EDITORIAL

Food and Drug Administration Regulation of Tobacco: Integrating Science, Law, Policy, and Advocacy

The Family Smoking Prevention and Tobacco Control Act (hereafter referred to as "the Act") became law in 2009. One of its key provisions grants the Food and Drug Administration (FDA) authority to regulate tobacco products "for the protection of the public health."[1] Recognizing that the traditional "safe and effective" standard governing drugs and devices was inappropriate for tobacco products, which are inherently lethal, Congress designed the "public health standard . . . to be a flexible standard that focuses on the overall goal of reducing the number of individuals who die or are harmed by tobacco products."[2] The language is intentionally broad, focusing on protecting the health of the population as a whole.

Before the FDA can adopt a tobacco product standard, it must consider the scientific evidence regarding: (1) the risks and benefits of the proposed standard to the entire population, including both users and nonusers of tobacco products; (2) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (3) the increased or decreased likelihood that those who do not currently use tobacco products, most notably youth, will start to use tobacco products.[1]

To assist the FDA with these determinations, a Tobacco Products Scientific Advisory Committee (TPSAC) was established, comprising individuals with expertise ranging from basic to population science. Congress mandated the TPSAC to issue its first report and set of recommendations to the FDA by March 2011 on the impact of menthol on public health, especially on "children, African-Americans, Hispanics, and other racial and ethnic minorities." The FDA is empowered to ban or reduce menthol in cigarettes if it determines such action would satisfy the public health standard.

Given the likely complex impact of product standards on patterns of tobacco use, a transdisciplinary perspective is needed to fully understand how the population will adapt to changes in the regulatory environment. This editorial explores the meaning of the new standard, and specifically how scientific evidence, including 3 articles in this month's *Journal*,[3–5] can help to inform the FDA's consideration of the menthol question.

EVALUATING EVIDENCE TO MEET THE PUBLIC HEALTH STANDARD

Congress framed the public health standard in terms of risks, benefits, and likelihoods. Accordingly, the TPSAC and the FDA should use a variety of tools and strategies to review and integrate the range of instructive scientific evidence to determine how a particular product standard is likely to impact smoking initiation, cessation, and the health of current smokers, all on a population level.

Identifying Relevant Data and Scientific Methods

Under the new standard, the FDA must determine what constitutes relevant evidence and how to weigh its quality and impact. It is rarely feasible to conduct randomized trials to address population-level questions. Moreover, given the limitations of generalizing results beyond randomized trials (or extrapolating from biological, animal, or human laboratory studies with small sample sizes), relevant data must depend upon population and other "systems sciences" (e.g. mathematical modeling, social networks, studies of how norms, peer groups, and policies influence individual behavior). Population impact can be examined utilizing data from epidemiology, economics, psychology, sociology, and other disciplines to make inferences from samples to populations, and to examine effects of a given variable on an outcome in the context of multiple competing and complementary influences on the complex system. Other forms of pertinent evidence include qualitative research, clinical and community studies, consumer behavior, and peer-reviewed literature, along with formerly secret tobacco industry documents and unpublished "rapid" research commissioned to inform proposed regulatory action.

By contrast, the tobacco industry has long argued that science should be considered narrowly through an individual-level causation prism.[6,7] Notably, for more than 30 years after publication of the landmark 1964 US Surgeon General's report (and many subsequent publications that replicated its conclusions), the industry challenged the scientific evidence that smoking caused lung cancer, stating falsely that the evidence was of insufficient methodological

rigor or causal strength.[8] Here too, the industry will likely challenge the strength of the science at every opportunity in an attempt to delay or discredit the regulatory procedures.

Prioritizing Population-Level Effects, Not Individual Harms to Users

A complex systems perspective means assessing strength of scientific evidence with a view to the potential population-level impact of each piece of evidence and the evidence as a whole. Scientists must broaden the traditional hierarchy of evidence that puts basic animal studies and randomized controlled human trials at the top of the heap. In the case of menthol, results from nationally representative surveys provide essential data on trends in menthol cigarette use and associations with initiation and cessation. Such studies are at least as rigorous and more informative to the regulatory decision at hand than studies of harms to individual users. Because scientific disciplines use a variety of methods, conclusions from any discipline can always be selectively criticized, are subject to new evidence, and can be weighed differently depending on the disciplinary perspective of the scientists or the agenda of the tobacco industry. A broader view is essential whereby scientists consider all types of credible studies relevant to answering the statutory question which, in this case, focuses on population-level behavior and specifically, smoking initiation, cessation, and potential deaths averted if mentholated cigarettes were to be banned.

Determining Equipoise of Evidence

The TPSAC has identified the concept of equipoise as a framework for classifying evidence on a given scientific question, based on a tradition dating back to Hill's guidelines[9] and the first and subsequent surgeon generals' reports. While we are mindful of the fact that the public health standard is framed in terms of risks, benefits, and likelihoods, and not certainty or causality, we believe that evidence showing that a proposed tobacco product standard is at equipoise or above—in other words, at least as likely as not to benefit the public health—satisfies the statutory requirement. This belief is consistent with the legal precept that remedial statutes, like the Act, should be interpreted broadly to accomplish their purposes, in this case, to improve the public's health.

Because the Act does not impose a causation standard, entreaties to analyze the evidence through the prism of causation would lead to a misapplication of the statutory standard. The industry fundamentally misunderstands the standard when it argues that the FDA should not ban menthol because of a lack of sufficient evidence on added harm to individual smokers of mentholated versus nonmentholated cigarettes.[6,7]

In this issue of the *Journal*, Levy et al.[3] report significant associations between menthol use and decreased long-term cessation at the population level and highlight the discrepancy between increased quit attempts and reduced quit success in menthol smokers, controlling for confounders. Using previously published data, this study adds to the coherence, consistency, and replication criteria of a body of evidence that demonstrates that a ban on menthol would likely benefit the public health as a result of improved cessation, thereby satisfying equipoise and the statutory standard.

Weighing the Risks and Benefits of Proposed Regulatory Action

Although the results of any proposed regulation are ultimately unknowable until that regulation goes into effect, scientists can make valuable contributions by conducting "rapid response" surveys and constructing plausible "what-if" simulation and economic modeling studies. In this issue of the *Journal*, Winickoff et al.[5] report that more than half of Americans support a ban on menthol, with greater support among African Americans who have the highest rates of menthol use; these results are buttressed by unpublished data from the 2010 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) showing that 39.0% of menthol smokers and 46.8% of African American menthol smokers report they would quit smoking if menthol cigarettes were no longer sold.[10] Levy et al.[4] (also in this issue) use simulation modeling of multiple influences to project a sizeable population benefit of a mentholated cigarette ban (340 000 deaths averted from 2011 to 2050, a third of them among African Americans).

INTEGRATING SCIENCE, LAW, POLICY, AND ADVOCACY

We underscore the need for transdiscipinary collaboration among scientists, policymakers, and advocacy groups, using a complex systems thinking perspective. We must not only educate one another, but also the general public, the press, and other stakeholders to properly understand the context of FDA rulemaking. Scientists must have a deeper understanding of the regulatory process, including how the framing of strength of evidence (e.g. equipoise or above vs strictly defined causation) plays a role in policymaking and how issues arise in litigation that could follow promulgation of a final regulation. Scientists across disciplines need to respect each other's methods, and develop guidelines for how science best informs the public health standard. Attention should be paid to tobacco industry tactics to undermine the science and oppose regulation, including close analysis of industry research and efforts to reframe evidence through a restrictive individual causation prism. The FDA need not find a formal causal connection between a specific characteristic (such as use of menthol) and a specific disease risk to pursue regulation. Because the regulatory decision-making and legal review process also implicates science, politics, advocacy, and economics, experts from all areas are needed to make a meaningful impact on our nation's tobacco epidemic through the policy tools afforded by the Act. ■

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