Tobacco Regulatory Science: Research to Inform Regulatory Action at the Food and Drug Administration’s Center for Tobacco Products

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Received November 8, 2013; accepted February 13, 2014

ABSTRACT

The U.S. Food and Drug Administration (FDA) promotes the development of regulatory science to ensure that a strong evidence base informs all of its regulatory activities related to the manufacture, marketing, and distribution of tobacco products as well as public education about tobacco product constituents and effects. Toward that end, the FDA’s Center for Tobacco Products (CTP) provides funding for research studies with scientific aims that fall within its defined regulatory authority. However, given their traditional biomedical focus on basic and applied research, some researchers may not understand the principles of regulatory science or the types of studies CTP funds.

The purpose of this paper is (1) to clarify the definition of regulatory science as a distinct scientific discipline, (2) to explore the role of tobacco regulatory science in order to help researchers understand the parameters and types of research that can be funded by CTP, and (3) to describe the types of research efforts that will inform the FDA’s public health framework for tobacco product regulation.

INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act), specifies the creation of the U.S. Food and Drug Administration’s (FDA) Center for Tobacco Products (CTP), which established an Office of Science (OS) to ensure that a robust science base informs the center’s regulatory actions (Family Smoking Prevention and Tobacco Control Act, 2009). To meet its mission, CTP-OS assesses existing scientific evidence and supports new research that will inform regulatory action to protect the public health.

A vast amount of research confirming tobacco’s addictive and toxic properties, its negative impact on health, and knowledge, attitudes, perception, and behaviors about tobacco provides a solid scientific rationale for numerous Tobacco Control Act provisions and regulatory actions based on those provisions. CTP-OS is continuing to develop the evidence base to inform regulation. Accordingly, CTP has identified seven categories of research priorities—product diversity, addiction, toxicity and carcinogenicity, health consequences, communications, marketing, and economics and policy—to promote the scientific advancement of regulatory authorities over tobacco products. CTP is currently funding research projects in collaboration with the National Institutes of Health (NIH), the FDA’s National Center for Toxicological Research, the Centers for Disease Control and Prevention, contract research organizations, and others and will continue to solicit and fund new research studies on an ongoing basis.

CTP funds research studies with scientific aims that fall within its defined regulatory authorities, which include regulation of tobacco products; regulation of tobacco product advertising, marketing, promotion, distribution, and sales; enforcement of regulations; supporting regulatory science; and public education (Husten & Deyton, 2013). For example, CTP can develop product standards such as those related to nicotine yields, constituents and harmful components, product construction, testing and measurement, and sale and distribution restrictions (Husten & Deyton, 2013). In fulfilling its regulatory authorities, CTP is charged with assessing the impact of tobacco products on the health of the population as a whole, taking into account product users and nonusers and assessing the increased or decreased likelihood of product initiation and cessation.

Given this regulatory and functional context, designing research studies that meet the criteria for CTP funding requires a shift in thinking for many researchers. Some researchers may not understand the principles of tobacco regulatory science—the scientific discipline that supports the evaluation of the risks and benefits of tobacco regulatory decisions and provides a robust scientific foundation for regulatory policies. Furthermore, even those researchers who understand the goals...
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of tobacco regulatory science still may not have a clear conception of the types of studies CTP supports.

This paper clarifies the definition of regulatory science as a discipline, explores the role of regulatory science in the context of regulating tobacco products, and describes the types of research efforts that will inform FDA’s public health framework for tobacco product regulation.

WHAT IS REGULATORY SCIENCE?

Regulatory science is a distinct scientific discipline with “independent goals and measures not found in either the basic or applied sciences” (Uchiyama, 1995, p. 186). In general, regulatory science focuses on ensuring that scientifically valid techniques, tools, and models are available to evaluate products and, subsequently, to inform regulatory actions that promote optimal health outcomes (Hamburg, 2010; Norman, 2012). In this light, regulatory science clearly plays a vital role in public health.

Although researchers began to develop scientific tools and techniques to evaluate product safety beginning in the early part of the 20th century (Patel & Miller, 2012), regulatory science has only relatively recently emerged as a discrete scientific discipline. In general, academic health research often focuses on basic mechanistic or applied studies that pursue a more precise characterization of disease processes or clarify treatment effects on disease pathophysiology, rather than studies that could directly inform regulatory activities, such as those that identify a dose–response relationship or products’ differential effects on disease risk, incidence, or progression. FDA Commissioner Margaret Hamburg and other regulators in the United States and abroad believe that investment in regulatory science has been inadequate (Sukkar, 2011); according to Hamburg, “Despite being a critical component of the scientific enterprise, regulatory science has long been underappreciated and underfunded” (Hamburg, 2011). To encourage a greater focus on regulatory science, in 2011, the FDA developed a strategic plan to promote the advancement of regulatory science (Food and Drug Administration, 2011; Goodman, 2012). The plan identifies eight priority areas: modernizing toxicology to enhance product safety, stimulating innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes, supporting new approaches to improve product manufacturing and quality, ensuring FDA readiness to evaluate innovative emerging technologies, harnessing diverse data through information sciences to improve health outcomes, implementing a new prevention-focused food safety system to protect public health, facilitating development of medical countermeasures to protect against threats to the United States and global health and security, and strengthening social and behavioral science to help consumers make informed decisions.

REGULATORY SCIENCE RELEVANT TO TOBACCO PRODUCTS

Regulatory science plays a key role in medical product development; FDA regulators rely upon scientific evidence that demonstrates the relative risks and benefits of new drugs and devices in their efforts to ensure a safe and expedient path toward patient use. However, FDA’s traditional “safe and effective” standard for evaluating drugs and other medical products does not apply to tobacco products. Accordingly, regulatory science requires a different definition in the context of tobacco control and has been defined as “the acquisition and analysis of data sufficient to inform decision making pertinent to ... the availability of tobacco-related products” (FitzGerald, 2011, p. 291).

Regulatory science in the manufacture, marketing, and distribution of tobacco products and related public education efforts is an area that is ripe for exploration. The FDA regulates tobacco products based on a public health standard that considers the product’s impact on the population as a whole, including users and nonusers. Thus, regulatory science serves as the critical bridge between tobacco products and public health by enabling the FDA to assess various products’ inherent risks and how they are used, and regulate them accordingly.

The need to identify and use the best available science is a clear mandate of the Tobacco Control Act, which highlights research opportunities on a wide variety of topics including consumer use, marketing, product development, testing, and public health (Ashley & Backinger, 2012). Appropriately designed research studies will help CTP meet this mandate.

Mechanistic studies analyzing tobacco’s effects on the human body offer important scientific insights but nevertheless are insufficient to inform regulatory decision making. For example, understanding how a tobacco product causes toxicity may not provide sufficient scientific evidence to inform regulatory activities. Rather, data regarding the varying levels of a specific tobacco constituent, its toxicity, and its interaction within the complex chemical mixture of tobacco and/or tobacco smoke will provide information that can be used to inform regulatory actions. In this context, research that evaluates measures to reduce tobacco-related harms and that tests the impact of current or future tobacco regulations would be of particular interest. Thus, research studies can inform several areas, including (but not limited to) evaluations to confirm measures of nonaddictive levels of nicotine, constituents, and carcinogens in tobacco products, as well as allowable particle smoke size and smoke pH (Hecht, 2012; Henningfield, 2011). A team of CTP scientists compiled a list of 56 research questions that could be addressed to inform regulatory activities (Ashley & Backinger, 2012). This list reflects the depth and breadth of tobacco-related research opportunities; topics include (but are not limited to) identification of biomarkers of health risks and exposure to a wide range of tobacco products and their constituents; consumer perceptions related to labeling, including ingredient and constituent disclosure; analysis of the effect of marketing and advertising practices on tobacco product use; the impact of product design and packaging (e.g., pack shape, pack size) on product use and health warning effectiveness; the impact of non-Federal initiatives on tobacco use; tobacco-related surveillance studies; and methods and measures for testing tobacco and other nicotine-containing products (DiFranza, 2012; Hammond, 2012; Hatuskami, Biener, Leischow, & Zeller, 2012; Leischow, Zeller, & Backinger, 2012; O’Connor, 2012; Ribisl, 2012). These and other scientific studies will inform regulatory and public education activities that will, in turn, reduce the death and disease caused by tobacco use. These research questions need to be considered in the context of the FD&C Act so that research findings will inform FDA’s activities regarding the manufacture, marketing, and distribution of tobacco products.
REGULATORY SCIENCE AND FDA’S PUBLIC HEALTH FRAMEWORK FOR TOBACCO

The FDA’s public health framework for tobacco regulation includes eight elements:

1. understand the regulated products;
2. restrict product changes to protect public health;
3. prohibit modified risk claims that state/imply reduced risk without an order;
4. restrict marketing and distribution to protect public health;
5. decrease harms of tobacco products;
6. ensure industry compliance with FDA regulation through education, inspections, and enforcement;
7. educate the public about FDA’s regulatory actions; and
8. expand the science base for regulatory action and evaluation.

The eighth element of this framework indicates the need for research activities that can inform the first seven elements. Descriptions of the other seven elements and their relationship to research activities are described below.

Element 1: Understand the Regulated Products

To support FDA’s mission related to regulated tobacco products, FDA scientists and regulators are interested in new scientifically derived information that will elucidate the current understanding of tobacco product content and design and the associated public health impact. Relevant research to support this element would include studies that clarify which tobacco product constituents are associated with a specific (e.g., respiratory, cardiovascular) disease burden, as well as how particular ingredients and design features (e.g., types of filters, ventilation) impact appeal, toxicity, and addictiveness.

Element 2: Restrict Product Changes to Protect Public Health

Under Section 910 of the Tobacco Control Act, a tobacco manufacturer must inform FDA about new tobacco products or changes to existing products that fall under FDA jurisdiction. Manufacturers must apply for and receive a written order from the FDA before they are allowed to legally market a new tobacco product in the United States. While manufacturers are fully responsible for providing the scientific evidence to support marketing decisions for specific products, research findings can help inform CTP’s decision-making process by elucidating the impact of tobacco product design and constituent modifications on the public health, thus aiding CTP in interpreting submitted data. For example, a study of use behavior and constituent exposure when using smokeless tobacco products with different levels of a specific ingredient could inform FDA’s interpretation of manufacturer data.

Element 3: Prohibit Modified Risk Claims That State/Imply Reduced Risk Without an Order

Once the new tobacco product has been authorized to be legally marketed, an additional pathway exists for manufacturers who wish to submit a Modified Risk Tobacco Product Application to represent a tobacco product, through its label, labeling, or advertising, as a modified risk tobacco product (MRTP). An MRTP is represented, either explicitly or implicitly, as having lower disease risk than other commercially marketed tobacco products. Under Section 911 of the Tobacco Control Act, manufacturers can legally market an MRTP only when claims are scientifically proven and FDA issues an order permitting marketing. FDA can issue such an order in two circumstances:

1. The manufacturer has provided evidence that the product as actually used by consumers will significantly reduce the harm and risk of tobacco-related disease and will benefit the public health (including both users and nonusers of the product).
2. The manufacturer, in absence of long-term epidemiological studies, can demonstrate (among other things) that the product’s use will result in substantially reduced exposure to harmful substances and would be reasonably expected to reduce death and disease and benefit the public health in the future.

Research regarding differences in consumer risk perceptions of various package designs, colors, descriptors, and statements can inform FDA’s effort to ensure that the risk of product use is accurately understood. For example, research into whether people accurately understand the risk of using a product when disclaimers are used to mitigate risk claims would inform FDA’s evaluations. In addition, research on development of measures to assess reduced harm and reduced exposure can inform FDA.

Element 4: Restrict Marketing and Distribution to Protect Public Health

The Tobacco Control Act includes authorities that may require restrictions on the sale and distribution of a tobacco product, including restrictions on access to, and the advertising and promotion of, the tobacco product if such restrictions would be appropriate for the protection of public health. As such, research to understand the impact of product labeling, advertisements, point-of-sale promotions, brand Web sites, direct mail/E-mail, and other tobacco product marketing strategies on product appeal, initiation, cessation, and relapse will inform these authorities.

Element 5: Decrease Tobacco Product Harms

Unlike decisions made in application review, which impact one manufacturer and one product, CTP’s guidance and regulation development activities may affect the entire market or a market segment (e.g., cigarettes, cigarette tobacco, roll-your-own tobacco, smokeless products). The Tobacco Control Act grants the FDA a broad authority to decrease tobacco product harms by promulgating regulations, guidance documents, and policies.

For example, the FDA can issue standards that are appropriate for the protection of public health under Section 907. The setting of tobacco product standards is an authority granted by the Tobacco Control Act that could have significant public health impact. The product standard could apply to all products or a complete class of products on the market and, given adequate scientific evidence, eliminate design features or reduce the delivery of constituents that impact the products’ appeal (especially to youth), addictiveness, or toxicity. As mandated by the Tobacco Control Act, the first product standard was implemented banning characterizing flavors except for tobacco and menthol in cigarettes in September 2009. While it is important to understand the underlying mechanisms of product design and constituents, research that addresses differences in health risk or health impact stemming from changes in the product or marketing and
distribution of the product will inform potential product standards. It is also important to evaluate unintended consequences of potential product standards and how they could be minimized in order to maximize the desired improvement in public health.

**Element 6: Ensure Industry Compliance With FDA Regulation Through Education, Inspections, and Enforcement**

CTP, its state contractors, and FDA’s Office of Regulatory Affairs conduct retail and manufacturer inspections to ensure that all regulatory requirements are met. CTP also evaluates compliance with regulations related to the promotion, advertising, and labeling of tobacco products via routine monitoring and surveillance of consumer materials, Web sites, publications, event promotions, and other tobacco marketing, advertising, and promotional activities. When potential violations of the FD&C Act, as amended by the Tobacco Control Act, are identified, CTP reviews the evidence and determines the appropriate action. CTP has established comprehensive training and assistance programs for tobacco retailers, manufacturers, distributors, wholesalers, importers, and compliance inspectors in order to provide education about Tobacco Control Act requirements. Although research to inform compliance is generally conducted via contracts or inspections, research such as whether product names, labeling, and packaging impact public perception of the product could inform CTP’s compliance activities.

**Element 7: Educate the Public About FDA’s Regulatory Actions**

FDA is authorized by the Act to develop and implement a comprehensive public communication and outreach effort. CTP provides the public with reliable, factual, science-based information about the contents of tobacco products and their associated health hazards. Activities include requiring smokeless tobacco product warnings on packages and advertisements, publishing a list of harmful and potentially harmful constituents, and developing graphic health warnings for cigarette packages.

The goal of CTP’s public communication activities is to reduce the public health burden of tobacco by encouraging tobacco use cessation and preventing initiation, especially among children, adolescents, and young adults. Accordingly, CTP is developing media campaigns and other ways to communicate information about tobacco product ingredients and the impact of tobacco product use, including graphic health warnings on cigarette packages and advertising, and communicating the harmful and potentially harmful constituents of tobacco products by brand and subbrand, as specified in the FD&C Act. Research studies to understand perceptions of tobacco products and studies to develop and evaluate the effectiveness of various messages, formats, and communication channels will help inform the development of public education and information dissemination campaigns.

**Research Focus Defined by Regulatory Authorities**

CTP’s regulatory authorities in general do not extend to banning specific classes of tobacco products, setting tax rates for tobacco products, regulating therapeutic products (such as those marketed to treat tobacco dependence), requiring the total elimination of nicotine from tobacco products, banning tobacco sales in a particular type of sales outlet, setting clean indoor air polices, or regulating tobacco farming (Husten & Deyton, 2013). Consequently, the types of research that can be supported by CTP are scientifically narrower than the broader tobacco control research field. For example, since CTP’s regulatory authority does not extend to regulating therapeutic uses of tobacco products, it will not fund a treatment intervention study designed to compare the effectiveness of various tobacco products on smoking cessation. In contrast, CTP could support a study that examines the natural history of whether participants quit smoking cigarettes while using a different tobacco product, or a study to assess whether communications regarding the health consequences of using tobacco products have an impact on usage rates. Another example of the type of research not funded by CTP is biomarker research where the primary focus is to inform treatment. Research appropriate for CTP funding, however, might include studies to identify biomarkers of specific tobacco product exposure and/or disease or biomarkers with the potential to differentiate exposure across various tobacco products, including genetic and epigenetic markers that are predictive of tobacco product adverse health outcomes. Research conducted outside of the United States can be supported if the study results can be generalized to FDA’s tobacco authorities. For example, studies evaluating toxicity, disease risk, consumer perceptions, and use of a new tobacco product could be supported if a similar product is planned to be or is marketed in the United States.

CTP’s regulatory science mission is more focused compared with the breadth of research funded by the NIH and the National Science Foundation (NSF). In general, CTP does not support research on the diagnosis of disease, the treatment of disease or tobacco use, the mechanisms of disease, or clinical practice. The traditional scientific review criteria that NIH and NSF use may also not be applicable with respect to research that CTP may support. For example, the “innovation” criterion used by NIH may not be germane because some of the research that would substantially inform CTP’s authorities may not require highly novel or innovative approaches. Investigators should note the review criteria outlines in each NIH funding opportunity announcement in order to ensure that they are being responsive.

**OPPORTUNITIES FOR RESEARCH**

Given this broad regulatory authority, many areas of scientific research are used to inform CTP’s regulatory activities. For example, CTP scientists are interested in the comparative toxicological, physiologic, and behavioral effects of tobacco products and their ingredients, constituents, and additives; dose–response studies and studies comparing the usage and effects of different tobacco products are useful as well. CTP-OS also evaluates research regarding the impact of marketing, advertising, labeling, and other communication mechanisms on consumer perceptions, beliefs, attitudes, and behaviors related to tobacco products in its regulatory activities.

A research study may inform more than one framework element. For example, a study that compares constituent levels among various tobacco products or blends could inform decisions regarding whether to allow a manufacturer to market a product with those constituent levels (Element 2, Control Product Changes that Affect Public Health) as well as the development of regulations that specify allowable levels of...
various constituents (Element 5, Decrease Harms of Tobacco Products). Findings demonstrating the impact of point-of-sale tobacco product advertising could inform regulations that restrict advertising (Element 4, Restrict Marketing and Distribution to Protect Public Health) as well as media campaigns to counteract the effects of advertisements (Element 7, Educate the Public about the Effect of Tobacco Products and FDA’s Regulatory Actions). Specific research topics can be found at the CTP Web site (www.fda.gov/TobaccoProducts/NewsEvents/ucm288107.htm) and at the NIH Tobacco Regulatory Science Program Web site (http://prevention.nih.gov/tobacco/default.aspx).

When formulating investigations for CTP’s consideration, researchers should keep the public health regulatory framework for tobacco in mind and carefully evaluate how the outcomes and findings of the research would inform research related to the regulation of tobacco products in order to decrease morbidity and mortality.

CONCLUSION

Tobacco regulatory science is an exciting and critically important discipline that has a meaningful impact on the public health. By establishing CTP, the Tobacco Control Act created an extraordinary opportunity for researchers to inform CTP as it works to mitigate the morbidity and mortality caused by tobacco product use. Researchers interested in making a scientific contribution to CTP’s mission should carefully consider FDA’s tobacco product regulation framework in the context of regulatory science and how this context differs from traditional biomedical research study aims and design.

FUNDING

This work was supported by the U.S. Food and Drug Administration Center for Tobacco Products.

DECLARATION OF INTERESTS

None declared.

ACKNOWLEDGMENTS

The authors wish to thank the members of the FDA’s Center for Tobacco Products who provided critical input into the content of this paper: Heather Althouse, Kimberly Benson, Conrad Choiniere, Matthew Holman, Corinne Husten, Ele Ibarra-Pratt, and Swati Kabaria. The views and opinions expressed in this article are those of the authors only and do not necessarily represent the views, official policy, or position of the U.S. Department of Health and Human Services or any of its affiliated institutions or agencies.

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