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PSYCHOLOGICAL
ASSOCIATION

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Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20815

Submitted electronically to <http://www.regulations.gov>

Re: Docket No. FDA-2014-D-1939 (Agency Document No. 2015-24218). Use of Investigational Tobacco Products: Draft Guidance for Industry and Investigators. Published in the Federal Register, September 24, 2015 (80 FR, pp. 57623-57627, 2015)

Overview

The Society for Research on Nicotine and Tobacco (SRNT), the College on Problems of Drug Dependence (CPDD), and the American Psychological Association (APA) submit these comments in response to the U.S. Food and Drug Administration's (FDA) request for comments on its draft guidance for industry and investigators entitled "Use of Investigational Tobacco Products" published in the Federal Register, September 24, 2015. Our organizations represent scientists who conduct valuable research on nicotine, tobacco products, and associated health-related outcomes. We are deeply concerned that the scientists who conduct research on novel nicotine products, including electronic nicotine delivery systems (ENDS, also known as electronic cigarettes or vaporizers), will be required to submit Investigational Tobacco Product (ITP) applications that, if based substantially on the Center for Drug Evaluation and Research (CDER) model for Investigational New Drug (IND) applications, will effectively curtail their ability to conduct this needed research. The proposed IND requirement would present overwhelming challenges for researchers to meet, given that they are not the sponsors of these diverse and rapidly changing nicotine/tobacco products, and thus would not have access to or be able to provide the information needed in an ITP/IND application. These potential requirements would severely damage researchers' ability to investigate the potential public health implications of these novel products and would drastically slow down and limit the science base needed for appropriate policy and public health decisions. The costs of such requirements, in halting needed scientific investigations, in placing unreasonable and impossible to meet demands on researchers, and in creating undue burden on academic researchers, would be a great disservice to the people in the United States.

Although the Draft Guidance does not specifically mention ENDS, we are concerned about their potential inclusion in the Guidance based on previous comments and discussion with FDA officials. For example, in a February 16, 2015 letter to FDA Commissioner Hamburg, we (SRNT, CPDD, along with the American Association for Cancer Research, AACR, and the International Association for the Study of Lung Cancer - IASLC) expressed concern about requirements for researchers to submit ITP and/or IND applications for ENDS research involving what might be broadly defined as "clinical investigations." Responding with a letter on April 28,

2015, Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research (CDER) discussed the applicability of this process for ENDS research. In addition, the National Institute on Drug Abuse (NIDA) website describes a similar application process for research involving ENDS. Thus, our concerns about the applicability of the Draft Guidance to ENDS follow from these public official comments.

The 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA) called for the FDA to regulate tobacco products based on a scientific foundation. To achieve this goal, the FSPTCA allocates funding for the FDA and the National Institutes of Health (NIH) to expand the science base for tobacco product regulation and to develop future generations of professionals trained in tobacco regulatory science. Both the FDA and NIH have made notable strides in cultivating and encouraging relevant research. However, the proposed Draft Guidance threatens to severely limit this needed research base and to discourage new and seasoned scientists from engaging in this line of research. Indeed, attempting to meet these requirements would potentially stop the pipeline of developing new investigators in this needed area of research.

Our comments are based on a number of key points:

- (1) There has been a dramatic increase in use of specific ENDS products (e.g., modular systems); for some of these ENDS products nicotine delivery is now comparable to that of cigarettes.
- (2) Rapidly changing products, local regulations, media, etc. requires flexibility that the ITP/IND process as outlined would not allow. Rapid evolution of ENDS products requires a fast turnaround and flexible process for approval of research ENDS products to ensure that the scientific evidence keeps pace with existing products on the market.
- (3) The lack of FDA coherence and guidance regarding the roles of CTP and CDER in tobacco regulatory science and requirements for an ITP/IND will hamper research efforts.
- (4) There is tremendous concern regarding the regulatory latitude for independent scientists to conduct research and the likely burden required of independent academic scientists to produce the same level of evidence for an IND as a tobacco product manufacturer to use a specific product in research.

ENDS Research is Needed

The FDA, NIH, and the broad scientific research community agree that there is a pressing need for a broad program of research to provide the science base for ENDS regulation and policy (Walton et al, 2015). Many of the key areas of needed research are likely to be considered "clinical" or "clinical endpoints" and thus would be subject to, and severely burdened by IND requirements such as those [described by NIDA](#) and the ITP requirements described in the Draft Guidance. For example, in a November, 2013 NIH electronic cigarettes workshop (Walton et al, 2015) several key areas of research were identified and now serve as guidance in identifying gaps and priority research targets. Yet, many of these would be unlikely to be achieved if subject to the requirements of the Draft Guidance.

ENDS Are Rapidly Evolving Products

ENDS are increasingly versatile products that are adaptive to individual users' needs (Yingst et al., 2015). These products, often called personal vaporizers and modular products,

allow users flexibility in how they operate and assemble their devices, with users being able to create personal vaporizers with parts and liquids made by different companies. These more advanced modular vaporizer products are growing rapidly in their prevalence and preferences among users (Dawkins et al., 2015). Such products, like many other consumer products regulated by FDA, might be regulated with standards for allowable ingredients and appropriate instructions to minimize harm. We look forward to finalization of the Deeming Rule that will presumably elaborate on FDA's approach to the draft guidance and likely have consequence for further research to guide regulation.

Draft Guidance Presents Barriers and Burdens That Will Slow Vital Research, Some of Which Appear Insurmountable

Because of the FDA's IND/ITP requirements, researchers represented by our organizations have already experienced barriers and delays in their ability to carry out the research that is needed to advance the tobacco regulatory science base. These researchers include scientists at the Tobacco Centers of Regulatory Science (TCORS) (FDA and NIH supported research) and several of the NIH Centers of Biomedical Research Excellence (COBRE), which together stand ready to provide the science foundation vital for FDA regulation of ENDS and other products. SRNT, CPDD and APA agree that research is needed to guide regulation, public health messaging, and policy, and this need is increasing by the day as products evolve and use expands. Indeed, our researchers have responded quickly with grant applications for new research and proposals to extend ongoing research to address these and other clinical endpoints with regards to ENDS. Most unfortunately, these researchers have learned that many of the highest research priority studies may not be possible in the near future, if at all. In fact, their efforts have already been hindered or prevented by FDA's requirements for IND/ITP applications in place since 2013.

One example of the challenges faced by researchers comes from an experience investigating very low nicotine products. Commercially available low tar and nicotine and very low nicotine products including Quest® brand cigarette have been included in clinical studies by NIDA extramural and clinical researchers over many years. The first harbinger of a potential serious impediment to research involving ENDS, in fact, was in the application of the IND/ITP requirement to a study involving the commercially available Quest® cigarettes at the NIDA intramural program in 2013. Completion of all required elements of the IND was not possible and after nearly a year of effort by the intramural researchers, the study plan was withdrawn; the study was ultimately conducted in Canada without NIH support or NIH researcher involvement. This one example highlights the burden and challenges that would be faced by researchers. Given that the intramural researchers at NIDA, with all their support and background, could not complete the IND, one could imagine that independent academic researchers, without the backing of the NIH, would find such requirements even more challenging, especially for early career investigators.

As was mentioned in the SRNT et al. February 16, 2015 letter to FDA, an informal survey of investigators by way of the SRNT membership email listserv in December 2014 revealed that several investigators had already learned that they would not be able to conduct studies that had been approved by NIH review committees, their institutional review boards (IRBs), and in some cases funded by the NIH/FDA. Other investigators who had been developing applications for grants to conduct such studies decided not to expend the effort to complete such applications until the IND/ITP issues were resolved and a workable process is in place. Some of these potential proposals represent truly creative ideas that were inspired by the November 2013 NIH FDA ENDS research conference and have the potential to address what

were determined by the FDA and NIH representatives as high priority research (e.g. Walton et al. 2015).

Additional polling in November 2015 of the SRNT members who are likely to conduct the needed research found that the reporting burden of the proposed requirements would be impossible to meet. Specifically, the SRNT members expressed strong concerns that it was unrealistic to expect academic researchers, with no affiliation with industry or manufacturers of ENDS components or devices, to be able to complete the required elements of the IND. Estimates of the time burden were grossly underestimated as well. The researchers also felt that given the rapidly changing ENDS products and components, any process or requirements that are developed will need to have great flexibility to accommodate the evolution of ENDS products.

Concerns Related to Safety

Most of what we know about the behavioral, cognitive, and clinical effects of tobacco products, including their abuse and dependence potential, comes from research conducted without the requirement of an IND, and includes effects on craving, withdrawal, patterns of use, and cessation. In fact, much of the science that laid the foundation for FDA's 1996 Rule to assert regulatory authority over tobacco (including "addiction-related" and "structure-function" research findings establishing the "drug effects") of tobacco and nicotine would not have occurred had the IND/ITP application requirement been exercised when much of this research flourished in the 1970s through 1990s.

This research included studies of a wide range of cigarette brands, nicotine delivery yields, research cigarettes from the National Cancer Institute, various modified types of cigarettes, including denicotinized cigarettes, carbon element and electrically heated cigarette like devices, smokeless tobacco products, lozenge-type tobacco products, tubular nicotine inhalers, dissolving strips and more. Study safety and ethical issues related to this body of work were addressed by ensuring that research participants were not exposed to higher levels of nicotine and other substances than they were already exposed to using licit and commercially available tobacco/nicotine products, with attention to subject inclusionary and exclusionary factors and more. As is the case with ENDS, those studies were conducted with products that were neither designed nor manufactured to the standards of drugs and with the information that would be needed to complete submission of Drug Master Files (DMF), and thus could not meet the standards of approved or potentially approvable drug products. Many of these studies simply would not have occurred had IND or ITP applications been required.

Our researchers have used, and will continue to use, a variety of other means to ensure the safe, ethical, and valid conduct of research. Measures taken to ensure the protection of research participants typically include, for example, examining the literature or other documents related to the investigational product's safety; if possible conducting content analysis of the product for the most relevant harmful constituents; and incorporating measures to monitor the safety of the participants. These measures depend on the nature of the study, but would include adequate exclusionary criteria, regular monitoring of vitals, health changes and adverse events, amount of product used, and assessment of exposure levels (e.g., carbon monoxide, cotinine).

Comment on the Drug Master File Approach (Draft Guidance, lines 309-332)

This regulatory hurdle makes clinical research with commercially available products difficult, if not impossible, because scientists do not have access to the required information that would allow them to obtain IND applications. Many products and product components are manufactured in China, and the detailed information necessary to complete the DMF section of the IND application is not available. In fact, several researchers have already found that US

ENDS marketing companies that have been approached do not have or are unwilling to share information required for the DMF, several claiming that they do not have access to such information.

Furthermore, the second and third generation products already on the market are designed to rely upon various commercially available fluid solutions (“juice”) made by broad range of manufacturers, large and small, many of which are based outside the US and with no practical way for investigators to obtain DMF information. It is possible that at some point in the future all allowed nicotine liquids will be subject to a Master File type process with FDA, but that is of little help in the nearer term and does not address the multitude of other kinds of information required for an ITP/IND application.

The focus of our comments is not on IND requirements that might be appropriate for sponsors of products seeking FDA approval of a specific ENDS product for therapeutic use, such as for approval and labeling as smoking cessation product via a New Drug Application (NDA). In such cases we would defer to negotiations between the FDA and the sponsor as to what information would be needed and if that would include an IND requirement as is typical in new drug product development. Our comments are not intended to represent NDA sponsors. We are researchers endeavoring, primarily with support of FDA and or NIH, to conduct research to serve FDA’s regulatory efforts, public health, and the advancement of science.

Comments on Specific Statements in the Draft Guidance

The following comments are neither exhaustive nor necessarily the largest concerns, but are presented to illustrate the sort of line by line evaluation needed for a thorough evaluation of the Draft Guidance, ideally with input from our organizations and members in public forums.

Line 159. The definition of “sponsor,” as used in the Draft Guidance is overly broad. As used in this guidance document, sponsor means “a person who takes responsibility for and initiates a nonclinical laboratory study or clinical investigation. In limited instances in which an individual both initiates and conducts an investigation, the individual is a sponsor-investigator. A sponsor of a study may be a tobacco manufacturer, a scientific institution, or any other person who takes responsibility for and initiates the scientific investigation of tobacco products.” Thus, based on this definition, an academic researcher with no ties to industry or means or intent to develop a product for market, or as a new tobacco product, or new drug product could be considered a “sponsor” and thus be required to fulfill the same obligations as a manufacturer, regardless of the research question. We believe this will stifle academic-generated research in this important area.

Line 220. One of the FDA proposals refers to “Whether the protocol for the clinical investigation and procedures used during the clinical investigation adequately provide for the protection of human subjects.” We believe that the current practice of submitting protocols to local Institutional Review Boards, like those used for many other tobacco, drug, and ENDS studies that do not happen to require a ITP/IND, are sufficient to ensure subject safety without increasing the burden on academic researchers.

Several specific information requests would be difficult, if not impossible, for academic researchers not working directly with an industry sponsor. The following are some examples of these difficult requests. In our opinion, had these been required in prior decades, we would not have established the basis for abolishing the FTC test method, nor would we have been able to safely and ethically address so many other issues fundamental to tobacco control policy and tobacco product regulation.

- a. **Line 293.** Lists, by FDA submission tracking number, cross references for all previous submissions referenced in the submission
- b. **Line 313.** 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
- c. **Line 317.** A complete list of, or a reference to the manufacturer's complete list of, uniquely identified components, ingredients, and additives by quantity in the tobacco product, including product chemistry and a table of any harmful or potentially harmful constituents (HPHCs), as well as the applicable specifications and a description of the intended function of each
- d. **Line 324.** A description of the methods, facilities, and controls used for the manufacture, processing, packing, and storage of the tobacco product
- e. **Line 326.** Data and information sufficient to demonstrate the tobacco product will be stable during the conduct of the study

The foregoing highlights the importance of a guidance that distinguishes between tobacco control research and research by product sponsors who are developing products for commercialization. The FSPTCA envisioned research to be led by NIH/FDA supported investigators, including through mechanisms such as TCORS, as vital to guide regulation and public health policy. We do not believe that the FSPTCA envisioned a pharmaceutical development model relying upon INDs and DMF requirements. For sponsors who seek to develop an ENDS product for a CDER approved indication with a New Drug Applications, FDA may well treat that sponsor for that application as any pharmaceutical product sponsor. We are not commenting on those potential scenarios.

The sorts of requirements in the Draft Guidance, if extended to ENDS research, on top of, or in place of, existing IND requirements, will be extremely burdensome and are more likely to stifle than to facilitate the very research that FDA and our nation need to progress in tobacco product regulation and tobacco control policy. Much of these proposed requirements are simply not feasible for an academic researcher who is not conducting the research on behalf of an industry sponsor.

Summary

The ITP/IND requirements would impose significant burdens on researchers, and in many cases, may make key research practically impossible. Millions of people in the U.S. are already using ENDS, and we need to address rapidly, and with integrity, many of the pressing research priorities about the public health implications of these products. Some of the most important questions, such as whether ENDS help facilitate cessation of combustible tobacco products, or whether they provide withdrawal relief, are unlikely to be answered adequately in the U.S. with these proposed requirements. The scientific community needs to be able to assess potential benefits as well as risks of these commercially-available products to make regulatory recommendations. This information is vital to the FDA's regulatory mission to protect public health.

We hope that the FDA considers our comments and the grave concerns of the research community on the draft guidance as it develops the regulations. We do not propose to provide specific advice as to how FDA should modify its approach, but instead urge FDA to consider these issues and concerns as it develops viable pathways for conducting the research that FDA seems to agree elsewhere is vital to guide regulation and policy.

We urge FDA to consider that ENDS should be treated similarly to a broad range of other tobacco products that have been studied for decades and are still being investigated in laboratories without INDs. These research studies have been invaluable for assessing the theoretical viability of various tobacco products to reduce withdrawal and/or cigarette smoking, promote cessation, and inform public policy and education. Such research does not supplant the considerable additional research that may be required by FDA for approval of NDAs, drug indications, and claims.

To adequately address the complexity of issues identified in the draft guidance, we strongly recommend that FDA hold public hearings on this issue as quickly as possible and include SRNT, CPDD and APA in these discussions. This type of forum will be essential to identifying workable pathways for the conduct of research. Constraining research on tobacco products is both harmful to the research community and to FDA as the agency depends on rigorous science to inform regulatory actions. Therefore, constructing barriers to research greatly hampers the FDA's ability to regulate tobacco products effectively. It is in the FDA's interest to engage in a constructive and collaborative approach with the research community in this process. Previous public hearings on tobacco products have provided invaluable forums for the Agency to learn from key stakeholders and vice versa.

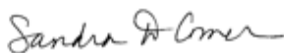
We offer our leadership and are eager to meet with your staff to provide additional perspectives, including the identification of more viable and more appropriate mechanisms of oversight than the ITP/IND application process. Together we can develop a workable path to make possible and expedite research on ENDS.

Our organizations and many of the members we represent are eager to serve and to do what they do best: conduct the highest quality research to serve public health, guide regulation, and advance science. We look forward to working with you to find a pathway that protects the safety of research participants and simultaneously allows this much-needed research to occur.

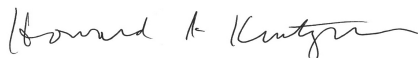
Sincerely,



Robin Mermelstein, Ph.D.
President, Society for Research on Nicotine and Tobacco



Sandra D. Comer, PhD
President, The College on Problems of Drug Dependence



Howard Kurtzman, Ph.D.
Acting Executive Director for Science, American Psychological Association

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