creasing to $243 million in fiscal year 2013. However, the CDC Division of Tuberculosis Elimination received nearly 30 to 42% less funding than authorized during these years.

There will be legitimate concerns that screening programs targeted at people with the highest risk of latent infection will inadvertently stigmatize or unfairly burden immigrant populations and fuel xenophobic sentiments.

Inadequate outreach is only part of the problem. One study found that 83% of people in the United States and Canada who tested positive for latent tuberculosis infection accepted treatment — but only 39% of those who were offered the recommended course of therapy completed it.[5] What would it take to radically improve rates of treatment acceptance and completion? Would the public health benefits justify the costs? It may be inevitable that in tuberculosis-elimination programs, the cost per case averted increases as the total number of cases decreases.

An audio interview with Dr. Bayer is available at NEJM.org

There are public health officials, health care providers, and activists committed to reducing the burden of tuberculosis in the United States — but we have not seen the type of mass movement that occurred when AIDS activists called on political, organizational, and financial resources to correct what the IOM called a "woefully inadequate response." Instead, we seem to be recapitulating what Lee Reichman termed the "U-shaped curve of concern": when investments in public health that are sparked by a sense of threat result in a decline in disease incidence, thereby reducing the perceived danger and leading to lower investments — ultimately setting the stage for disease resurgence.

To be sure, there are constraints on what public health policy in the United States can achieve as long as the global burden of tuberculosis persists. But we believe that there is no justification for the continued failure to press forward with interventions that could have a marked effect on the incidence of tuberculosis domestically. The late George Comstock famously stated that "TB anywhere is TB everywhere." From the perspective of an ethics of public health, the lack of action to reduce rates of latent tuberculosis infection in the United States represents both the government's failure to protect its people from infectious threats and society's failure to provide care to its most vulnerable.

Disclosure forms provided by the authors are available at NEJM.org.

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A Nicotine-Focused Framework for Public Health

Scott Gottlieb, M.D., and Mitchell Zeller, J.D.

Despite extraordinary progress in tobacco control and prevention, tobacco use remains the leading cause of preventable disease and death in the United States. Combustible cigarettes cause the overwhelming majority of tobacco-related disease and are responsible for more than 480,000 U.S. deaths each year. Indeed, when used as intended, combustible cigarettes kill half of all long-term users.[1]

With the tools provided to the Food and Drug Administration (FDA) under the Family Smoking Prevention and Tobacco Control Act of 2009, the agency has taken consequential steps to prevent sales of tobacco products to children, expand the science base for understanding traditional and newer tobacco products, and conduct public education campaigns. But the agency needs to do more to protect Americans; in particular, we must shape a regulatory framework that reduces their use of combustible cigarettes. The agency's new tobacco strategy has two primary parts: reducing the addictiveness of combustible cigarettes while recognizing and clarifying the role that potentially less harmful tobacco products could play in improving public health. We must also work toward a greater role for medicinal nicotine and other therapeutic products in helping smokers to quit and remain nonsmokers.

Evidence shows that most cigarette smokers are concerned about their health and are interested in quitting and that most have tried to quit.[2] Reducing cigarettes' addictiveness could help addicted users quit more easily and help keep those who are experimenting — young people, in particular — from becoming regular smokers. And the availability of potentially less harmful tobacco products could reduce risk while delivering satisfying levels of nicotine for adults who still need or want it.

The regulatory framework for reducing harm from tobacco must include nicotine — the chemical responsible for addiction to tobacco products — as a centerpiece. Nicotine, though not benign, is not directly responsible for the tobacco-caused cancer, lung disease, and heart disease that kill hundreds of thousands of Americans each year. The FDA's approach to reducing the devastating toll of tobacco use must be rooted in this foundational understanding: other chemical compounds in tobacco, and in the smoke created by combustion, are primarily to blame for such health harms.

Nicotine is, however, responsible for getting smokers addicted to cigarette smoking in the first place — usually while they are children or young adults and their brains are still developing — and keeping them addicted long-term. Combustible cigarettes' efficient method of nicotine delivery means that nicotine inhaled from a cigarette can travel through the lungs and to the brain in less than 10 seconds,[3] adding to the addictive potential.

The Tobacco Control Act gave the FDA a regulatory tool called a tobacco product standard that can be used to alter the addictiveness of combustible cigarettes. Standards may be issued to set requirements related to an ingredient or constituent in a tobacco product, or related to any other aspect of product composition, construction, or other property. Establishing the right product standard could alter the addictiveness of combustible cigarettes by setting maximum nicotine levels in these products.

Section 907 of the Food, Drug, and Cosmetic Act authorizes the FDA to establish tobacco product standards that it has determined to be appropriate for the protection of the public health. The statute specifically notes that such a standard may address nicotine yields, among other characteristics. Although it prohibits the FDA from "requiring the reduction of nicotine yields of a tobacco product to zero," the agency has clear authority to otherwise reduce nicotine levels.

A nicotine-limiting standard could make cigarettes minimally addictive or nonaddictive, helping current users of combustible cigarettes to quit and allowing most future users to avoid becoming addicted and proceeding to regular use. Disrupting that progression — from experimentation to regular use to tobacco-related disease and even death — could save millions of American lives.

The FDA will consider peer-reviewed studies in proposing a maximum nicotine level. Rigorous studies of very-low-nicotine cigarettes have evaluated the potential effects of various nicotine levels on smoking behaviors and biomarkers,[4] and findings from such studies could inform decision making on a possible maximum nicotine level in tobacco filler. As on all matters of public health policy, the FDA will be led by the science in this important area.

As we pursue a product standard, the FDA will explore possible adverse effects of such measures, so that any final standard may anticipate and address potential unintended consequences. For instance, compensatory smoking — altering smoking behavior to continue obtaining enough nicotine to satisfy addiction — is a possible countervailing effect of setting a nicotine product standard. Several recent studies have assessed this potential, and some evidence suggests that compensation may be minimal; studies have shown reductions in cigarettes smoked per day and in exposure to harmful constituents.[4]

A recent 6-week study by Donny et al. showed that cigarettes with lower nicotine content reduced nicotine exposure and dependence, as well as the number of cigarettes smoked, as compared with cigarettes with standard nicotine levels.[5] These results are encouraging, but the FDA will scrutinize all relevant science as part of a transparent, public rulemaking process.

Our assessment of expected population health benefits will also consider the potential for migration — smokers turning to tobacco products other than cigarettes, in combination or as replacements, to maintain their nicotine dependence. Finally, we intend to explore the possibility that regulation might give rise to an illicit market for higher-nicotine products; the FDA will seek input on this issue from experts as we develop our regulatory policy.

With these considerations in mind, and led by the best available evidence, the FDA will pursue a regulatory framework that focuses on nicotine and supports innovation to promote harm reduction. This framework will recognize that the core problem of nicotine lies not in the drug itself but in the risk associated with the delivery mechanism. In contrast to combustible cigarettes, nicotine delivery mechanisms such as medicinal gums, skin patches, or lozenges can be so safe and effective in helping smokers quit that they may be sold without a prescription.

To truly protect the public, the FDA's approach must take into account the continuum of risk for nicotine-containing products. We are examining possible steps the agency could take to address the pharmacokinetic performance of FDA-approved medicinal nicotine products to help more smokers quit. Factors for consideration may include the speed with which nicotine is delivered and other possible innovations.

There are already products, such as electronic nicotine delivery systems, that could conceivably deliver nicotine without posing the dangers associated with tobacco combustion. Experts on both sides of the "harm reduction" debate have expressed strongly held views about the potential benefits and risks of e-cigarettes. We must continue to build on our understanding of the potential benefits for addicted cigarette smokers, in a properly regulated marketplace, of products capable of delivering nicotine without having to set tobacco on fire. The FDA's ongoing investment in regulatory science will contribute to this understanding.

Rendering cigarettes minimally addictive or nonaddictive, within a landscape including other, noncombustible products such as e-cigarettes, represents a promising foundation for a comprehensive approach to tobacco harm reduction. In working toward this vision, the FDA is committed to striking an appropriate balance between protecting the public and fostering innovation in less harmful nicotine delivery.

We are at a crossroads in efforts to reduce tobacco use, with the lives of tens of millions of currently addicted cigarette smokers and future generations hanging in the balance. Even as we evaluate the characteristics of various nicotine-delivery products — and watch the sometimes-divisive debate over these products' pros and cons — the FDA is focusing squarely on nicotine as the centerpiece of a comprehensive, lifesaving tobacco regulatory strategy. In developing this strategy, we will rigorously assess the best available evidence and provide extensive opportunities for stakeholder input. As a first step, the agency is working on an advance notice of proposed rulemaking to obtain information relevant to reducing the nicotine levels in combustible cigarettes and to ask key questions related to the benefits and potential unintended consequences of such a policy.

Led by the best available evidence, the FDA will pursue a regulatory framework that focuses on nicotine and supports innovation to promote harm reduction.

The public health benefits of implementing a nicotine-reduction policy for combustible cigarettes could be enormous: we would expect smoking-related morbidity and premature mortality to decrease considerably. Ultimately, we may be able to transform the tobacco marketplace and the delivery of nicotine to protect future generations of young people and save many millions of lives.

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The Fate of FDA Postapproval Studies

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Both Congress and the Food and Drug Administration (FDA) have sought to accelerate the availability of new drugs by allowing sponsors to wait to resolve many questions about safety and benefit until after their drugs receive marketing approval. As a result, most approval letters require phase 4 studies to address issues such as optimal dosing, potential long-term side effects, and use in children or to confirm the clinical benefit of drugs that receive conditional approval on the basis of preliminary evidence.

In response to widespread criticism over the lax oversight of postapproval studies and low completion rates, Congress included in the FDA Amendments Act of 2007 (FDAAA) additional power for the FDA to require companies to complete such studies. Before that law, the FDA had no specific statutory authority to order postapproval studies; instead, it established "commitments" with the sponsor as a condition of approval. Under the FDAAA, the agency can establish both requirements and commitments when it approves a drug (or later, if there is new safety information). In addition, the FDAAA empowered the FDA to specify when certain study milestones must be reached — and to issue fines or rescind marketing approval for noncompliance. The FDA must also issue annual reports on the status of postapproval studies.

To assess the effects of the 2007 legislation, we used the latest *Federal Register* status report to evaluate 614 postapproval requirements and commitments imposed in 2009 and 2010, the earliest years covered by the report (see Table 1).[1] After 5 to 6 years, 20% of postapproval studies had not been started, 25% were delayed or ongoing, and 54% had been completed. We analyzed the FDA's database of postapproval requirements and commitments for instructive examples of studies that had not been completed (see Table 2).[2]

Incomplete studies fell into several categories. A total of 16%

Table 1. Status of Postapproval Studies Established in 2009 and 2010.*

Study Status	2009	2010	Total
		number (percent)	
Total	296	318	614
Never started	78 (26)	47 (15)	125 (20)
Pending	17 (6)	13 (4)	30 (5)
Terminated	2 (1)	0	2 (<1)
Released	59 (20)	34 (11)	93 (15)
Still ongoing	68 (23)	88 (28)	156 (25)
Delayed	27 (9)	30 (9)	57 (9)
On schedule	41 (14)	58 (18)	99 (16)
Completed	150 (51)	183 (58)	333 (54)
Submitted	11 (4)	27 (8)	38 (6)
Fulfilled	139 (47)	156 (49)	295 (48)

* Individual components may not add to totals because of rounding. Some delayed studies have not been started because they are delayed at the protocol stage. Status is as of September 2015. Adapted from the Food and Drug Administration annual *Federal Register* report.[1]