



## The FDA, E-Cigarettes, and the Demise of Combusted Tobacco

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In April 2014, nearly 8 years after e-cigarettes were introduced into the U.S. market, the Food and Drug Administration (FDA) made a long-awaited announcement regarding its intention to regulate

the devices, deeming them to be subject to regulation as tobacco products.<sup>1</sup> The term “e-cigarette” (which the regulations do not define) generally refers to a variety of battery-powered inhaler devices that deliver aerosolized, refined nicotine in a humectant.

In 2014, Americans will spend about \$2.2 billion on e-cigarettes — numbers that exceed those for nicotine-replacement therapy (NRT) and begin to compete with the \$85 billion in annual sales (including all taxes) of lethal combusted tobacco. The popularity of e-cigarettes has spawned acrimonious debate over their usefulness in harm reduction, which has obscured a key point established over the past 20 years:

carefully constructed, clean nicotine-delivery devices for NRT (e.g., nicotine patches, chewing gums, and inhalers) are safe and can effectively drive smoking cessation. Marked interdevice and intermanufacturer variability of e-cigarettes, which use various chemicals and aerosolization techniques that result in variable nicotine and contaminant delivery, makes it hard to draw conclusions about the safety or efficacy of the whole device class. Nevertheless, published evaluations of some products suggest that e-cigarettes can be manufactured with levels of both efficacy and safety similar to those of NRT products,<sup>2</sup> resulting in profoundly reduced risk as compared with cigarettes.

The FDA Center for Tobacco Products (CTP) is required to regulate tobacco products in a public health framework that considers effects not only on users but also on nonusers, especially young people. The CTP’s “deeming” statement on how e-cigarettes should be regulated represents the first phase in determining how refined-nicotine products are to be designed, marketed, and sold outside the pharmaceutical regulation of NRT. If e-cigarettes (and other refined-nicotine products) are thoughtfully regulated, they could play the same role as NRT but at a truly national, population scale. Their use could shift smokers permanently away from lethal cigarettes to cleaner, safer nicotine products, saving innumerable lives.

As written, the CTP regulations would largely require manufacturers to register their products and to accurately disclose

and label ingredients and would prohibit sales to young people and distribution of free samples. Previous legal rulings prohibited the marketing of e-cigarettes as smoking-cessation devices unless they are approved by the FDA as pharmaceutical products — an expensive and time-consuming process that no manufacturer has yet attempted. Currently lacking and urgently needed are product standards for device safety, nicotine content, additives, and carrier compounds. The standards that are eventually developed will determine the role that e-cigarettes play in a national harm-reduction framework. However, to compete with and displace combusted-tobacco products, e-cigarettes will need to remain relatively convenient, satisfying, and inexpensive even under regulation.

To allow for those goals, the FDA can balance the harm-reduction potential of the products against other variables, including the risks and benefits of both current alternatives and future versions of e-cigarettes. The current e-cigarette models represent a single instance of a nicotine product on a shifting spectrum of toxicity, addiction liability, and consumer satisfaction. As Big Tobacco's scientists shift from blending leaves and additives to manipulating circuit boards, chemicals, and dosing schedules, they're unlikely to relinquish their tolerance for risk and toxicity that prematurely kills half their users in their efforts to ensure high levels of customer "satisfaction," addiction, and retention. Absent clear regulations and enforcement, these products will evolve, resulting in variants whose safety and addiction liability no longer approximate those of NRT

products or current e-cigarettes and which therefore may offer far less harm-reduction potential.

One might ask what harm more-addictive products might cause: surely any world where refined nicotine displaces lethal cigarettes will experience less harm, disease, and deaths? That scenario is one endgame model for tobacco control<sup>3</sup>: smokers flee cigarettes en masse for refined nicotine and ultimately quit all use entirely. This vision, however, ignores Big Tobacco's power and corporate self-interest in retaining the existing \$85 billion U.S. combusted-cigarette market. Emerging companies that sell only refined-nicotine products can build smaller yet profitable businesses by appropriating customers from Big Tobacco and retaining them only until they transition to complete cessation. Tobacco companies and their investors, however, need millions of heavily addicted smokers to remain customers for decades, including a replenishing stream of young people. No publicly traded company could tolerate the downsizing implicit in shifting from long-term addiction to harm reduction and cessation. If afforded the opportunity, tobacco companies may try to avoid disruption of their business model<sup>4</sup> by marketing innovations designed to sustain high levels of addiction and synergistic "poly-use" of their existing combusted products. If effective, such a strategy could severely hamper any transition to an endgame while effectively eliminating competition from NRT and independent e-cigarette makers.

How will this risk affect tobacco-control efforts and FDA rulemaking? We believe that us-

ing the public health standard will allow the agency to set clear boundaries favoring a transition away from the big tobacco companies' lethal combustible products. At least two multinational companies have acquired intellectual property allowing inhalation products to achieve alveolar deposition and thus the arterial delivery of nicotine that drives combusted tobacco's unique addiction liability. Such fundamental product shifts could blur risk perceptions across product classes, thereby perpetuating lethal cigarette use through polyuse or increased uptake of lethal combustibles by more young people. Regulation can address this problem through clear class definitions for nicotine content, humectants, vaporization methods, and additives (all of which Big Tobacco has historically manipulated), and rigorous but rapid premarketing review and postmarketing surveillance by the FDA can ensure that products and marketing adhere to manufacturers' stated guarantees. Innovation that causes products to diverge from class-defining properties could, without preventing sale, trigger additional scrutiny so that unintended consequences could be caught and prevented.

The FDA, in concert with tobacco-control advocates, state governments, and Congress, can do even more to drive a wedge between regulated clean-nicotine products and the toxic combustible products that predominate today. The CTP can use its product-standard authority in conjunction with e-cigarette growth to cripple the addictive potential of lethal combusted products by mandating a reduction in nicotine levels to below those of e-cigarettes

and NRT products and eliminating flavorings such as menthol that make cigarettes more palatable. States and Congress can work to minimize taxes on all clean-nicotine products while increasing cigarette taxes to drive substitution through significant price differentials. Furthermore, it would be helpful if companies that invest in research to demonstrate efficacy for cessation were not penalized with additional regulatory burdens, such as being forced under the regulatory category for pharmaceuticals. The FDA Center for Drug Evaluation

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

and Research can streamline the approval process for smoking-cessation indications and, more important, can regulate these products flexibly to ensure that clean-nicotine products with a cessation indication can be marketed more appealingly and widely than products lacking evidence of such efficacy.

These recommendations are not meant to dismiss immediate consumer safety issues. The FDA has proposed creating a 2-year window before warning labels or product

safety and quality standards for e-cigarettes would go into effect. The delay is disturbing, given the variability in product quality and a documented spike in cases of accidental nicotine poisoning.<sup>5</sup> We believe that no product subject to FDA regulation should be exempt (even temporarily) from basic supply-chain monitoring or simple safety devices, such as child-resistant containers, ensuring that they're as safe as possible.

Until the FDA enforces oversight and regulation of e-cigarettes, the safety of individual devices cannot be assumed. For smokers choosing among forms of refined nicotine, NRT products still represent safer, more predictable choices, even if they are more expensive and less appealing. This discrepancy is unfortunate, given the public health potential of e-cigarettes that consumers could assume to be safe, reliable, and effective. We would encourage the FDA to accelerate their regulations to eliminate uncertainty regarding safety, drive the substitution and use of clean nicotine, and hasten the demise of lethal combusted tobacco.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## Diversity Dynamics — Challenges to a Representative U.S. Medical Workforce

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In an era when the proportion of the U.S. population that is nonwhite has surged to 37%, two notable trends are shaping the composition of the physician workforce: the “overwhelming majority” of medical school graduates continue to be white,<sup>1</sup> and

the number of black men completing medical school has been trending downward since 1997.<sup>2</sup> By comparison, medical school graduates of Hispanic and Asian descent have increased in number and as a percentage of total graduates. Although the Obama

administration trumpets its support for improving opportunities for minority young people — and specifically black men — it has dismayed medical educators for 3 years running by proposing elimination of the Health Careers Opportunity Program (HCOP),