform tobacco product regulation. Our demonstration begins with a comprehensive evaluation of electronic cigarettes (ECIGs) (see Attachment A for a description of major CSTP projects). However, new products may use designs not yet envisioned, requiring methodological innovations in order to be evaluated comprehensively. Regulatory science will need to keep up with these new designs, so that we do not find ourselves yet again following the lead of tobacco industry marketing. The Center’s pilot research program will help address the need for methodological innovation by ensuring that we have the flexibility to evaluate any novel tobacco product. We will also seek to incorporate other methods of product evaluation. The CTSP funds two pilot studies per year in which investigators throughout the Commonwealth of Virginia are eligible to apply.

AREAS OF INTEREST

The Pilot Research Program may be used to support research covering the broad spectrum of methods and approaches related to increasing our understanding and improving the regulation of tobacco products, especially new and emerging tobacco products. Initially, a priority will be to
encourage methodological innovation and to extend our demonstration of the evaluative model from ECIGs to other products (e.g., novel oral products).

Given the current status of tobacco regulatory science and research on new and emerging tobacco products, we are particularly encouraging applications addressing the following topics:

1. What are the constituents, components, and design features of new and emerging tobacco products (e.g., dissolvable tobacco products, e-cigarettes, hookah tobacco); and how do these features differ within the same class of products?

2. How do components and design features of new and emerging tobacco products affect the bioavailability of nicotine, other addictive substances, and harmful tobacco constituents?

3. How do design features of emerging tobacco products affect their abuse liability?

4. What are the tobacco use behaviors of individuals using new and emerging tobacco products, including the multiple tobacco use behaviors?

5. What are the cognitive and affective factors (e.g., perceptions, attitudes, beliefs) associated with use of new and emerging tobacco products; how does product labeling and marketing influence behaviors related to tobacco product use?

6. What biomarkers of exposure should be used to measure exposure to new and emerging tobacco products?

7. What adverse health effects might be expected from exposure to the constituents of new and emerging tobacco products?

8. What are the factors, including menthol and other flavorings that influence the appeal of tobacco products to both users and non-users, including youth and other vulnerable populations? What is the impact of these factors on experimentation, initiation, cessation, switching tobacco products, and multiple use?

9. What role do additives and flavors have on the abuse liability and toxicity of tobacco products?

10. At what level do changes to constituent exposure, as well as tobacco product components and design features affect consumer perceptions of the product?

11. What is the impact of state and local policies addressing the manufacture, sale and distribution of new and emerging tobacco products that may inform FDA tobacco product regulatory authority?

Specifically excluded is research on tobacco cessation. Other priority areas for tobacco regulatory science have been provided by the FDA (see: http://www.fda.gov/downloads/TobaccoProducts/NewsEvents/UCM293998.pdf). For the purposes of this RFA, the research questions identified by the FDA must be applied to the study of new and emerging tobacco products (e.g., electronic cigarettes, dissolvable tobacco).
FUNDS AVAILABLE

A total of $100,000 is available for this program per year. Two awards will be made each year with an individual award not to exceed $50,000. Awards will be for a maximum of 12 months.

Special Requirements:
- One no-cost extension, not to exceed 3 months, may be granted at the discretion of the grantor. Requests for no-cost extensions must be submitted in writing at least 60 days prior to the initially agreed upon completion date and must fully document and justify why the extension is needed.
- Grant funds may be used only for expenses clearly related and necessary to conduct the research.
- Allowable costs will follow OMB Circular A-21 (revised).
- Indirect/administrative costs will not be paid by this grant.
- Applicants should budget sufficient funds and time for the PI to attend a meeting in Richmond, Virginia to present the results of their studies to CSTP faculty and staff, as well as sufficient funds to present their studies at one national conference.

ELIGIBLE INSTITUTIONS

Applications are open to all public universities and colleges in the Commonwealth of Virginia and the CSTP’s partner university, American University of Beirut.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any full-time university faculty/staff with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for this award. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are encouraged to apply, as are new investigators or senior investigators with a new interest in new and emerging tobacco products. Faculty/staff currently receiving funding from the CSTP are not eligible to apply for this award.

PROTECTION OF HUMAN AND ANIMAL SUBJECTS

Grants funded under this program are subject to all applicable state and Federal laws and regulations regarding the protection of human and animal subjects. Before an award can be issued, the grantee will be required to show documentation of approval by the applicable institutional review board (IRB) or institutional animal care and use committee (IACUC). Applicants are solely responsible for securing appropriate IRB or IACUC approval and ensuring the protection of human and animal subjects.

APPLICATION PROCEDURES

Applicants must complete the attached Research Award Application Form and the Research Budget Form. A research plan must also be submitted which shall not exceed 12 pages, single spaced. Applications exceeding the page limit will be returned. Additional pages are allowable.
for relevant appendices. Appendices may not be used to merely extend the narrative. There is no
expectation that applications use the entire 12 pages.

The application package must be submitted as a **pdf document** sent by email to
jrkoch@vcu.edu. Please put “CSTP Pilot Research Program Application” in the subject line.
Where signatures are required, the applicant may use either a hand written or electronic
signature. The deadline for receipt of all applications is **May 1, 2015 at 5:00 pm EDT**.
Applications received after that date and time will not be considered.

CSTP staff persons are available throughout the grant process to provide consultation on the
preparation of the application.

**APPLICATION CHARACTERISTICS**

A complete application will include, **in the following order:**
- Research Award Application Form (see attached)
- Project Budget Form (see attached)
- Research Plan (limited to 12, single-spaced pages, 1 inch margins, 12-point font)
- Bibliographic References
- Biographical Sketches of Key Staff-- PHS 398/2590 Biographical Sketch, is preferred.
- Appendices (if any), including:
  - Measures
  - Letters of Agreement/Support (see Staff/Management Plan on p.5)

**REQUIREMENTS OF THE PROPOSAL RESPONSE**

To ensure that sufficient information is included for technical merit review, the **Research Plan**
should include the following and be organized under the following major headings. This section
is **limited to 12, single-spaced pages, 1 inch margins, 12-point font**.

**Specific Aims**
- The broad, long-term goals;
- Specific objectives and hypotheses to be tested;
- Summary of the expected outcomes; and
- The impact of this research on the regulation of tobacco products.

**Significance**
- The state of existing knowledge, including literature citations and highlights of
  relevant data;
- The rationale of the proposed research;
- Gaps that the project is intended to fill; and
- The potential contribution of this research to tobacco regulatory science and public
  health.
Innovation
- Why concepts and methods are novel to the research field, and
- Description how the study design and outcomes are innovative.

Approach
- Investigators’ preliminary studies, data, and experience relevant to the application and the experimental design;
- Overview of the experimental design;
- Description of methods and analyses to be used to accomplish the specific aims of the project;
- Discussion of potential difficulties and limitations and how these will be overcome or mitigated;
- Expected results, and alternative approaches that will be used if unexpected results are found;
- Projected sequence or timetable (work plan);
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work;
- Detailed discussion of the way in which the results will be collected, analyzed, and interpreted;
- Description of any new methodology used and why it represents an improvement over the existing ones.

Staffing/Management Plan
- A description of the role of all key project staff.
- Management plan that identifies the organizational location for the project, lines and mechanisms of authority and responsibility, and how the project will be managed.
- Written agreements/letters of support for other participating organizations should be included in an appendix. Written agreements should specify the roles and responsibilities of each party.

Future Research and Capacity Building
- How the project will enhance the capacity of the institution/PI to conduct research tobacco regulatory science, particularly as it applies to new and emerging tobacco products.
- What steps will be taken to extend this line of research upon completion of the grant and, in particular, what sources of funding will be sought.
- How the results of the research will be disseminated and, in particular, what publications, grant applications and/or other products are anticipated as a direct result of the research. Specifically identify one or more journals to which you will submit your work for publication and one or more grant programs/announcements to which you will respond.

Budget Narrative/Justification
- A detailed, justified line item budget.
Animal and Human Subjects (not included in the 12 page limit)

- For human subjects, describe their proposed involvement; inclusion/exclusion criteria; the inclusion of any vulnerable populations; recruitment and consent procedures; copy of consent forms; potential risks, their likelihood and seriousness; procedures for protecting against risks; and the reasonableness of the risks in relation to the benefits of the study.
- For animal subjects, describe the proposed use of animals; the justification for the use of animals and choice of species; the veterinary care of the animals involved; procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research; and the method of euthanasia to be used and if it is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association, and if not, the justification.

Failure to submit any component of the proposal response may result in finding the proposal non-responsive.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness and responsiveness by staff of the CSTP. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration, as determined by the director of the CSTP Pilot Research Program.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by a multi-disciplinary committee drawn from the CSTP Executive Committee. In addition, if proposals are received requiring expertise not possessed by members of the scientific review group, in order to provide a competent review consultation from persons with appropriate technical expertise will be sought.

REVIEW CRITERIA

All proposals will be evaluated using the criteria below. Proposals will be ranked according to their accumulated scoring.

1. **Significance/Relevance.** What is the relevance of the proposed study to the regulation of new and emerging tobacco products? Does the study address an important problem in the field of tobacco regulatory science? If the aims of the study are achieved, how do they advance scientific knowledge? (Weight = 20 points)

2. **Approach.** Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the study? Are potential problem areas acknowledged and alternative tactics considered? (Weight = 25 points)

3. **Innovation.** Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the study challenge existing paradigms or develop new methodologies or technologies? (Weight = 15 points)
4. **Investigator.** Are key staff appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the staff’s experience? (Weight = 10 points)

5. **Environment.** Does the scientific environment in which the work will be done contribute to the probability of success? Is there evidence of institutional support? Is there a commitment of the resources, cooperation and/or collaborative arrangements needed to implement all components of the study? Is there demonstrated access to research subjects or databases to conduct the research? (Weight = 15 points)

6. **Capacity.** To what extent will implementation of the proposed research build the institution’s and PI’s capacity to engage in tobacco regulatory science research? Are the plans for the dissemination of research findings and the pursuit of future funding support adequate? What is the likelihood of obtaining other funding support in the future? (Weight = 10 points)

7. **Budget.** Are the proposed budget and the requested period of support in relation to the proposed research reasonable? (Weight = 5 points)

In addition to the above criteria, the following will be considered in the review, if applicable.

8. **Protections.** The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project.

9. **Inclusion.** The adequacy of plans to include subjects from both genders and all racial and ethnic groups (and subgroups) as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

**RECEIPT AND REVIEW SCHEDULE**

<table>
<thead>
<tr>
<th>Application</th>
<th>Receipt Date</th>
<th>Award Notification</th>
<th>Start Date</th>
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<tbody>
<tr>
<td>May 1, 2015</td>
<td>August 1, 2015</td>
<td>September 1, 2015</td>
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**SPECIFIC REQUIREMENTS OF THE GRANTEE**

1. Each PI will submit a brief, written progress report at the study’s midpoint that will describe progress to date (including adherence to research timelines and participant enrollment data), any preliminary findings, challenges encountered and strategies to address challenges.

2. Each PI will present the results of his/her study at one of the CSTP’s monthly seminars. This will be done prior to the submission of a final written report so that critical feedback can be incorporated into the report. This presentation shall be made within three months of completing the study.

3. Each PI will prepare a final written report that includes implications/recommendations for the regulation of tobacco products. These reports should be in journal manuscript format to speed the process of dissemination.
4. Webinars using voice over PowerPoint software will be produced of each pilot research presentation so that these can be easily shared across centers and with the broader scientific and regulatory communities.

5. Final reports, PowerPoint presentations and webinars will be posted on the CSTP website. They will also be made available to other TCORS for posting on their websites.

6. A brief executive summary (no more than two pages), appropriate for a non-technical audience, must be prepared and submitted to the CSTP.

7. Pilot research PIs will budget for one national conference presentation to aid in wider dissemination.

8. Each PI will provide, on a biannual basis, information required for the evaluation of the CSTP. This will include: (a) information on applications for funding that extend the pilot research work, (i.e., the pilot research is used as a preliminary study in the application); (b) the number of peer reviewed publications resulting from the pilot research; and (c) the number of conference presentations resulting from the pilot research.

**WHERE TO SEND INQUIRIES AND APPLICATIONS**

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Attachment A
CSTP Major Projects

Overview

The U.S. tobacco marketplace is changing quickly, with a seemingly endless number of new tobacco products entering the market. However, the science base required to develop effective regulations for these products lags far behind. One necessary tool is a model for evaluating all types of “modified risk tobacco products” (MRTPs). MRTPs are novel tobacco products marketed with the claim that they reduce harm or risk associated with conventional products. Predicting tobacco product harm or risk requires an understanding of MRTP constituents using analytic methods, toxicant exposure and abuse liability using human lab methods, longer-term effects using randomized control trial (RCT) methods, and attitudes, beliefs, and perceived effects using quantitative and qualitative methods. The overarching goal of the Center for the Study of Tobacco Products (CSTP) (Thomas Eissenberg and Robert Balster, Co-Directors) is to demonstrate empirically an integrated, iterative MRTP evaluation model that uses all of these approaches to inform tobacco product regulation across all product types. The initial focus of our efforts is on “electronic cigarettes” (ECIGs). Strictly defined, ECIGS are not MRTPs, but they are novel, marketed now, increasingly popular, and should be subject to regulatory action. Thus they offer an outstanding opportunity to demonstrate how the model we propose can inform regulatory policy. The Center’s major research projects are described below.

Analytic Lab Methods

Project 1, Analytic Lab Methods for Modified Risk Tobacco Product Evaluation (Alan Shihadeh, Project Director), shows how our analytic lab methods can inform pre-market evaluation to determine whether a proposed MRTP (i.e., ECIGS) has potential to modify disease risk by producing physiologically relevant doses of nicotine while reducing toxicant yield. Project 1 will also show the utility of these analytic lab methods for post-market evaluation of toxicants produced by ECIGS, especially when they are used in non-marketed, “unorthodox” ways. Thus, Project 1 demonstrates how FDA regulation can be informed by analytic lab methods before and after an MRTP is brought to market. The specific aims of Project 1 are to demonstrate how analytic lab methods can be used to: 1) Determine how design features and behavior interact to influence MRTP nicotine yield; 2) Predict MRTP user toxicant exposure; and 3) Study how unorthodox use behavior influences MRTP nicotine and other toxicant yields. In sum, in Project 1 we draw on our engineering expertise and record of innovation in tobacco product testing to demonstrate application of physical principles for rapid screening and empirical methods for the systematic study of ECIG toxicant yields under real-life use conditions. These principles and methods will provide FDA analytical tools essential for regulating MRTPs efficiently and scientifically. This study is funded by the Food and Drug Administration (1P50DA036105-01), Thomas Eissenberg and Robert Balster Co-Principal Investigators, and is one of four major projects funded by the Tobacco Centers of Regulatory Science Program.
**Human Lab Methods**

Project 2, Human Lab Methods for Modified Risk Tobacco Product Evaluation (Alison Breland, PD), will show how human lab methods can inform pre-market evaluation by determining the behavior, effects, and toxicant exposure associated with ECIG use, and also how these methods can inform abuse liability assessment, a critical factor in effective regulation. It also demonstrates the utility of human lab methods for post-market evaluation of MRTPs, especially when products are used differently than intended. The specific aims of Project 2 are to: 1) Demonstrate how human lab methods can reveal product use behaviors, toxicant exposure, and effects; 2) Demonstrate how human lab methods can determine product abuse liability; and 3) Determine how unorthodox use behavior influences ECIG effects. In sum, Project 2 draws on our record of expertise and innovation in human lab evaluation of tobacco products to demonstrate how these methods contribute to an integrated and iterative model of MRTP evaluation that will inform FDA regulation of these products. This study is funded by the Food and Drug Administration (1P50DA036105-01), Thomas Eissenberg and Robert Balster Co-Principal Investigators, and is one of four major projects funded by the Tobacco Centers of Regulatory Science Program.

**Randomized Controlled Trial Methods**

Project 3, Randomized Controlled Trial Methods for Modified Risk Tobacco Product Evaluation (Thomas Eissenberg, PD), will show how RCT methods can inform product evaluation by examining the influence of real-world product use on biomarkers of toxicant exposure and disease risk, reports of adverse events, and concurrent use of traditional tobacco products. Despite the popularity of electronic cigarettes (ECIGS), little robust evidence is available regarding ECIG safety or effectiveness. Instead, assertions are made that ECIGs likely will reduce tobacco toxicant exposure, probably produce no adverse events, and therefore may lessen the risk of tobacco-caused disease by reducing cigarette use. In fact, the data addressing how long-term ECIG use influences toxicant exposure, user health, and concurrent cigarette smoking are very limited. However, each of these issues can be addressed empirically using an RCT. This project’s goal is to demonstrate how RCT methods can be used to evaluate MRTPs generally and ECIGS particularly. This study is funded by the Food and Drug Administration (1P50DA036105-01), Thomas Eissenberg and Robert Balster Co-Principal Investigators, and is one of four major projects funded by the Tobacco Centers of Regulatory Science Program.

**Quantitative and Qualitative Methods**

Project 4, Quantitative and Qualitative Methods for Modified Risk Tobacco Product Evaluation (Aashir Nassim, PD), will show how, once an MRTP (e.g., ECIGS) is marketed, mixed method approaches can provide context that helps explain patterns of MRTP consumption and prevalence. Project 4 will also demonstrate how mixed methods can be used to generate empirically-based, descriptive models of MRTP-related attitudes, beliefs, motivations and perceived effects (including adverse events) associated with the product when it is used as it is marketed, as well as non-marketed, “unorthodox” use behaviors. Finally, Project 4 will demonstrate how alternative data sources can be used to refine regulation by providing detailed information about marketed and unorthodox MRTP use methods. There are two specific aims for
Project 4. First, we will characterize and describe the attitudes and beliefs, motivations, and perceived effects associated with ECIG behaviors. Concept mapping (CM), an integrated mixed method participatory research approach, will be used to characterize and describe user attitudes and beliefs regarding ECIGs, motivations or reasons for ECIG use and perceived beneficial and adverse effects of ECIG use. Second, we will examine methods of unorthodox MRTP behaviors. We will use alternative data sources (e.g., YouTube, internet forums) to conduct a descriptive content analysis of videos and text depicting unorthodox ECIG use behavior such as mixing high-dose nicotine liquids and/or dripping liquid directly on the ECIG heater. In sum, Project 4 demonstrates how an innovative, mixed method approach can be used to describe the attitudes, beliefs, and motivations of MRTP users and investigate MRTP effects as well as describe unorthodox MRTP use behavior. These methods are relevant to developing and refining MRTP regulation in a comprehensive and iterative fashion, as described in the Center’s overarching evaluation model. Thus, this project provides FDA essential tools for ongoing, empirically-driven MRTP regulation. This study is funded by the Food and Drug Administration (1P50DA036105-01), Thomas Eissenberg and Robert Balster Co-Principal Investigators, and is one of four major projects funded by the Tobacco Centers of Regulatory Science Program.